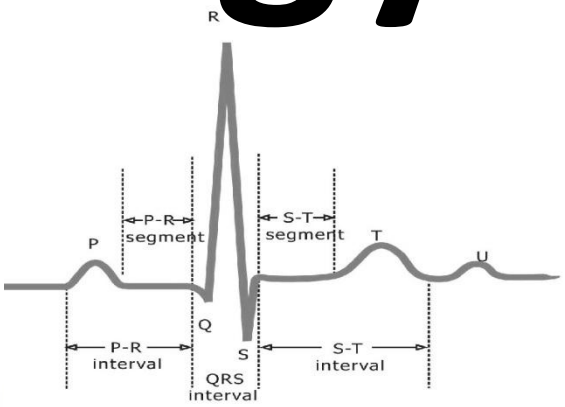
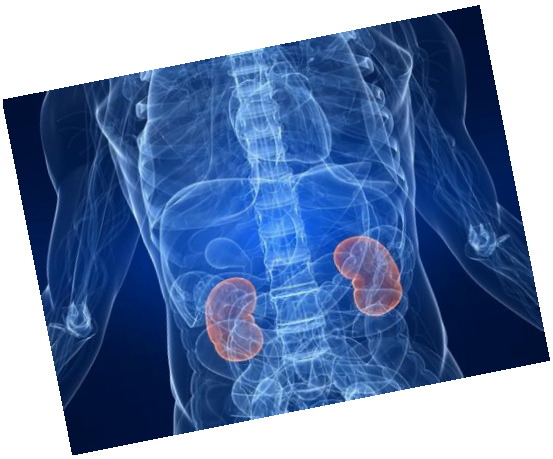
## Review of

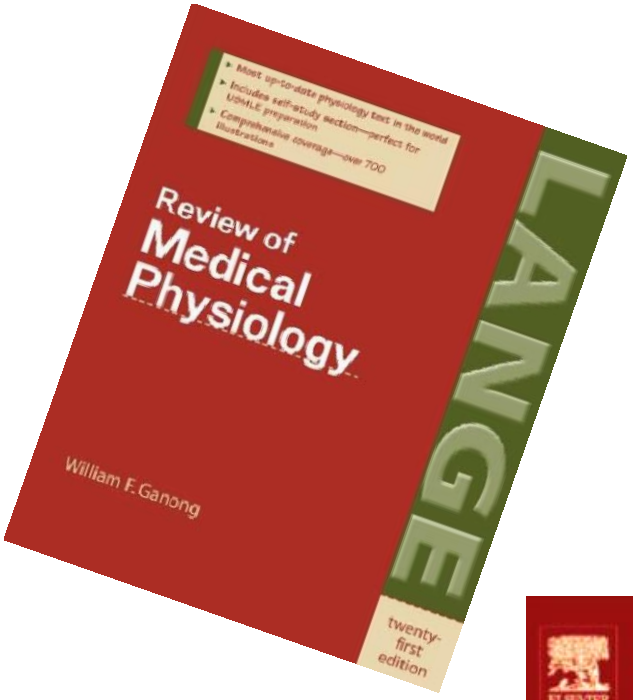
# Physiology



## 1st edition

***By: REBAND AHMED***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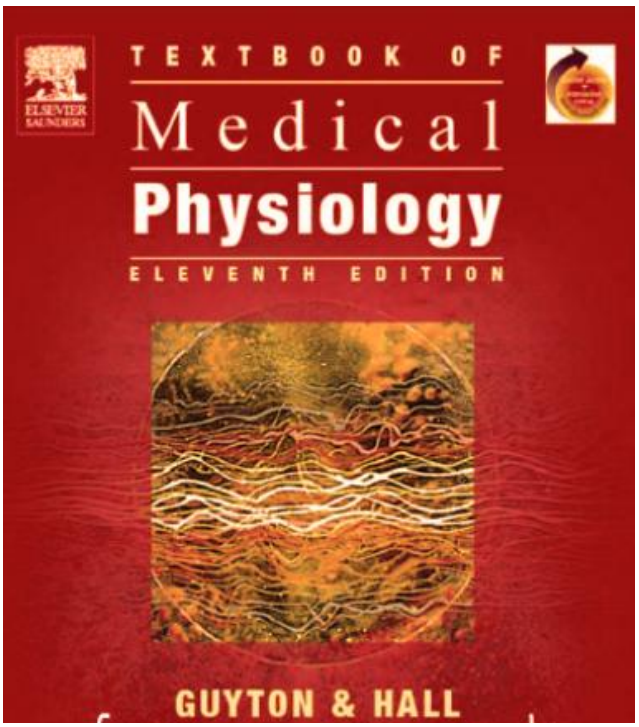
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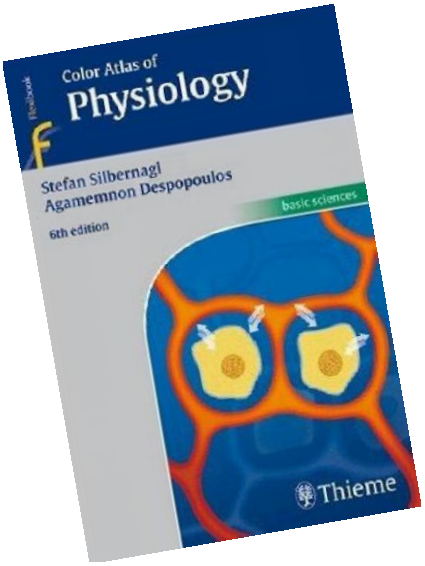
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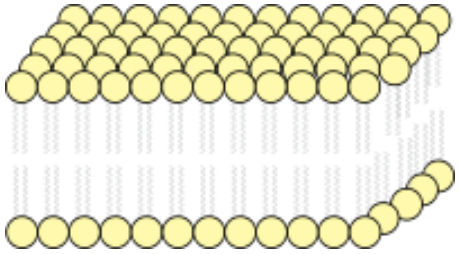
# Part A

## 1. Structure and function of cell membranes

### Structure

#### Lipid bilayer



The cell membrane consists primarily of a thin layer of *amphipathic phospholipids* which are arranged so that the hydrophobic "tail" regions are shielded from the surrounding polar fluid, causing the more hydrophilic "head" regions to associate with the cytosolic and extracellular faces of the resulting bilayer. This forms a continuous, spherical lipid bilayer.

The arrangement of hydrophilic heads and hydrophobic tails of the lipid bilayer prevent polar solutes (e.g. amino acids, nucleic acids, carbohydrates, proteins, and ions) from diffusing across the membrane, but generally allows for the passive diffusion of hydrophobic molecules.

#### Integral membrane proteins

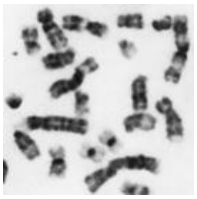
The cell membrane contains many integral membrane proteins. These structures, which can be visualized by electron microscopy or fluorescence microscopy, can be found on the inside of the membrane, the outside, or membrane spanning. These may include *integrins*, *cadherins*, *desmosomes*, *clathrin-coated pits*, *caveolaes*, and different structures involved in cell adhesion.

### Function

The cell membrane surrounds the protoplasm of a cell and, in animal cells, physically separates the intracellular components from the extracellular space, thereby serving a function similar to that of skin. In fungi, some bacteria, and plants, an additional cell wall forms the outermost boundary; however, the cell wall plays mostly a mechanical support role rather than a role as a selective boundary. The cell membrane also plays a role in anchoring the cytoskeleton to provide shape to the cell, and in attaching to the extracellular matrix and other cells to help group cells together to form tissues. The barrier is differentially permeable and able to regulate what enters and exits the cell, thus facilitating the transport of materials needed for survival. The movement of substances across the membrane can be either *passive*, occurring without the input of cellular energy, or active, requiring the cell to expend energy in moving it. The membrane also maintains the cell potential.

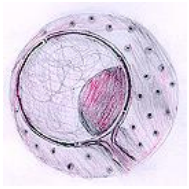
Specific proteins embedded in the cell membrane can act as molecular signals that allow cells to communicate with each other. Protein receptors are found ubiquitously and function to receive signals from both the environment and other cells

## 2. Structure and functions of cell organelles



**Chromosomes**

- Usually in the form of chromatin
- Contains genetic information
- Composed of DNA
- Set number per species (i.e. 23 pairs for human)



**Nuclear membrane**

- Surrounds nucleus
- Composed of two layers
- Numerous openings for nuclear traffic

**Nucleolus**

- Spherical shape
- Visible when cell is not dividing
- Contains RNA for protein manufacture

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**Centrioles**

- Paired cylindrical organelles near nucleus
- Composed of nine tubes, each with three tubules
- Involved in cellular division
- Lie at right angles to each other

**Chloroplasts**

- A plastid usually found in plant cells
- Contain green chlorophyll where photosynthesis takes place

**Cytoskeleton**

- Composed of microtubules
- Supports cell and provides shape
- Aids movement of materials in and out of cells

**Endoplasmic reticulum**

- Tubular network fused to nuclear membrane
- Goes through cytoplasm onto cell membrane
- Stores, separates, and serves as cell's transport system
- Smooth type: lacks ribosomes
- Rough type (pictured): ribosomes embedded in surface

**Golgi apparatus**

- Protein 'packaging plant'
- A membrane structure found near nucleus
- Composed of numerous layers forming a sac

**Lysosome**

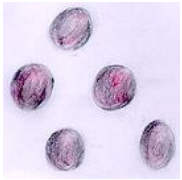
- Digestive 'plant' for proteins, lipids, and carbohydrates
- Transports undigested material to cell membrane for removal
- Vary in shape depending on process being carried out
- Cell breaks down if lysosome explodes

**Mitochondria**

- Second largest organelle with unique genetic structure
- Double-layered outer membrane with inner folds called *cristae*
- Energy-producing chemical reactions take place on cristae
- Controls level of water and other materials in cell
- Recycles and decomposes proteins, fats, and carbohydrates, and forms urea

**Ribosomes**

- Each cell contains thousands
- Miniature 'protein factories'
- Composes 25% of cell's mass
- Stationary type: embedded in rough endoplasmic reticulum
- Mobile type: injects proteins directly into cytoplasm



**Vacuoles**

- Membrane-bound sacs for storage, digestion, and waste removal
- Contains water solution
- Contractile vacuoles for water removal (in unicellular organisms)

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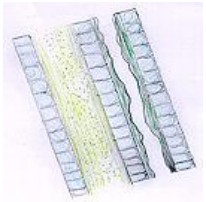
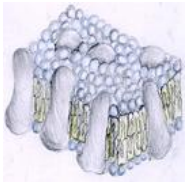


**Cell wall**

- Most commonly found in plant cells
- Controls turgity
- Extracellular structure surrounding plasma membrane
- Primary cell wall: extremely elastic
- Secondary cell wall: forms around primary cell wall after growth is complete



**Plasma membrane**

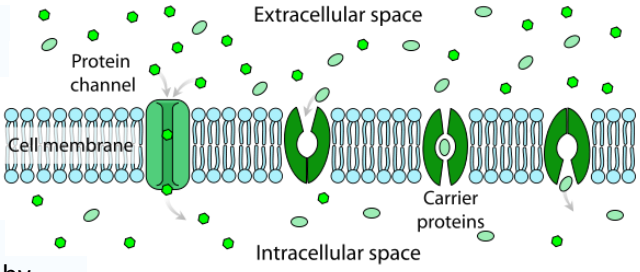
- Outer membrane of cell that controls cellular traffic
- Contains proteins (left, gray) that span through the membrane and allow passage of materials
- Proteins are surrounded by a phospholipid bi-layer.

## 3. Passive transport across membranes. Cotransport.

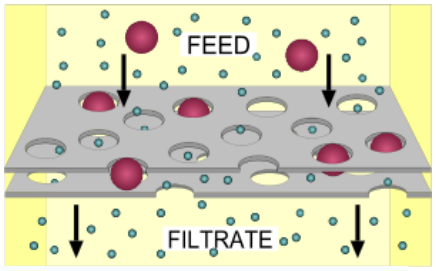
Passive transport means moving biochemicals and atomic or molecular substances across the cell membrane. Unlike active transport, this process does not involve chemical energy.
The four main kinds of passive transport are *diffusion*, *facilitated diffusion*, *filtration* and *osmosis*.

I. **Diffusion** is a process by which there is a net flow of matter from a region of high concentration to one of low concentration. It is driven by a conc. gradient. It can be measured using the following equation: **$J = -PA (C_1 – C_2)$**
where: J = flux (flow) [mmol/sec], P = permeability (cm/sec), A = area ($cm^2$), $C_1$ = conc.$_1$ (mmol/L), $C_2$ = conc.$_2$ (mmol/L)

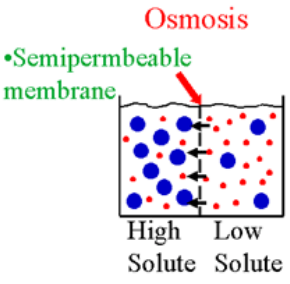
II. **Facilitated diffusion** is the spontaneous passage of molecules or ions across a biological membrane passing through specific transmembrane transport proteins. It occurs down an electrochemical gradient (“downhill”), similar to simple diffusion. Glucose transport in muscle an adipose cells is “downhill”, is carrier-mediated, and is inhibited by sugars as galactose; therefore, it is categorized as facilitated diffusion.




III. **Filtration** is a mechanical or physical operation which is used for the separation of solids from fluids (liquids or gases) by interposing a medium through which only the fluid can pass. Oversize solids in the fluid are retained, but the separation is not complete; solids will be contaminated with some fluid and filtrate will contain fine particles (depending on the pore size and filter thickness).




IV. **Osmosis** is the diffusion of water molecules across a selectively permeable membrane. The net movement of water molecules through a partially permeable membrane from a solution of high water potential to an area of low water potential.




### Co-transport

Also known as coupled transport, refers to the simultaneous or sequential passive transfer of molecules or ions across biological membranes in a fixed ratio. Cotransporters can be classified as **symporters** and **antiporters** depending on whether the substances move in the same or opposite directions.

## 4. Compartmentalization of body fluids

The total body fluid is distributed mainly between two compartments: the ***extracellular fluid*** and the ***intracellular fluid***. The extracellular fluid is divided into the ***interstitial fluid*** and the **blood *plasma*.**

There is another small compartment of fluid that is referred to as ***transcellular fluid***. This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.

In the average 70-kilogram adult human, the total body water is about 60 per cent of the body weight, or about 42 liters. This percentage can change, depending on age, gender, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight.

### Intracellular Fluid Compartment

About 28 of the 42 liters of fluid in the body are inside the 75 trillion cells and are collectively called the *intracellular fluid.* Thus, the intracellular fluid constitutes about 40 per cent of the total body weight in an "average" person.

### Extracellular Fluid Compartment

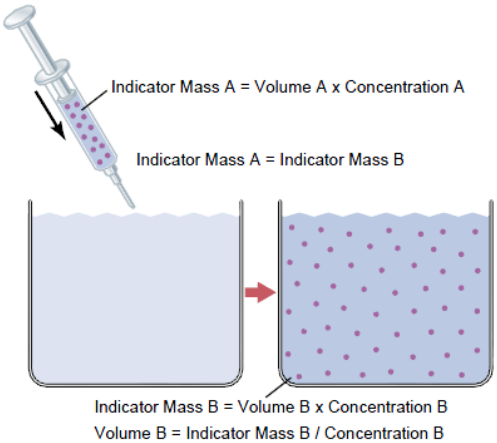
All the fluids outside the cells are collectively called the *extracellular fluid.* Together these fluids account for about 20 per cent of the body weight, or about 14 liters in a normal 70-kilogram adult. The two largest compartments of the extracellular fluid are the ***interstitial fluid,*** which makes up more than three fourths of the extracellular fluid, and the ***plasma,*** which makes up almost one fourth of the extracellular fluid, or about 3 liters. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so that the plasma and interstitial fluids have about the same composition except for proteins, which have a higher concentration in the plasma.

#### Measurement

The volume of a fluid compartment in the body can be measured by placing an indicator substance in the compartment, allowing it to disperse evenly throughout the compartment's fluid, and then analyzing the extent to which the substance becomes diluted.

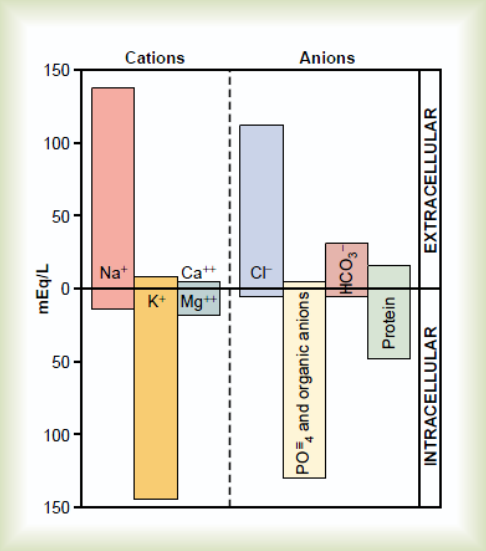
**Measurement of Body Fluid Volumes**

| Volume | Indicators |
|---|---|
| Total body water | $^{3}H_2O$, $^{2}H_2O$, antipyrine |
| Extracellular fluid | $^{22}Na$, $^{125}I$-iothalamate, thiosulfate, inulin |
| Intracellular fluid | (Calculated as Total body water – Extracellular fluid volume) |
| Plasma volume | $^{125}I$-albumin, Evans blue dye (T-1824) |
| Blood volume | $^{51}Cr$-labeled red blood cells, or calculated as Blood volume = Plasma volume/ (1 – Hematocrit) |
| Interstitial fluid | (Calculated as Extracellular fluid volume – Plasma volume) |



## 5. Differences between intra- and extracellular fluids

### Ionic Composition of Plasma and Interstitial Fluid Is Similar




Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their ionic composition is similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues.
Because of the *Donnan effect,* the concentration of positively charged ions (cations) is slightly greater (about 2 per cent) in the plasma than in the interstitial fluid.

### Important Constituents of the Intracellular Fluid

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but not to most of the electrolytes in the body.

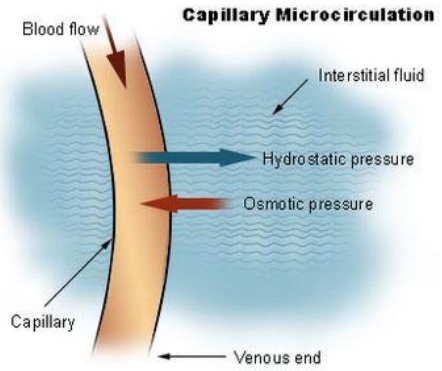
In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein, almost four times as much as in the plasma.

**Osmolar Substances in Extracellular and Intracellular Fluids**

| | Plasma (mOsm/L $H_2O$) | Interstitial (mOsm/L $H_2O$) | Intracellular (mOsm/L $H_2O$) |
|---|---|---|---|
| $Na^+$ | 142 | 139 | 14 |
| $K^+$ | 4.2 | 4.0 | 140 |
| $Ca^{++}$ | 1.3 | 1.2 | 0 |
| $Mg^+$ | 0.8 | 0.7 | 20 |
| $Cl^-$ | 108 | 108 | 4 |
| $HCO_3^-$ | 24 | 28.3 | 10 |
| $HPO_4^-$, $H_2PO_4^-$ | 2 | 2 | 11 |
| $SO_4^-$ | 0.5 | 0.5 | 1 |
| Phosphocreatine | | | 45 |
| Carnosine | | | 14 |
| Amino acids | 2 | 2 | 8 |
| Creatine | 0.2 | 0.2 | 9 |
| Lactate | 1.2 | 1.2 | 1.5 |
| Adenosine triphosphate | | | 5 |
| Hexose monophosphate | | | 3.7 |
| Glucose | 5.6 | 5.6 | |
| Protein | 1.2 | 0.2 | 4 |
| Urea | 4 | 4 | 4 |
| Others | 4.8 | 3.9 | 10 |
| Total mOsm/L | 301.8 | 300.8 | 301.2 |
| Corrected osmolar activity (mOsm/L) | 282.0 | 281.0 | 281.0 |
| Total osmotic pressure at 37°C (mm Hg) | 5443 | 5423 | 5423 |

= major cation =major anion

## 6. Production and resorption of interstitial fluid (Starling forces)




**Interstitial fluid** is a solution that bathes and surrounds the cells of multicellular animals. It is the main component of the extracellular fluid, which also includes plasma and transcellular fluid.
The interstitial fluid is found in the interstitial spaces, also known as the tissue spaces.

On average, a person has about 11 litres (2.4 imperial gallons) of interstitial fluid, providing the cells of the body with nutrients and a means of waste removal.

Formation of interstitial fluid

*Hydrostatic pressure* is generated by the systolic force of the heart. It pushes water out of the capillaries **(Starling forces)**.

The water potential is created due to the ability of small solutes to pass through the walls of capillaries. This buildup of solutes induces osmosis. The water passes from a high concentration (of water) outside of the vessels to a low concentration inside of the vessels, in an attempt to reach an equilibrium. The osmotic pressure drives water back into the vessels. Because the blood in the capillaries is constantly flowing, equilibrium is always reached.

The balance between the two forces differs at different points on the capillaries. At the arterial end of a vessel, the hydrostatic pressure is greater than the osmotic pressure, so the net movement favors water and other solutes being passed into the tissue fluid. At the venous end, the osmotic pressure is greater, so the net movement favors substances being passed back into the capillary. This difference is created by the direction of the flow of blood and the imbalance in solutes created by the net movement of water favoring the interstitial fluid.

Removal of interstitial fluid

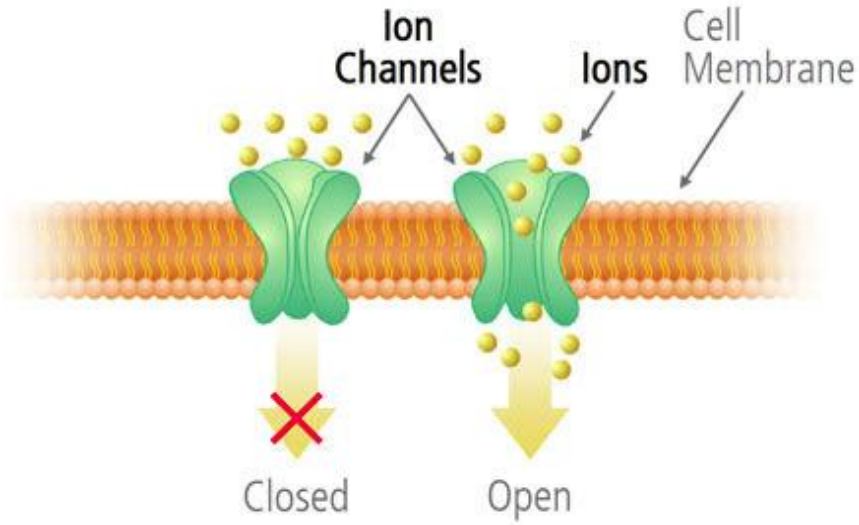
To prevent a build-up of interstitial fluid surrounding the cells in the tissue, the lymphatic system plays a part in the transport of interstitial fluid. Interstitial can pass into the surrounding lymph vessels, and eventually ends up rejoining the blood.

Sometimes the removal of tissue fluid does not function correctly, and there is a build-up. This causes swelling, and can often be seen around the feet and ankles, for example *Elephantiasis*. The position of swelling is due to the effects of gravity.

## 7. Ion channels

Ion channels are **integral proteins** that span the membrane and, when open, permit the passage of certain ions.

1. **Ion channels are selective**; they permit the passage of some ions, but not others. Selectively is based on the size of the channel and the distribution of charges that line it.
2. **Ions channels may be opened or closed**. When the channel is open, the ion(s) for which it is selective can flow through it. When the channel is closed, ions cannot flow through them.
3. **The conductance of a channel** depends on the probability that the channel is open. The higher the probability that a channel is open, the higher the conductance, or **permeability**. Opening and closing of channels are controlled by **gates**.
    a. ***Voltage-gated channels*** are open or closed by changes in membrane potential.
        - The **activation gate of the $Na^+$ channel** in nerve is opened by depolarization; when open, the nerve membrane is permeable to Na+ (e.g., during the upstroke of the nerve action potential).
        - The **inactivation gate of the Na+ channel** in nerve is closed by depolarization; when closed, the nerve membrane is impermeable to Na+ (e.g., during the repolarization phase of the nerve action potential).
    b. ***Ligand-gated channels*** are opened or closed by hormones, second messengers, or neurotransmitters.
        - For example, the **nicotinic receptor** for acetylcholine (ACh) at the motor end plate is an ion channel that opens when Ach binds to it. When open, it is permeable to Na+ and K+, causing the motor end plate to depolarize.



# 8. Intercellular communication

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

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.

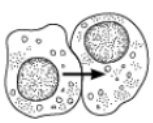
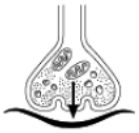
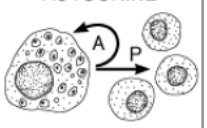
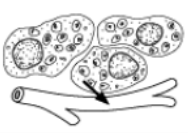
For several types of intercellular signaling molecules that are unable to permeate the hydrophobic cell membrane due to their hydrophilic nature, the target receptor is expressed on the membrane. When such signaling molecule activates its receptor, the signal is carried into the cell usually by means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

Within endocrinology (the study of intercellular signalling in animals) and the endocrine system, intercellular signalling is subdivided into the following classifications:

- ***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*** signals affect only cells that are of the same cell type as the emitting 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.

## Intercellular connections

1. ***Tightjunctions (zonula occludens)***
   - are the attachments between cells (often epithelial cells).
   - may be an intercellular pathway for solutes, depending on the size, charge, and characteristics of the tight junction.
   - may be **"tight"** (impermeable), as in the renal distal tubule, or **"leaky"** (permeable), as in the renal proximal tubule and gallbladder.
2. ***Gap junctions***
   - are the attachments between cells that permit intercellular communication.
   - for example, permit current flow and electrical **coupling between myocardial cells**.

| | 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 molecules that relay signals from receptors on the cell surface to target molecules inside the cell, in the cytoplasm or nucleus. They relay the signals of hormones like epinephrine (adrenalin), growth factors, and others, and cause some kind of change in the activity of the cell. They greatly amplify the strength of the signal.

## Types of secondary messenger molecules

There are three 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.

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 second messenger systems

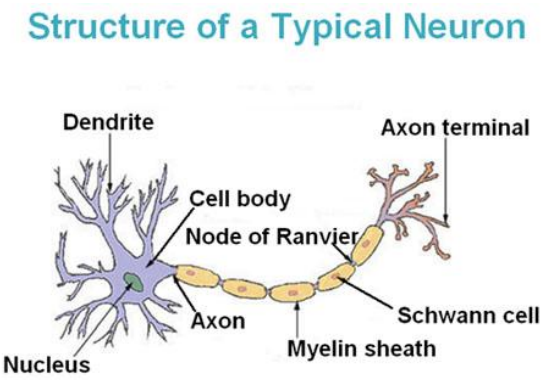
There are several different secondary messenger systems (cAMP system, phosphoinositol system, and arachidonic acid system), but they all are quite similar in overall mechanism, though the substances involved in those mechanisms and effects are different.

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.

## 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*.

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** (contains the nucleus and the main conc. of organelles), the **dendrites** (their number varies in a great range, theoretically from one to several hundred; they are usually short and conduct impulses to the perikaryon), and the **axon** or **neurite** (it is mostly very long and always single, it conducts the impulses away from respective cell. Terminally, each axon ends in twiglike branching or arborizations – the **telodendria**, which touch the perikarya, dendrites or axons of one or more neurons. The sites of contact between neurons are called *synapses*.

**1.** 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*.

**2. Dendrites** are always present near the cell body and they tend to branch, forming arborizations. Many dendrites have short, spinous processes that touch the axon endings of other neurons. Dendrites contain the same organelles as the cell body proper, except the Golgi network.

**3. Axon** is only for each neuron and may be often extremely long. The part of the axon that joins to the cell body is cone-shaped and it is called ***axon hillock***. The **initial segment** is a portion of the axon between the axon hillock and the point at which myelination begins. The initial segment is the site where the nerve impulses are generated.

## 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 (they are rare).

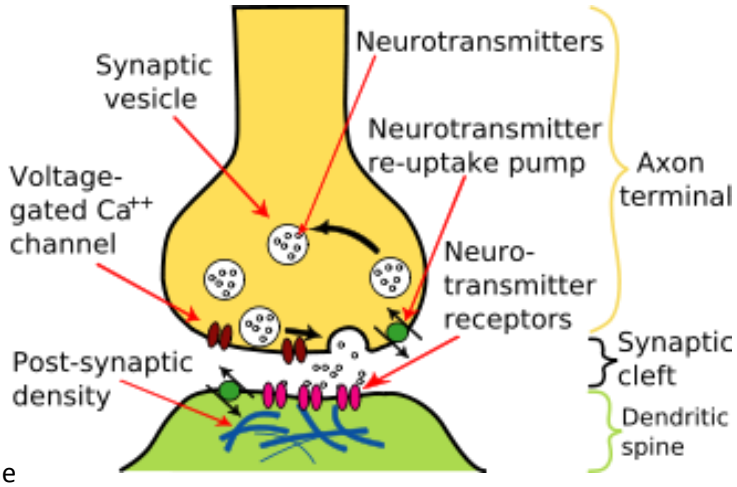
In addition to the **chemical synapses**, in which a chemical substance mediates the transmission of the nerve impulse, there are also the **electrical synapses**. Here the nerve cells are linked through a **gap junction**. Electrical synapses are less numerous then chemical synapses.

Principle of transmission of impulses:

When an impulse reaches the axonal ending (presynaptic knob), **$Ca^{2+}$** enter the ending. The action of calcium causes the vesicles to migrate to and fuse with the presynaptic membrane and then discharge the transmitter into the synaptic cleft by *exocytosis*.

The transmitter diffuses across the synaptic cleft and binds to receptors in the postsynaptic membrane (membrane of dendrite or perikaryon).

This process results in depolarization of the postsynaptic membrane which is propagated to the initial segment – the site where nerve impulses are generated.




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

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

## 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*.

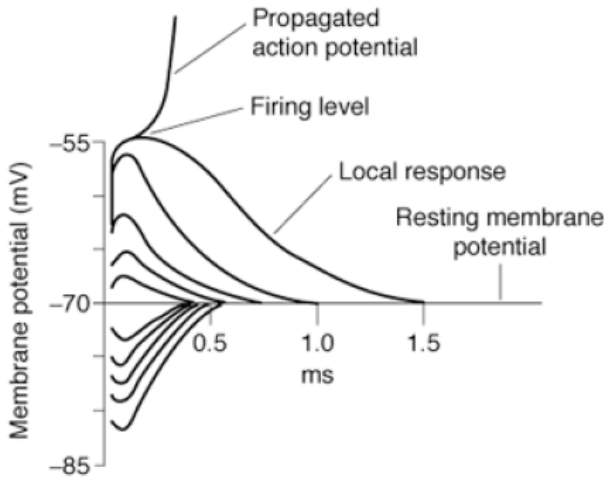
## Degradation and elimination

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.

## 15. Local Response of membrane potential

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

An **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a stereotyped trajectory. Action potentials occur in several types of excitable cells, including neurons, muscle cells, and endocrine cells.

Definitions

→***Depolarization*** makes the membrane potential less negative (the cell interior becomes less negative)

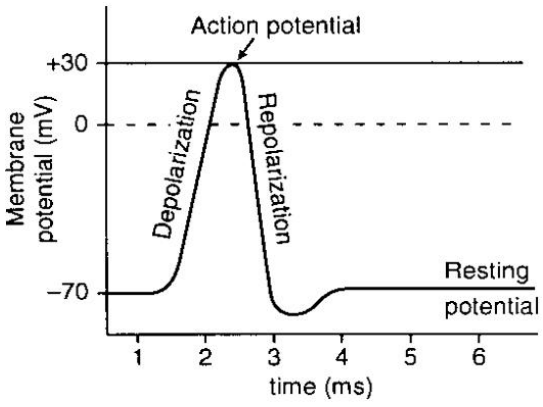
→ ***Hyperpolarization*** makes the membrane potential more negative (the cell interior becomes more negative)

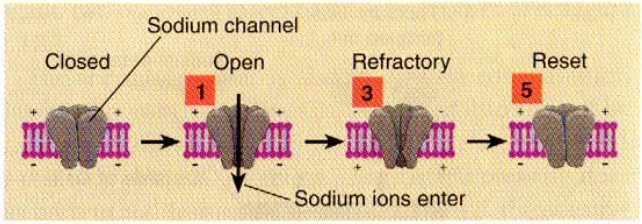
→ ***Inward current*** is the flow of positive charge into the cell. Inward current **depolarizes** the membrane potential.

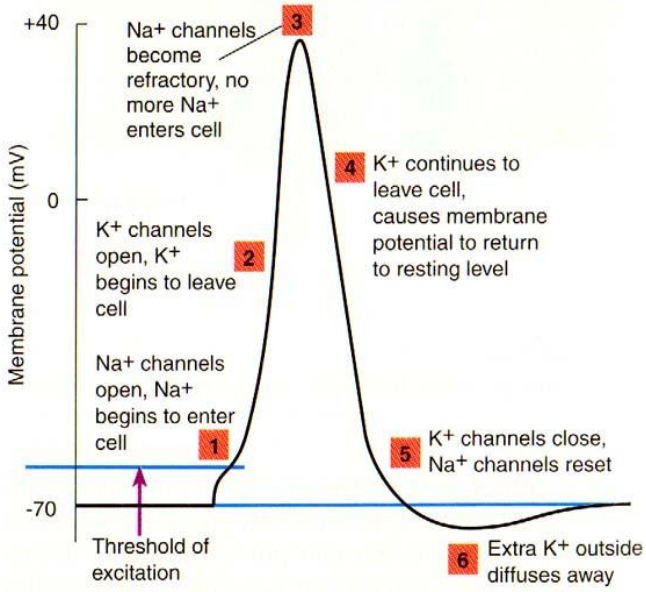
→ ***Outward current*** is the flow of positive charge out of the cell. Outward current **hyperpolarizes** the membrane potential.

→ ***Action potential*** is a property of excitable cells (i.e., nerve, muscle) that consists of a rapid depolarization, or upstroke, followed by repolarization of the membrane potential. Action potentials have **stereotypical size and shape**, are **propagating**, and are *all-or-none*.

→ ***Threshold*** is the membrane potential at which the action potential is inevitable. At threshold potential, net inward current becomes larger than net outward current. The resulting depolarization becomes self-sustained and gives rise to the upstroke of the action potential. If the net inward current is less than outward current, no action potential will occur (i.e., all-or-none response).



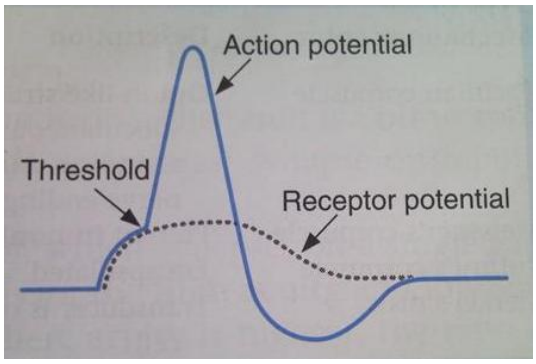



## 17. Receptor potential

The change in membrane potential produced by the stimulus is the **receptor potential**, or **generator potential**.

→ If the receptor potential is depolarizing, it brings the membrane potential closer to threshold. If the receptor potential is large enough, the membrane potential will exceed threshold and an action potential will fire in the sensory neuron.

→ Receptor potentials are **graded in size** depending on the size of the stimulus.




Receptor (generator) potential and how it may led to an action potential.

## 19. Up- and down regulation of receptors

- Hormones determine the sensitivity of the target tissue by **regulating the number of or sensitivity of receptors**.

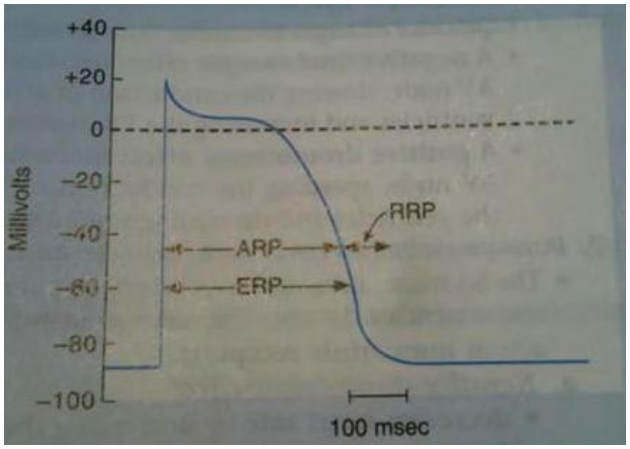
**1.** ***Down-regulation of receptor***
- A hormone **decreases the number or affinity of receptors** for itself or for another hormone.
- For example, in the uterus, *progesterone down-regulates its own receptor and the receptor for estrogen*.

**2.** ***Up-regulation of receptors***
- A hormone **increases the number or affinity of receptors** for itself or for another hormone.
- For example, in the ovary, *estrogen up-regulates its own receptor and the receptor of LH*.

## 20. Excitability and refrectoriness

Excitability (of cardiac cells)

– is the ability of cardiac cells to initiate action potentials in response to inward, depolarizing current.
– reflects the recovery of channels that carry the inward currents for the upstroke of the action potential.
– changes over the course of the action potential. These changes in excitability are described by **refractory periods** (se figure).




**1.** ***Absolute refractory period (ARP)***
- begins with the upstroke of the action potential and ends after the plateau.
- reflects the time during which **no action potential can be initiated**, regardless of how much inward current is supplied.

**2.** ***Effective refractory period (ERP)***
- is slightly longer than the ARP.
- is the period during which a **conducted action potential cannot be elicited**.

**3.** ***Relative refractory period (RRP)***
- is the period immediately after the ARP when repolarization is almost complete.
- is the period during which an **action potential can be elicited, but more than usual inward current is required**.

## 21. Excitation-contraction coupling

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

Steps in excitation-contraction coupling in skeletal muscle:

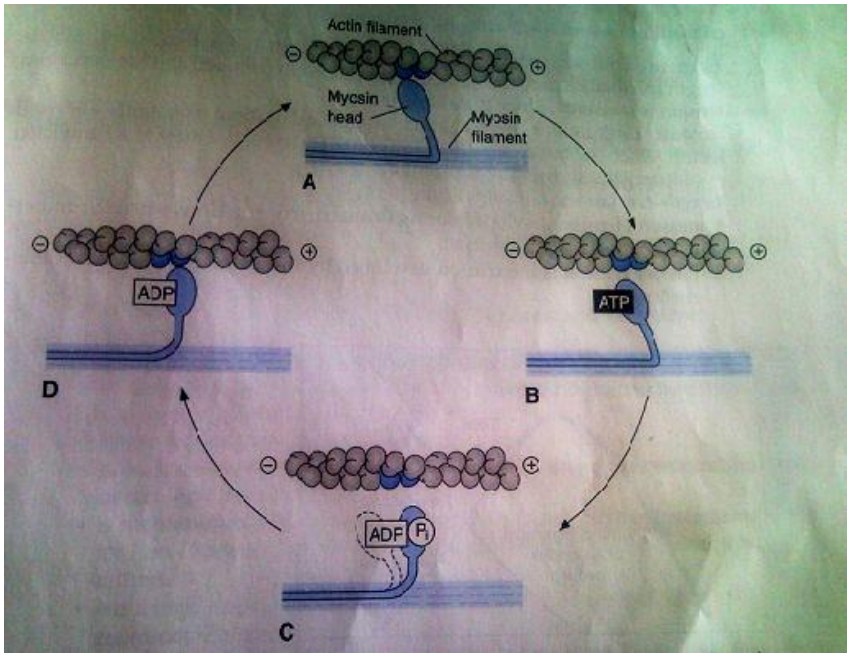
**1.** ***Action potentials*** in the muscle cell membrane initiate depolarization of the T tubules.

**2.** ***Depolarization of the T tubules*** causes a conformational change in its *dihydropyridine receptor*, which opens **$Ca^{2+}$ release channels** (ryanodine receptors) in the nearby **SR**, causing release of $Ca^{2+}$ from the SR into the intracellular fluid.

**3.** ***Intracellular [Ca2+] increases.***

**4.** ***$Ca^{2+}$ 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 begins**:

- **a.** At first, **no ATP is bound** to myosin **(A)**, and myosin is tightly attached to actin. In rapidly contracting muscle, this stage is brief. In the absence of ATP, this state is permanent (i.e., **rigor**).
- **b. ATP then binds to myosin (B),** producing a conformational change in the myosin that causes myosin to be released from actin.
- **c. Myosin is displaced toward the plus end of actin.** There is hydrolysis of ATP to ADP and inorganic phosphate ($P_i$). ADP remains attached to myosin **(C)**.
- **d.** Myosin attaches to a new site on actin, which constitutes the **power (force generating) stroke (D)**. ADP is then released, returning myosin to its rigor state.
- **e.** The cycle repeats as long as $Ca^{2+}$ is bound to troponin C. Each cross-bridge cycle "walks" myosin further along the actin filament.

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***! Steps in excitation-contraction coupling in smooth muscle*** → *Costanzo 4th ed. page 22*

***! Steps in excitation-contraction coupling in cardiac muscle*** → *Costanzo 4th ed. page 79*

## 23. Electrical and mechanical behavior of skeletal muscle

Steps in excitation-contraction coupling in skeletal muscle:

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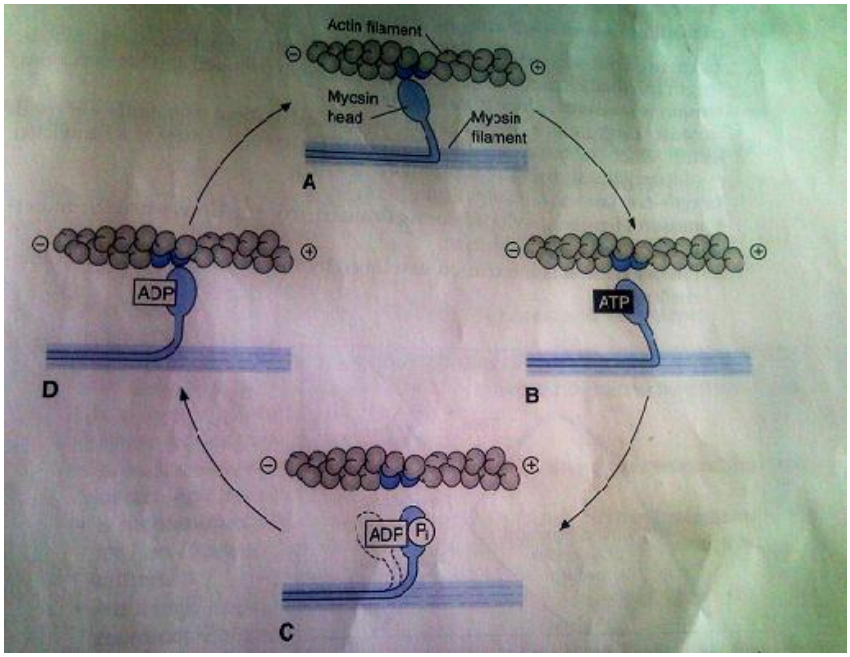


# 24. Electrical and mechanical behavior of smooth muscle

### *Smooth muscle - Contraction*

- source of $Ca^{2+}$: ECF (VOC, ROC), SR
- there is no troponine C, but two other regulatory proteins binding calcium – calmodulin + caldesmon
- calcium-calmodulin complex ($Ca^{2+}$-CM) activates MLCK (myosin light chain kinase)
- activated MLCK catalyzes the phosphorylation of myosin
- phosphorylated myosin is capable to make complex with actin ⇒ **contraction**

### *Smooth muscle - Relaxation*

Two relaxing processes occur:

1. Removing intracellular $Ca^{2+}$ from ICF (like in cardiac m.)
2. MLC-phosphatase catalyzes the hydrolysis of phosphorylated myosin:

$$MLC\text{-}P + H_2O \rightarrow P_i + MLC$$

MLC **does not** bind to actin ⇒ relaxation

### The influence of cAMP on smooth muscles

- cAMP activates protein kinase A (PK-A)
- PK-A phosphorylates MLC-kinase:

$$MLCK \rightarrow MLCK\text{-}P$$

- MLCK-P is inactive, does not phosphorylates MLC ⇒ no interaction between actin and myosin ⇒ **relaxation**

Smooth muscle cells are characterized by the instability of its membrane potential and the fact that it shows continuous, irregular contractions that are independent on nerve supply => ***Tonus***

To maintain organ dimensions against force, cells are fastened to one another by adherent junctions. As a consequence, cells are mechanically coupled to one another such that contraction of one cell invokes some degree of contraction in an adjoining cell.

Smooth muscle may contract spontaneously (via ionic channel dynamics) or as in the gut special pacemakers cells ***interstitial cells of Cajal*** produce rhythmic contractions

Specialized smooth muscle cells within the afferent arteriole of the juxtaglomerular apparatus of kidney produces renin which activates the angiotensin II system.

# 25. Electrical and mechanical behavior of cardiac muscle

## *Cardiac muscle – contraction*

- In sarcoplasm, $Ca^{2+}$ ions bind to:

⇨ troponin C ⇒ **contraction**

⇨ calmodulin ⇒ autoregul. - **relaxation**

## Cardiac muscle: Three sources of calcium

- Extracellular $Ca^{2+}$ (~ 10 %) enters by voltage operated channels (VOC)
- This influx of calcium triggers the release of calcium ions from SR and mitochondria (~ 90 %)

CICR = calcium-induced calcium release

## *Cardiac muscle - relaxation*

- $Ca^{2+}$ ions are liberated from troponin C and removed from sarcoplasm

1. $Ca^{2+}$-ATPase in SR
2. $Ca^{2+}$-ATPase in sarcolemma
3. $Na^{+}/Ca^{2+}$ antiport in sarcolemma
4. $Ca^{2+}$ re-entry to mitochondria

## *Excitation – contraction coupling*

- Contraction of the heart is called **systole** whilst relaxation of the heart is called **diastole.**
- As the function of the heart is that of a pump, both actions are important - a pump has to fill up with fluid before it can pump it out. The filling process occurs during diastole.
- One systole and its following diastole are called **one cardiac cycle**.
- In the normal heart, beating at a rate of 75 beats/min, the duration of ventricular systole is around 0.3 sec while diastole is around 0.5 sec (total length of cycle 0.8 sec)

**Mechanism**

The key role = $Ca^{2+}$ (T-tubules & sarcoplasmic reticulum)

During the action potential of cardiac muscle the **plateau phase** is the result of slow sodium/calcium channels that remain open for several hundred milliseconds.

$Ca^{2+}$ ⇨ diffuses to the cytosol, it catalyses sliding of actin and myosin (similar to the mechanism in skeletal muscle):

- $Ca^{2+}$ binds to troponin and removes it from the actin binding site
- Exposed actin binding site is available for attachment of myosin heads to produce actin myosin bridges.
- Myosin heads detach and attach to the next binding site, causing both filaments to slide against each other causing contraction.

### Autoregualtion in cardiac muscle

- intracellular calcium is in the complex with protein calmodulin: CM-$4Ca^{2+}$
- $Ca^{2+}$-CM stimulates **all** $Ca^{2+}$-pumps (some by phosphorylation) which decrease the $Ca^{2+}$ concentration in sarcoplasm
- **the increase of intracellular [$Ca^{2+}$] triggers contraction but, at the same time, stimulates relaxation processes**

## 26. Isometric and isotonic contraction. Length-tension relation

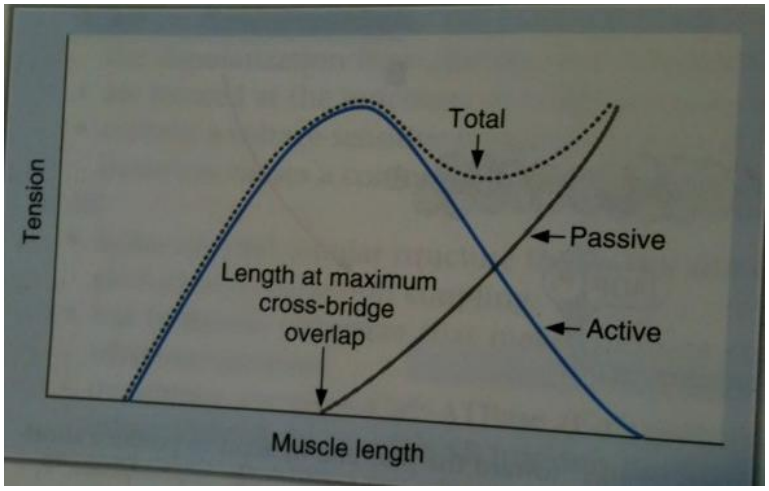
**Isometric contractions** => are measured when **length is held constant**. Muscle length (**preload**) is fixed, the muscle is stimulated to contract, and the developed tension is measured. There is ***no*** **shortening**.

**Isotonic contractions** => are measured when **load is held constant**. The load against which the muscle contracts (**afterload**) is fixed, the muscle is stimulated to contract, and shortening is measured.

Length-tension relationship

- measures tension developed during isometric contractions when the muscle is set to fixed lengths (preload).

- **Passive tension** is the tension developed by stretching the muscle to different lengths.
- **Total tension** is the tension developed when the muscle is stimulated to contract at different lengths.
- **Active tension** is the difference between total tension and passive tension.
  - Active tension represents the active force developed from contraction of the muscle. It can be explained by the cross-bridge cycle model.
  - **Active tension is proportional to the number of cross-bridges formed**. Tension will be maximum when there is overlap of thick and thin filaments. When the muscle is stretched to greater lengths, the number of cross-bridges is reduced because there is less overlap. When muscle length is decreased, the thin filaments collide and tension is reduced.

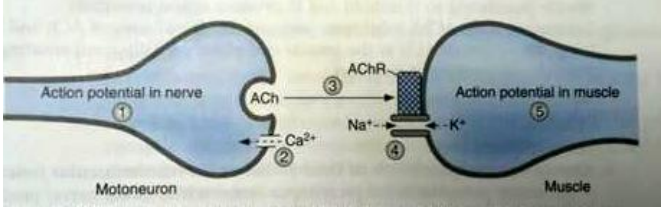



Length-tension relationship in skeletal muscle

# 27. Neuromuscular junction

– is the synapse between axons of motoneurons and skeletal muscle.
– The neurotransmitter released from the presynaptic terminal is **Ach**, and the postsynaptic membrane contains a **nicotinic receptor**.

1. ***Synthesis and storage of Ach in the presynaptic terminal***
   - **Choline acetyltransferase** catalyzes the formation of Ach from acetyl coenzyme A (CoA) and choline in the presynaptic terminal.
   - Ach is stored in the **synaptic vesicles** with ATP and proteoglycan for later release.
2. ***Depolarization of the presynaptic terminal and $Ca^{2+}$ uptake***
   - Action potentials are conducted down the motoneurons. Depolarization of the presynaptic terminal opens **$Ca^{2+}$ channels**.
   - When $Ca^{2+}$ permeability increases, $Ca^{2+}$ rushes into the presynaptic terminal down its electrochemical gradient.
3. ***$Ca^{2+}$ uptake causes release of Ach into the synaptic cleft***
   - The synaptic vesicles fuse with the plasma membrane and empty their contents into the cleft by **exocytosis**.
4. ***Diffusion of Ach to the postsynaptic membrane (muscle end plate) and binding of Ach to nicotinic receptors***
   - The nicotinic ACh receptor is also a **$Na^+$ and $K^+$ ion channel**.
   - Binding of Ach to α subunits of the receptor causes a conformational change that opens the central core of the channel and increases its conductance to $Na^+$ and $K^+$. These are examples of **ligand-gated channels**.
5. ***End plate potential (EEP) in the postsynaptic membrane***
   - Because the channels opened by ACh conduct both $Na^+$ and K+ ions, the postsynaptic membrane potential is depolarized to a value halfway between the $Na^+$ and $K^+$ equilibrium potential (approx. 0 mV).
   - The contents of one synaptic vesicle produce a **miniature end plate potential** (MEPP), the smallest possible EPP.
   - MEPPs summate to produce a full-fledged EPP. **The EEP is not an action potential**, but simply a depolarization of the specialized muscle end plate.
6. ***Depolarization of adjacent muscle membrane to threshold***
   - Once the end plate region is depolarized, local currents cause depolarization and action potentials in the adjacent muscle tissue. Action potentials in the muscle are followed by contraction.
7. ***Degradation of ACh***
   - The EPP is transient because ACh is degraded to acetyl CoA and choline by **acetylcholinesterase** (AChE).
   - One-half of the choline is taken back into the presynaptic ending by $Na^+$-choline cotransport and used to synthesize new ACh.
   - **AChE inhibitors (neostigmine)** block the degradation of ACh, prolong its action at the muscle end plate, and increase the size of the EPP.
   - **Hemicholinium** blocks choline reuptake and depletes the presynaptic endings of ACh stores.



# 28. Temporal and space summation (summation and recruitment) in skeletal muscle

See PRACTICALS *page 75 + resp. protocol*

# 29. Energy production and conservation

### 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.

### *"Free Energy"*

The amount of energy liberated by complete oxidation of a 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.

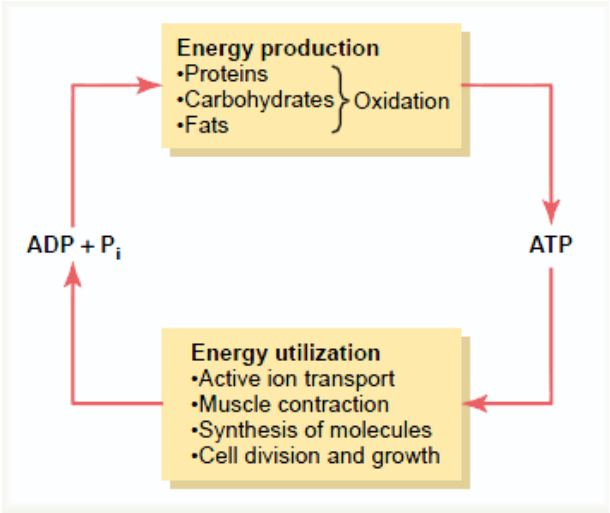
### Role of Adenosine Triphosphate in Metabolism

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).



# 30. 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 Calories (1 Calorie equals 1 kilocalorie), 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 Calories.

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 | **Calories** |
|---|---|
| Carbonhydrate | 4 |
| Fat | 9 |
| Protein | 4 |

**Protein, Fat, and Carbohydrate Content of Different Foods**

| Food | % Protein | % Fat | % Carbohydrate | Fuel Value per 100 Grams (Calories) |
|---|---|---|---|---|
| Apples | 0.3 | 0.4 | 14.9 | 64 |
| Asparagus | 2.2 | 0.2 | 3.9 | 26 |
| Bacon, fat | 6.2 | 76.0 | 0.7 | 712 |
| broiled | 25.0 | 55.0 | 1.0 | 599 |
| Beef (average) | 17.5 | 22.0 | 1.0 | 268 |
| Beets, fresh | 1.6 | 0.1 | 9.6 | 46 |
| Bread, white | 9.0 | 3.6 | 49.8 | 268 |
| Butter | 0.6 | 81.0 | 0.4 | 733 |
| Cabbage | 1.4 | 0.2 | 5.3 | 29 |
| Carrots | 1.2 | 0.3 | 9.3 | 45 |
| Cashew nuts | 19.6 | 47.2 | 26.4 | 609 |
| Cheese, cheddar, American | 23.9 | 32.3 | 1.7 | 393 |
| Chicken, total edible | 21.6 | 2.7 | 1.0 | 111 |
| Chocolate | 5.5 | 52.9 | 18.0 | 570 |
| Corn (maize) | 10.0 | 4.3 | 73.4 | 372 |
| Haddock | 17.2 | 0.3 | 0.5 | 72 |
| Lamb, leg (average) | 18.0 | 17.5 | 1.0 | 230 |
| Milk, fresh whole | 3.5 | 3.9 | 4.9 | 69 |
| Molasses | 0.0 | 0.0 | 60.0 | 240 |
| Oatmeal, dry, uncooked | 14.2 | 7.4 | 68.2 | 396 |
| Oranges | 0.9 | 0.2 | 11.2 | 50 |
| Peanuts | 26.9 | 44.2 | 23.6 | 600 |
| Peas, fresh | 6.7 | 0.4 | 17.7 | 101 |
| Pork, ham | 15.2 | 31.0 | 1.0 | 340 |
| Potatoes | 2.0 | 0.1 | 19.1 | 85 |
| Spinach | 2.3 | 0.3 | 3.2 | 25 |
| Strawberries | 0.8 | 0.6 | 8.1 | 41 |
| Tomatoes | 1.0 | 0.3 | 4.0 | 23 |
| Tuna, canned | 24.2 | 10.8 | 0.5 | 194 |
| Walnuts, English | 15.0 | 64.4 | 15.6 | 702 |

## Direct Calorimetry

Direct Calorimetry Measures Heat Liberated from the Body.

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.

## 31. Energy balance. Indirect calorimetry.

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. 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 Calories of energy are released; when metabolized with starches, 5.06 Calories are released; with fat, 4.70 Calories; and with protein, 4.60 Calories.

For the average diet, the *quantity of energy liberated per liter of oxygen used in the body averages about 4.825 Calories.* 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.

## 32. Physiological role of calcium

It plays an important role in signal transduction pathways, where it acts as a *second messenger*, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. 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, 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: is related to the intracellular $Ca^{2+}$ concentration. **The magnitude of the tension that develops is proportional to the intracellular [$Ca^{2+}$]**.

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

# 33. Vitamins – overview

## 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.

**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 |

## 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

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 $B_1$)

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

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 $B_{12}$)

Vitamin $B_{12}$ 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: (1) promotion of growth and (2) promotion of red blood cell formation and maturation. It is only found in animal products.

## Folic Acid (Vitamin $B_{11}$)

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 $B_6$)

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

Pantothenic acid mainly is incorporated in the body into *coenzyme A* (CoA), which has many metabolic roles in the cells. Two of these are (1) conversion of decarboxylated pyruvic acid into acetyl-CoA before its entry into the citric acid cycle, and (2) 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 Deficiency Weakens Collagen Fibers Throughout the Body.**
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.

# 34. 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 deficiency** causes beriberi
- **niacin deficiency** causes pellagra
- **vitamin $B_{12}$ deficiency** leads to megaloblastic anemia
- **vitamin C deficiency** leads to scurvy
- **vitamin D deficiency** causes rickets
- **vitamin K deficiency** causes impaired coagulation

## 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.

# 35. Basal Metabolism

Basal metabolic rate

- the energy necessary to maintain essential processes in basal conditions
- the BMR of men (70 kg) is 6300 – 7350 kJ/day
- BMR is about 10% lower in women

- Factors affecting BMR:
  - Surface area
    - BMR is standardised to the surface of the body and expressed as **kJ/m2/h**
    - Increase in weight and height will lead to increase in BMR
    - $s = W^{0.425} \cdot H^{0.725} \cdot 0.007184$ where s = surface area in $m^2$
    - the formula is derived from nomograms
    - and is used to determine the surface area of the body
    - standard value for BMR → 167 kJ/m2/h · surface in $m^2$ (men)
      → 150 kJ/m2/h · surface in $m^2$ (women)
    - using ***Harris-Benedict formula***
      - ***BMR man = 66.5 + (13.8 · b.w.) + 5 · hight (cm) - 6.8 · age***
      - ***BMR woman = 66.5 + (9.5 · b.w.) + 1.8 · hight (cm) - 4.7 · age***
  - **Sex** – man = 167 kJ/m2/h (40 kcal/ m2/h)
    women = 150 kJ/ m2/h (36 kcal/m2/h)
  - **Age** – newborn → low BMR which increases during childhood and puberty
    Old age → decreasing BMR
  - **Hormones**
    - Catecholamines
    - Thyroid hormones
    - Insulin
    - Growth hormone
  - **Body temperature**
    - BMR increases by 10% every increase in 1°C
  - **Climate** – higher temperatures → lower BMR
    lower temperatures → higher BMR
  - **Nutritional status** – fasting and undernutrition → decrease in BMR

## 36. Principle 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
  - Insufficient caloric intake → fat and protein stores of the body are catabolized
  - 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 Calorie, 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.

# 37. 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

Is the 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.

Symptoms: sweating, double vision, headache, heart palpation, tremor, fatigue and more.

## 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.

Causes:
> *Diabetes mellitus* - usually caused by low *insulin* levels.
> *Drugs* – i.e. beta blockers, epinephrine, thiazide diuretics, corticosteroids, niacin.
> *Critical illness* - patients suffering an acute stress such as *stroke* or *myocardial infarction*.
> *Physiological stress* - When the body is stressed, endogenous *catecholamines* are released that - amongst other things - serve to raise the blood glucose levels.

Symptoms: polyphagia, polydipsia, *polyuria*, *blurred vision, fatigue* (sleepiness), *weight loss, dry mouth, dry or itchy skin, cardiac arrhythmia*

# 38. Acid-base balance

**Acid-base homeostasis** is the part of human homeostasis concerning the proper balance between acids and bases, in other words, the pH.

## 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).

**1.** ***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 $H_2PO_4^-$/$HPO_4^{2-}$ buffer pair is 6.8.
– Phosphate is most important as **urinary buffer**; excretion of $H^+$ as $H_2PO_4^-$ is called **titratable acid**.

**2.** ***Intracellular buffers***

**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**.

**3.** ***Using the Henderson-Hasselbalch equation to calculate pH***

$$\mathrm{pH} = \mathrm{pK}_a + \log \frac{[\mathrm{A}^-]}{[\mathrm{HA}]}$$

*where:*
pH = - $\log_{10}$ $[H^+]$ (pH units)
pK = - $\log_{10}$ equilibrium constant (pH units)
$[A^-]$ = base form of buffer (mM)
[HA] = acid form of buffer (mM)

- $A^-$, the base form of the buffer, is the $H^+$ acceptor.
- HA, the acid form of the buffer, is the $H^+$ donor.
- When the concentrations of $A^-$ and HA are equal, the **pH of the solution equals the pK of the buffer**, as calculate by the Henderson-Hasselbalch equation.

## Renal acid-base

**1.** ***Reabsorption of filtered $HCO_3^-$***

- occurs primarily in the **proximal tubule**.

**a.** ***Key features of reabsorption of filtered $HCO_3^-$***

**(1)** $H^+$ and $HCO_3^-$ are produced in the proximal tubule cells from $CO_2$ and $H_2O$. $CO_2$ and $H_2O$ combine to form $H_2CO_3$, catalyzed by **intracellular carbonic anhydrase**; $H_2CO_3$ dissociates into $H^+$ and $HCO_3^-$. H+ is secreted into the lumen via the $Na^+$-$H^+$ exchange mechanism in the luminal membrane. The $HCO_3^-$ is reabsorbed.

**(2)** In the lumen, the secreted H+ concentration combines with filtered $HCO_3^-$ to form $H_2CO$, which dissociates into $CO_2$ and $H_20$ catalyzed by **brush border carbonic anhydrase**. $CO_2$ and $H_2O$ diffuse into cell to start the cycle again.

**(3)** The process results in net reabsorption of filtered $HCO_3^-$. However, it does not result in net secretion of $H^+$.

**b. *Regulation of reabsorption of filtered $HCO_3^-$***

**(1)** *Filtered load*

– Increases in the filtered load of $HCO_3^-$ result in increased rates of $HCO_3^-$. However, if the plasma $HCO_3^-$ conc. becomes very high (e.g., metabolic alkalosis), the filtered load will exceed the reabsorptive capacity, and $HCO_3^-$ will be excreted in the urine.

**(2)** *$PCO_2$*

– **Increases in *$PCO_2$*** result in increased rates of $HCO_3^-$ reabsorption because the supply of intracellular $H^+$ for secretion is increased. This mechanism is the basis of the **renal compensation for respiratory acidosis.**

– **Decrease in *$PCO_2$*** result in decreased rates of $HCO_3^-$ reabsorption because the supply of intracellular $H^+$ for secretion is decreased. This mechanism is the basis of the **renal compensation for respiratory alkalosis.**

**(3)** *ECF volume*

– **ECF volume expansion** results in decreased $HCO_3^-$ reabsorption.

– **ECF volume contraction results in increased** $HCO_3^-$ reabsorption (contraction alkalosis).

**(4)** Angiotensin II

– stimulates $Na^+$-$H^+$ exchange and thus increases $HCO_3^-$ reabsorption, contributing to the **contraction alkalosis** that occurs secondary to ECF volume contraction.

**2. *Excretion of fixed $H^+$***

– Fixed $H^+$ produced from the catabolism of protein and phospholipid is excreted by two mechanism, *titratable acid ($H_2PO_4^-$)* and *$NH_4^+$*.

**I. Excretion of $H^+$ as titratable acid ($H_2PO_4^-$)**

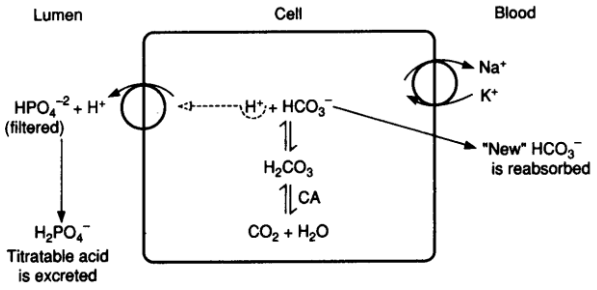
– The amount of $H^+$ excreted as titratable acid depends on the **amount of urinary buffer** present (usually $HPO_4^{-2}$) and the **pK of the buffer.**

(1) $H^+$ and $HCO_3^-$ are produced in the cell from $CO_2$ and $H_2O$. The $H^+$ is secreted into the lumen by an $H^+$-ATPase, and the $HCO_3^-$ is reabsorbed into the blood ("new" $HCO_3^-$). In the urine, the secreted $H^+$ combines with filtered $HPO_4^{-2}$ to form $H_2PO_4^-$, which is excreted as **titratable acid.**

(2) This process results in **net secretion of $H^+$** and **net reabsorption of newly synthesized $HCO_3^-$.**

(3) As a result of $H^+$ secretion, the pH of urine becomes progressively lower. **The minimum urinary pH is 4.4.**

(4) The amount of $H^+$ excreted as titratable acid is determined by the **amount of urinary buffer** and the **pK of the buffer.**




**II. Excretion of $H^+$ as $NH_4^+$**

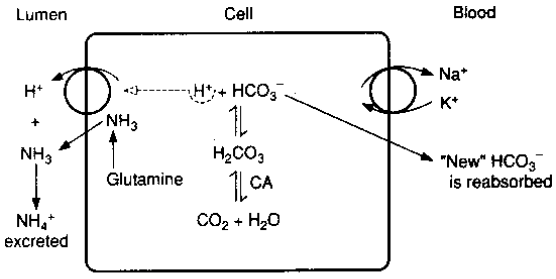
– The amount of $H^+$ excreted as $NH_4^+$ depends on both the **amount of $NH_3$ synthesized** by renal cells and the **urine pH.**

(1) $NH_3$ is produced in renal cells from glutamine. It diffuses down its concentration gradient from the cells into the lumen.

(2) $H^+$ and $HCO_3^-$ are produced in the cells from $CO_2$ and $H_2O$. The $H^+$ is secreted into the lumen via an $H^+$-ATPase and combines with $NH_3$ to form $NH_4^+$, which is excreted **(diffusion trapping).** The $HCO_3^-$ is reabsorbed into the blood ("new" $HCO_3^-$).

(3) The lower the pH of the tubular fluid, the greater the excretion of $H^+$ as $NH_4^+$; at low urine pH, there is more $NH_4^+$ relative to $NH_3$ in the urine, thus increasing the gradient for $NH_3$ diffusion.

(4) In acidosis, an **adaptive increase in $NH_3$ synthesis** occurs and aids in the excretion of excess $H^+$.




Mechanism for excretion of $H^+$ as $NH_4^+$. *CA* = carbonic anhydrase.

Summary of Acid–Base Disorders

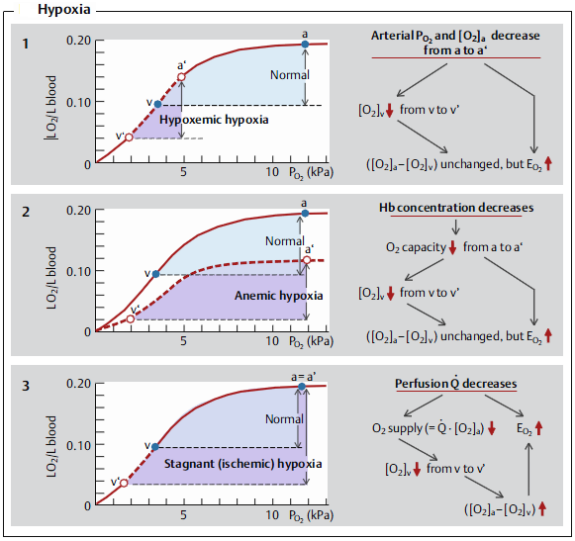
| Disorder | $CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$ | | | Respiratory Compensation | Renal Compensation |
|---|---|---|---|---|---|
| Metabolic acidosis | ↓ (respiratory compensation) | ↑ | ↓ | Hyperventilation | ↑ $H^+$ excretion<br>↑ "new" $HCO_3^-$ reabsorption |
| Metabolic alkalosis | ↑ (respiratory compensation) | ↓ | ↑ | Hypoventilation | ↑ $HCO_3^-$ excretion |
| Respiratory acidosis | ↑ | ↑ | ↑ | None | ↑ $H^+$ excretion<br>↑ $HCO_3^-$ reabsorption |
| Respiratory alkalosis | ↓ | ↓ | ↓ | None | ↓ $H^+$ excretion<br>↓ $HCO_3^-$ reabsorption |

*Heavy arrows* indicate *primary* disturbance.

# 39. Hypoxia and ischemia

## *Hypoxia.*

An abnormally reduced $O_2$ supply to tissue is classified as follows:
**1.** *Hypoxic hypoxia*: an insufficient $O_2$ supply reaches the blood due, for example, to decreased atmospheric $P_{O_2}$ at high altitudes, reduced alveolar ventilation, or impaired alveolar gas exchange.
**2.** *Anemic hypoxia* : reduced $O_2$-carrying capacity of blood, e.g., due to decreased total Hb in iron deficiency anemia.
**3.** *Stagnant* or *ischemic hypoxia*: insufficient $O_2$ reaches the tissue due to reduced blood flow. The cause can be systemic (e.g., heart failure) or local (e.g., obstructed artery). The reduction of blood flow must be compensated for by a rise in ($[O_2]_a - [O_2]_v$) to maintain an adequate $O_2$ delivery. This is not the case in hypoxic and anemic hypoxia. The influx and efflux of substrates and metabolites is also impaired in stagnant hypoxia. Anaerobic glycolysis is therefore of little help.
**4.** Hypoxia can also occur when the *diffusion distance* is increased due to tissue thickening without a corresponding increase in the number of blood capillaries. This results in an insufficient blood supply to cells lying outside the $O_2$ supply radius (R) of the Krogh cylinde.
**5.** *Histotoxic* or *cytotoxic hypoxia* occurs due to impaired utilization of $O_2$ by the tissues despite a sufficient supply of $O_2$ in the mitochondria, as observed in *cyanide poisoning*. **Cyanide (HCN)** blocks oxidative cellular metabolism by inhibiting *cytochromoxidase*.




## *Ischemia*

Is a restriction in blood supply, generally due to factors in the blood vessels, with resultant damage or dysfunction of tissue.

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.

# 40. Heat production and heat loss

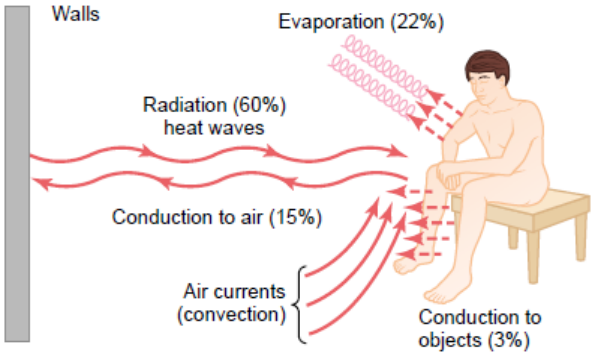
## Heat production

The amount of heat produced is determined by *energy metabolism*. At rest, approximately 56% of total heat production occurs in the internal organs and about 18% in the muscles and skin.
During *physical exercise*, heat production increases several-fold and the percentage of heat produced by muscular work can rise to as much as 90%. To keep warm, the body may have to generate additional voluntary (limb movement) and involuntary (shivering) muscle contractions.
Newborns also have tissue known as **brown fat**, which enables them to produce additional heat without shivering. Cold stimulates a reflex pathway resulting in norepinephrine release ($\beta_3$-adrenergic receptors) in fatty tissues, which in turn stimulates (1) lipolysis and (2) the expression of *lipoprotein lipase (LPL)* and *thermogenin (UCP1)*. LPL increases the supply of free fatty acids. Thermogenin localized in the inner mitochondrial membrane is an uncoupling protein that functions as an H+ uniporter. It short-circuits the H+ gradient across the inner mitochondrial membrane thereby uncoupling the (heat-producing) respiratory chain of ATP production.

Heat produced in the body is absorbed by the bloodstream and conveyed to the body surface. In order for this **internal flow of heat** to occur, the temperature of the body surface must be lower than that of the body interior. The *blood supply to the skin* is the chief determinant of heat transport to the skin.

## Heat loss

**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.

# 41. Hormone-receptor complex

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

- **Endocrine hormones**, i.e., those transported in the bloodstream, are produced in *endocrine glands* such as the hypothalamus, thyroid, parathyroid glands, adrenal medulla, pancreatic islets, ovaries and testes. They are also synthesized in diffusely scattered *endocrine cells* of the CNS, in C cells of the thyroid, and in the thymus, atria, kidneys, liver, gastrointestinal tract, etc.
- **Paracrine hormones**, i.e., those that affect nearby cells only (tissue hormones or *mediators*; see below) are secreted by cells widely distributed throughout the body.

## 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.

## Hormone receptors

The receptors (docking sites) for glycoprotein hormones, peptide hormones and catecholamines are transmembrane proteins that bind to their specific hormone on the outer cell surface.
Many of these hormones induce the release of intracellular **second messengers** that transmit the hormone signal inside the cell.

Some peptide hormones like **insulin**, **prolactin**, **atriopeptin** and numerous growth factors bind to cell surface receptors with cytosolic domains with *enzymatic activity*. Steroid hormones, on the other hand, enter the cells themselves. Once they bind to ***cytosolic receptor proteins***, steroid hormones (as well as calcitriol, T3 and T4) are transported to the cell nucleus, where they influence transcription (genomic action).

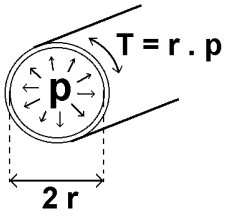
A target cell can have different receptors for different hormones (e.g., insulin and glucagon) or different receptors for a single hormone (e.g., $\alpha_1$ and $\beta_2$ adrenoceptors for epinephrine).

## 42. Physiological applications of law of Laplace

According to Laplace's law for cylindrical (or spherical) hollow bodies,

$$P_{tm} = T/r \text{ (or } P_{tm} = 2\,T/r\text{, resp.)}$$

Here, *T* is the *total mural tension*, regardless how thick the wall is.




*Laplace Law*

**Tension T in walls of some blood vessels:**

| vessel | r(m) | p(kPa) | T(N.m$^{-1}$) |
|---|---|---|---|
| aorta | 0.012 | 13 | 156 |
| artery | 0.005 | 12 | 60 |
| capillary | $6 \times 10^{-6}$ | 4 | 0.024 |
| vein | 0.005 | 2 | 10 |
| vena cava | 0.015 | 1.3 | 20 |

Application in medicine

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.

In this context, the pressure differential is a force pushing inwards on the surface of the alveolus. The *law of Laplace states that 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 small alveolus will be more likely to collapse, expelling its contents into the large alveolus.

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.

## 43. Invasive assessment of blood pressure

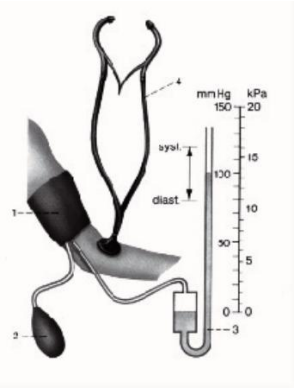
Arterial blood pressure (BP) is most accurately measured invasively through an arterial line. Invasive arterial pressure measurement with intravascular cannulae involves direct measurement of arterial pressure by placing a cannula needle in an artery (usually radial, femoral, dorsalis pedis or brachial).

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.

# 44. Non-invasive assessment of blood pressure




1. 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

2. 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.

3. 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 2-3mmHg 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 and an inflatable bladder 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.

The first step in this method is determining the proper unloaded diameter of the finger arteries, the point at which finger cuff pressure and intra-arterial pressure are equal and at which the transmural pressure across the finger arterial walls is zero. Then the arteries are clamped (kept at this unloaded diameter) by varying the pressure of the finger cuff inflatable bladder using the fast cuff pressure control system.

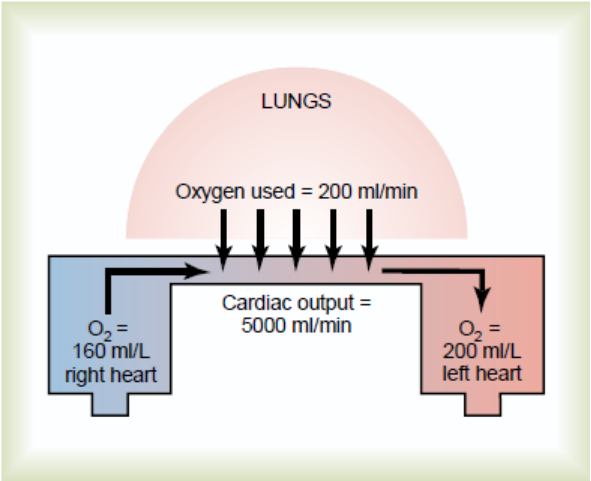
A servo-controller system usually defines a target value or setpoint and a measured value that is compared with this setpoint. In the servo-controller the setpoint is the signal of the plethysmograph (unloaded diameter of the arteries) that must be clamped. The measured value comes from the light detector. The amplified difference between the setpoint and measured value, "the error signal," is used to control a fast pneumatic proportional valve in the frontend unit. This proportional valve modulates the air pressure generated by the air compressor, thus causing changes in the finger cuff pressure in parallel with intra-arterial pressure in the finger so as to dynamically unload the arterial walls in the finger. The cuff pressure thus provides an indirect measure of intra-arterial pressure.

Physiocal is the automatic algorithm that calibrates the finger arterial size at which finger cuff air pressure equals finger arterial blood pressure.

## 45. Measurement of cardiac output

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:

$$\text{Cardiac output (L/min)} = \frac{\text{O}_2 \text{ absorbed per minute by the lungs (ml/min)}}{\text{Arteriovenous O}_2 \text{ difference (ml/L of blood)}}$$

In applying this Fick procedure for measuring cardiac output in the human being, *mixed 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 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, giving a curve.

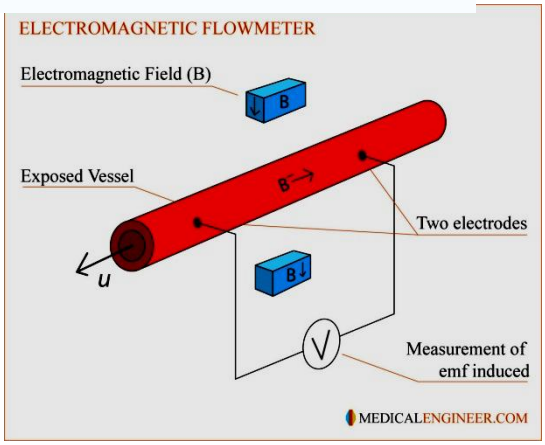
The cardiac output can be determined using the following formula:

$$\textit{Cardiac output} = \textit{ml of dye injected} \times 60 \Big/ \left[\begin{array}{l}\textit{Average concentration of dye}\\ \textit{in each ml of blood}\\ \textit{for the duration of the curve}\end{array}\right] \times \left[\begin{array}{l}\textit{Duration of}\\ \textit{the curve}\\ \textit{in seconds}\end{array}\right]$$

## 46. Measurement of blood flow

### Electromagnetic Flowmeter

A blood vessel is placed between the poles of a strong magnet, and electrodes are placed on the two sides 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.



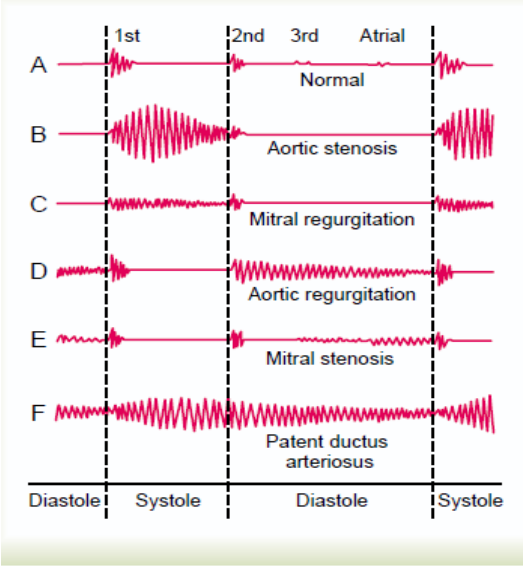

A special advantage of the electromagnetic flowmeter is that it can record changes in flow in less than 1/100 of a second, allowing accurate recording of pulsatile changes in flow as well as steady flow.

### Ultrasonic Doppler Flowmeter

A microscopic piezoelectric crystal is mounted at one end in the wall 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.

## 47. 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, or "Recording of the sounds made by the heart during a cardiac cycle." The sounds are thought to result from vibrations created by closure of the heart valves. There are at least two: the first when the atrioventricular valves close at the beginning of systole and the second when the aortic valve closes at the end of systole. It allows the detection of subaudible sounds and murmurs, and makes a permanent record of these events. In contrast, the ordinary stethoscope cannot detect such sounds or murmurs, and provides no record of their occurrence.




Phonocardiograms from normal and abnormal hearts.

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.

# 48. ECG leads

There are several ways in which the ECG can be connected to electrodes placed on the body. These are referred to as leads, and they fall into 2 categories:

a) **bipolar** – when the ECG is connected between 2 electrodes on the surface of the body
b) **unipolar** – when ECG is connected between one electrode and an indifferent point representing the body as whole

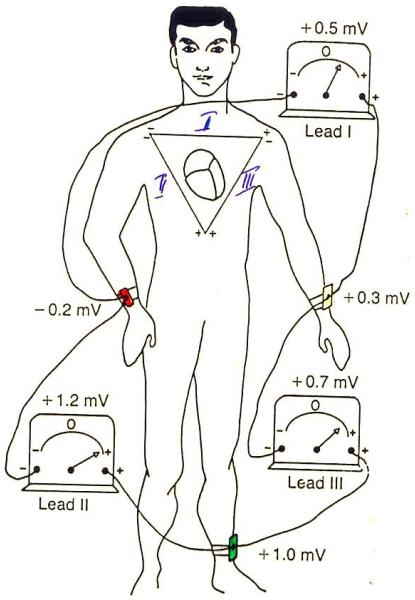
12 Leads used for routine purposes are:

**Standard limb leads – (BIPOLAR)**
These leads measure the difference in electric potential between 2 points. The leads are bipolar (1 –ve 1 +ve). Electrodes are placed on right arm (**red**), left arm (**yellow**), left leg (**green**) and a ground electrode on the right leg (**black**).

**Lead I** = Right arm (negative) – Left arm (positive)

**Lead II** = Right arm (negative) – Left leg (positive)

**Leads III** = Left arm (negative) – Left leg (positive)




*Note* – **Einthovens triangle** is used to represent the heart in the middle of a isosceles triangle with the 2 upper corners representing the shoulders and the bottom corner representing the symphysis pubis.

## Unipolar leads

Is based on recording potential difference between an exploring electrode and an indifferent electrode.

There are 4 types of unipolar leads:

**a)** Unipolar limb leads – VR, VL, VF. The indifferent electrode is Wilson electrode (5kΩ) *(NOT USED AS OFTEN. AUGMENTED IS USED)*

**b)** Augmented limb leads (goldberger) – **aVR** = +ve terminal on right arm
– **aVL** = +ve terminal on the left arm
– **aVF** = +ve terminal on the left leg

**c)** unipolar chest leads (precordial leads)

**d)** Esophageal electrode (extra)
This is used to study atrial activity. This electrode is inserted in a catheter and swallowed. Each esophageal electrode is identified by the letter E + number (cm from teeth to electrode)

**Exploring electrodes:**

**$V_1$** - Rt, 4th intercostal space

**$V_2$** - Lt, 4th intercostal space

**$V_3$** - Lt, midway between $V_2$ and $V_4$

**$V_4$** - Lt, 5th intercostal space, mid-clavicular line

**$V_5$** - Lt, 5th intercostal space, anterior axillary line

**$V_6$** - Lt, 5th intercostal space, mid-axillary line

### *Relationship between direction of the lead and amplitude of ECG*

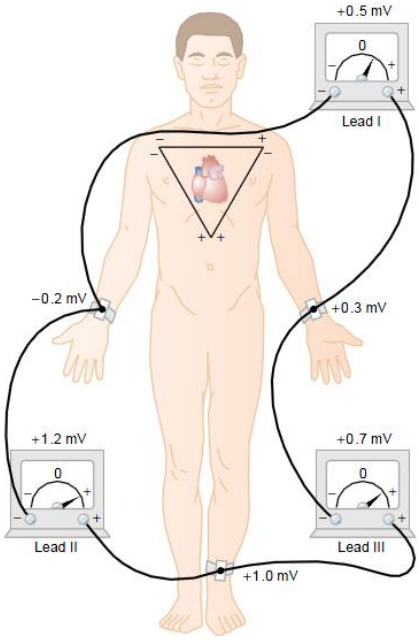
In the unipolar leads

- if the depolarization is travelling towards the explorating electrode ⇨ positive deflection
- if the depolarization is travelling outwards explorating electrode ⇨ negative deflection

In the bipolar leads

- in direction from the negative to the positive electrode ⇨ positive deflection
- in direction from the positive to the negative electrode ⇨ negative deflection
- If no potential at all is recorded in the ECG when the ventricular muscle is either completely polarized or completely depolarized.

# 49. ECG recording in different leads




## Electrocardiographic Leads Three Bipolar Limb Leads

The figure to the right demonstrates electrical connections between the patient's limbs and the electrocardiograph for recording electrocardiograms from the so-called *standard bipolar limb leads.* The term "bipolar" means that the electrocardiogram is recorded from *two* electrodes located on different sides of the heart, in this case, on the limbs.

**Lead I.** In recording limb lead I, the *negative terminal of the electrocardiograph is connected to the right arm* and the *positive terminal to the left arm.* Therefore, when the point where the right arm connects to the chest is electronegative with respect to the point where the left arm connects, the electrocardiograph records positively, that is, above the zero voltage line in the electrocardiogram. When the opposite is true, the electrocardiograph records below the line.

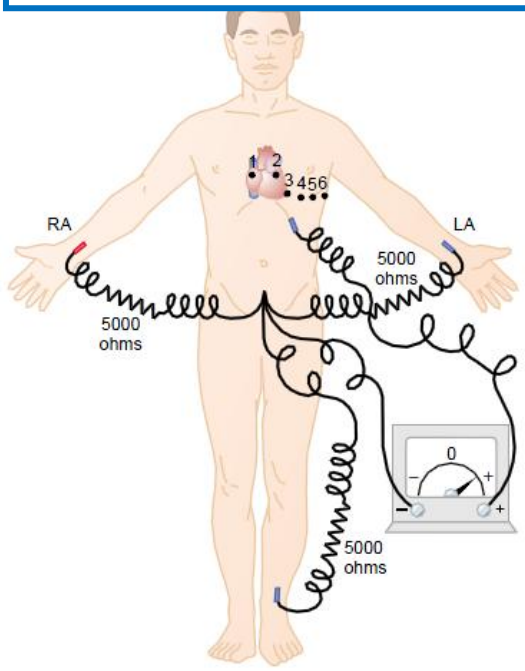
**Lead II.** To record limb lead II, the *negative terminal of the electrocardiograph is connected to the right arm* and the *positive terminal to the left leg.* Therefore, when the right arm is negative with respect to the left leg, the electrocardiograph records positively.

**Lead III.** To record limb lead III, the *negative terminal of the electrocardiograph is connected to the left arm* and the *positive terminal to the left leg.* This means that the electrocardiograph records positively when the left arm is negative with respect to the left leg.

**Einthoven's Law.** Einthoven's law states that if the electrical potentials of any two of the three bipolar limb electrocardiographic leads are known at any given instant, the third one can be determined mathematically by simply summing the first two (but note that the positive and negative signs of the different leads must be observed when making this summation).

## Chest Leads (Precordial Leads)

Often electrocardiograms are recorded with one electrode placed on the anterior surface of the chest directly over the heart at one of the points shown in the figure (right). This electrode is connected to the positive terminal of the electrocardiograph, and the negative electrode, called the *indifferent electrode,* is connected through equal electrical resistances to the right arm, left arm, and left leg all at the same time. Usually six standard chest leads are recorded, one at a time, from the anterior chest wall, the chest electrode being placed sequentially at the six points shown in the diagram. The different recordings are known as leads $V_1$, $V_2$, $V_3$, $V_4$, $V_5$, and $V_6$.




Because the heart surfaces are close to the chest wall, each chest lead records mainly the electrical potential of the cardiac musculature immediately beneath the electrode. Therefore, relatively minute abnormalities in the ventricles, particularly in the anterior ventricular wall, can cause marked changes in the electrocardiograms recorded from individual chest leads.

In leads $V_1$ and $V_2$, the QRS recordings of the normal heart are mainly negative because the chest electrode in these leads is nearer to the base of the heart than to the apex, and the base of the heart is the direction of electronegativity during most of the ventricular depolarization process. Conversely, the QRS complexes in leads $V_4$,$V_5$, and $V_6$ are mainly positive because the chest electrode in these leads is nearer the heart apex, which is the direction of electropositivity during most of depolarization.

**Augmented Unipolar Limb Leads**

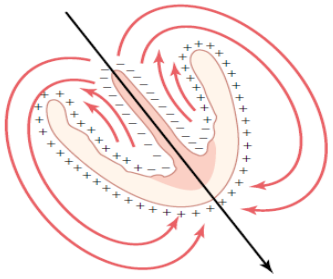
Another system of leads in wide use is the *augmented unipolar limb lead.* In this type of recording, two of the limbs are connected through electrical resistances to the negative terminal of the electrocardiograph, and the third limb is connected to the positive terminal.

When the positive terminal is on the right arm, the lead is known as the aVR lead; when on the left arm, the aVL lead; and when on the left leg, the aVF lead.

# 50. Estimation of electric axis of the heart (Guyton chap. 12)

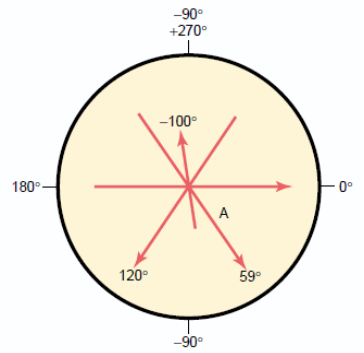
### Use of Vectors to Represent Electrical Potentials

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.*



Mean vector through the partially depolarized ventricles.

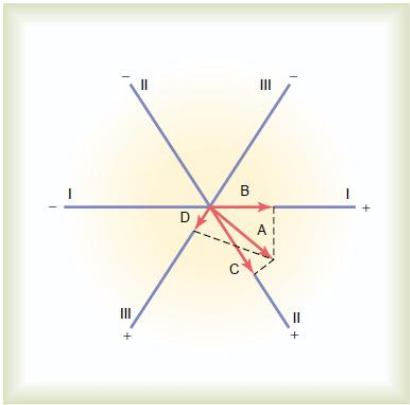
Electrical current flows between the depolarized areas inside the heart and the nondepolarized areas on the outside of the heart. Some current also flows inside the heart chambers directly from the depolarized areas toward the still polarized areas. Overall, considerably more current flows downward from 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.

### Vectocardigram

The so-called *vectorcardiogram* depicts these changes at different times during the cardiac cycle, as shown in Figure 12–10.




**Vectorial Analysis of Potentials in the Three Standard Bipolar Limb Leads**

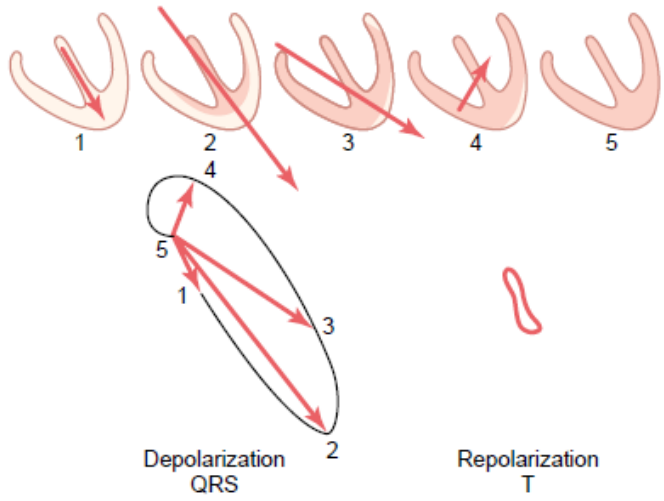



**Figure 12–10**

QRS and T vectorcardiograms.

# 51. 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.

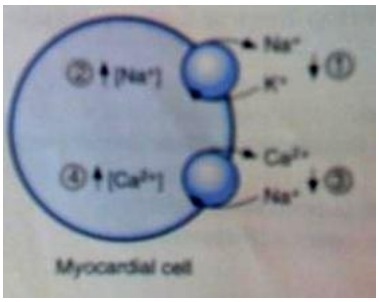
**1.** ***Factors that increase contractility (positive inotropism)***

**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.

**b. Sympathetic stimulation (cathecholamines) via $\beta_1$ 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 (figure).
– 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 [$Ca^{2+}$].

**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.




*Stepwise explanation how ouabain (digitalis9 causes an increase in intracellular [Ca2+] and myocardial contractility.*

## Ejection fraction

– is the fraction of the end-diastolic volume ejected in each stroke volume.
– is related to **contractility**.
– is normally 0.55, or **55%**.
– is expressed by the following equation:

*Ejection fraction = Stroke volume / End-diastolic volume*

## Cardiac failure ("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 **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 lead 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. When a larger arterior venous fistula is present, in *thyrotoxicosis*, and in thiamine deficiency, cardiac output may be elevated in absolute terms but still be inadequate to meet the needs of the tissues **(high-output failure).**

### 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 positively 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.

# 52. 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 guidwire 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.

### Indications for investigational use

This technique has several goals:

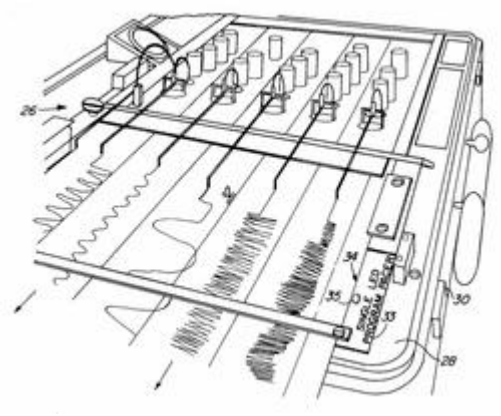
- confirm the presence of a suspected heart ailment
- quantify the severity of the disease and its effect on the heart
- seek out the cause of a symptom such as shortness of breath or signs of cardiac insufficiency
- make a patient assessment prior to heart surgery

**Investigative techniques used with cardiac catheterization**

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

# 53. Polygraphic methods



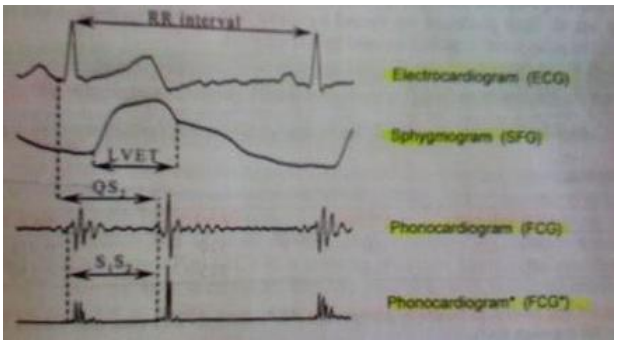
A **polygraph** (or "**lie detector"**) is an instrument that measures and records several physiological indices such as blood pressure, pulse, respiration, breathing rhythms/ratios, and skin conductivity while the subject is asked and answers a series of questions, in the belief that deceptive answers 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)
**$QS_2$**: ***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)
**$S_1S_2$**: duration of mechanical systole (time between 1st and 2nd heart sound on FCG or FCG* recording)

Calculated parameters:
**$S_2S_1$:** mechanical diastole duration **($S_2S_1$= RR interval - $S_1S_2$)**
**PEP: preejection period** – time from electrical activation of septum to opening of seminlunar valves **(PEP = $QS_2$ – LVET)**
**IVC: isovolumic contraction duration (IVC = $S_1S_2$ – LVET) EML: electromechanical latency** – time from electrical activation of septum to closing of atrioventricular valves and beginning of systole of ventricles (EML=**$QS_2$ - $S_1S_2$**)

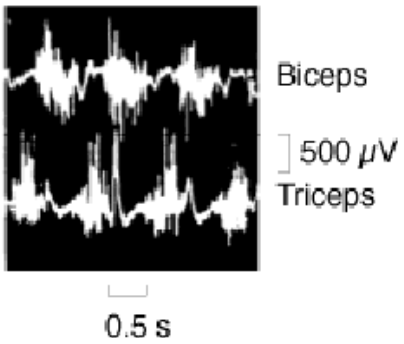
Indexes:
**ΔP/Δt** = average speed of pressure increase in isovolumic phase of systole
**PEP/LVET** =it is index of cardiac contractility

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**:

$I_c = I_m / \sqrt{RR}$ , where $I_c$ is corrected interval, $I_m$ is measured interval in milliseconds and RR is cycle length in seconds

# 54. 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.




*Electromyographic tracings from human biceps and triceps muscles during alternate flexion and extension of elbow*

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).

# 55. 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 etc. 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, gases are liberated on the surface of the electrodes.

- Non-polarisable electrode: accurate measurements 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 ensured by a conducting gel. Their shape is often dish-like. **Needle electrodes** are used for recording of biopotentials from a small area of tissue. Made of a noble metal. Used mainly for muscle biopotentials or long-term recording of heart or brain potentials.

# 56. External signs of breathing

Check for Breathing

- ✓ Look for signs of breathing. Watch the victim's chest to see if it is rising and falling, which would indicate breathing is occurring.
- ✓ Listen for signs of breathing by placing your ear near the victim's nose. Weak breathing may not produce obvious rising and falling of the chest, but you may still be able to hear the breathing.
- ✓ Place your hand in front of the victim's nose and mouth to see if you can feel warm air being expelled during breathing. If you have a mirror, such as one from a cosmetic case, hold it under the victim's nose and see if it fogs with expelled breath.
- ✓ Smell of breath

## Examination of the chest

The physical examination of the chest consists of *inspection*, *palpation*, *percussion*, and *auscultation*.

Inspection – one looks at the shape of the chest, deformities; checks the respiratory movements and soft parts.
– ***Respiratory movements:*** During respiratory movements we watch the type of respiration and check whether both sides of the chest participate in the air exchange equally and with the same force; we also check the respiratory rate (frequency).

The "abdominal type" of respiration is common in men: breathing movements are accomplished mostly by the diaphragm with a rhythmic protrusion of the abdominal wall.

In women the "costal type" of respiration is common, mainly with elevation and lowering of the ribcage.
In diseases of the pleura, in *pleuropneumonic adhesion*, *pleural effusion* or *pneumothorax*, the movements of the chest on the affected side may be diminished or absent. Respiratory rate in resting adult is approx. 16-20 beats per minute. This normal respiration is called **eupnea**. During exercise and under pathologic conditions respiration may greatly change in the number of breaths per minute, as well as in depth and regularity.

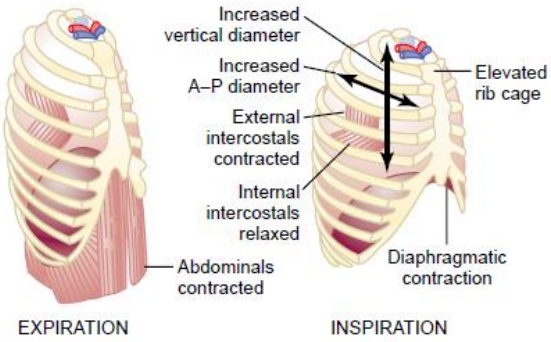
**Tachypnea** is and increased breathing rate (frequency); it may be an important sign of lung disease.
**Bradypnea** is a decreased number of breaths per minute.
**Apnea** is a temporary cessation of respiration (e.g. the apneic phase of Cheyne-Stokes periodic respiration).
**Hyperpnea** is a deepened respiration (increases minute volume if air in lungs).
**Dyspnea** is "shortness of breath".

Palpation of the Chest: by ***Vocal Fremitus***; the perception of vibration of the chest wall caused by phonation (talking) of the patient. The patient loudly pronounces certain words to cause resonance (for instance, "one-two-three, or ninety-nine") of the chest wall. The voice is transmitted from the vocal cords through the trachea and bronchi into the lung tissue, and from there the voice is transferred to the chest wall, which acts as a resonator. One places the palms of both hands (bilaterally) over corresponding areas on the hemithoraces and compares the vibrations evoked by the spoken sounds.

Percussion of the Chest: The percussion sound over normal lungs is sonorous, resonant, and clear, with a slightly hyperresonant character toward the lung bases. It may change under pathological conditions to:
**1. Hypersonorous (hyperresonant)**- if the lungs become more expanded and filled with air: this is found in emphysema, or if there is some air in the pleural cavity (pneumothorax).
**2. dull to flat:** e.g., if the lung tissue loses its air content and becomes consolidated, dense (e.g. in pneumonia).

Auscultation of the Lungs: One may utilize the direct method by placing one's ear directly on the chest wall – or the preferred indirect method – with the aid of a ***stethoscope***.
Breath Sounds: **vesicular breathing** and **bronchial (tubular) breathing**

# 57. Lung ventilation, volumes, measurement




## Mechanism of Breathing

The lungs can be expanded and contracted in two ways: (1) by downward and upward movement of the diaphragm to lengthen or shorten the chest cavity, and (2) by elevation and depression of the ribs to increase and decrease the anteroposterior diameter of the chest cavity.

## Muscles of inspiration

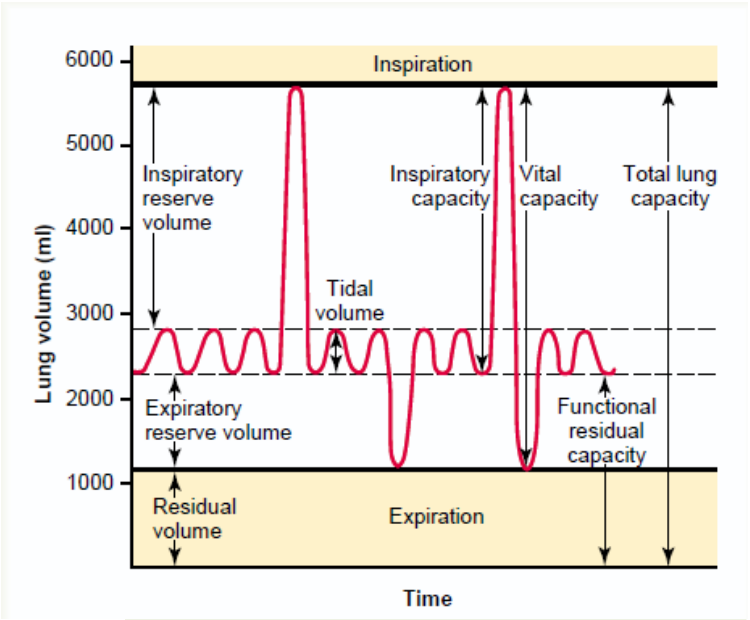
**1. *Diaphragm*** – when it contracts, the abdominal contents are pushed downward, and the ribs are lifted upward and outward, increasing the volume of the thoracic cavity.
**2. External intercostals and accessory muscles –** are used during **exercise** and in **respiratory distress**.

## Muscles of expiration

– expiration is **normally passive**. Because the lung-chest wall system is elastic, it returns to its resting position after inspiration.
– Expiratory muscles are used **during exercise** or when airway resistance is increased because of disease (e.g., **asthma**).
**1. *Abdominal muscles*** – compress the abdominal cavity, push the diaphragm up, and push air put of the lungs.
**2. *Internal intercostals* –** pull the ribs downward and inward.

## Pulmonary Volumes

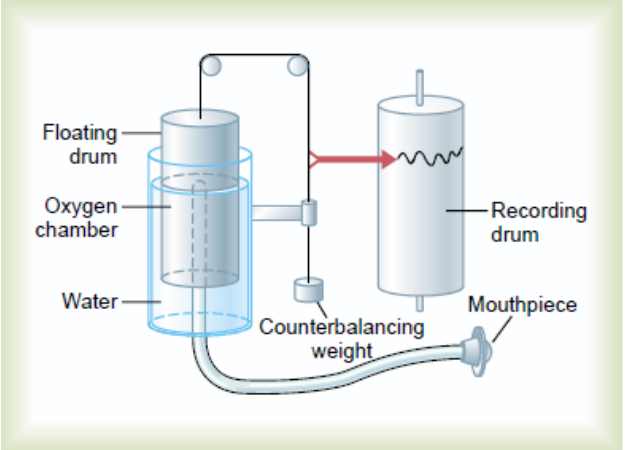
**1.** The ***tidal volume*** is the volume of air inspired or expired with each normal breath; it amounts to about 500 milliliters in the adult male.
**2.** The ***inspiratory reserve volume*** is the extra volume of air that can be inspired over and above the normal tidal volume when the person inspires 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.




## Recording Changes in Pulmonary Volume - Spirometry

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.




Spirometer.

## 58. Dead space, measurement

Some of the air a person breathes never reaches the 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.

**a. *Anatomic dead space***
- – is the volume of the conducting airways.
- – is normally approximately 150 mL.

**b. *Physiological dead space***
- – is a functional measurement.
- – is defined as the volume of the lungs that does not participate in gas exchange.
- – is approx. equal to the anatomic dead space in normal lungs.
- – may be greater than the anatomic dead space in lung diseases in which there are ventilation/perfusion (V/Q) defects.
- – is calculated by the following equation:

$$V_D = V_T \times \frac{P_{A_{CO2}} - P_{E_{CO2}}}{P_{A_{CO2}}}$$

where:

$V_D$ = physiological dead space (mL)

$V_T$ = tidal volume (mL)

$P_{A_{CO2}}$ = $P_{CO2}$ of alveolar gas (mm Hg) = $P_{CO2}$ of arterial blood

$P_{E_{CO2}}$ = $P_{CO2}$ of expired air (mm Hg)

- In word, the equation states that physiological dead space is tidal volume multiplied by a fraction. The fraction represents the dilution of alveolar $P_{CO2}$ by dead-space air, which does not participate in gas exchange and does not therefore contribute $CO_2$ to expired air.

# 59. Resistance of airways, measurement

## Calculating resistance of the airways

→ Resistance can be calculated using Ohm's law or Poiseuille's law.

**Ohm's law**

$$R = \frac{\Delta P}{\dot{V}} = \frac{P_{\text{mouth}} - P_{\text{alveoli}}}{\dot{V}}$$

- *R* = resistance
- *P* = pressure
- $\dot{V}$ = airflow (the dot over the letter is used to denote rate in respiratory physiology.)

**Poiseuille's law**

$$R = \frac{8nl}{\pi r^4}$$

- R = resistance
- n = viscosity
- l = length
- r = radius

➢ Because of the fourth power in the denominator, resistance increases rapidly as diameter decreases.

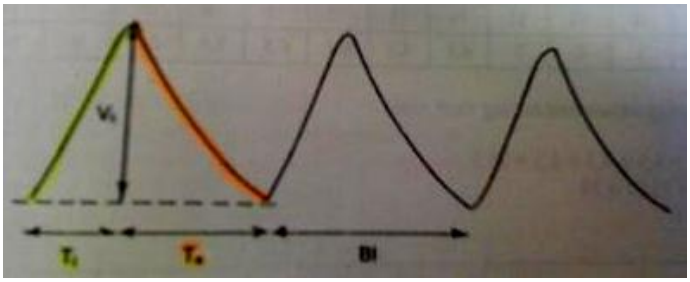
## Factors that change airway resistance

a. **Contraction or relaxation of bronchial smooth muscle**
   – changes airway resistance by altering the radius of the airways.
   **(1)** *Parasympathetic stimulation*, irritants, and the slow-reacting substance of anaphylaxis **(asthma)** constrict the airways, decrease the radius, and increase the resistance to airflow.
   **(2)** *Sympathetic stimulation* and sympathetic agonists **(isoproterenol)** dilate the airways via **$\beta_2$ receptors,** increase the radius, and decrease the resistance to airflow.
b. **Lung volumes**
   **(1)** *High lung volumes* are associated with greater traction and decreased airway resistance.
   **(2)** *Low lung volumes* are associated with less traction and increased airway resistance.
c. **Viscosity or density of inspired gas**
   – *During a deep-sea dive*, both air density and resistance to airflow are increased.
   – *Breathing a low-density gas*, such as **helium**, reduces the resistance to airflow.

# 60. Pneumography and pneumotachography

## Pneumography

***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.



***Pneumography –recording, the way of evaluation***

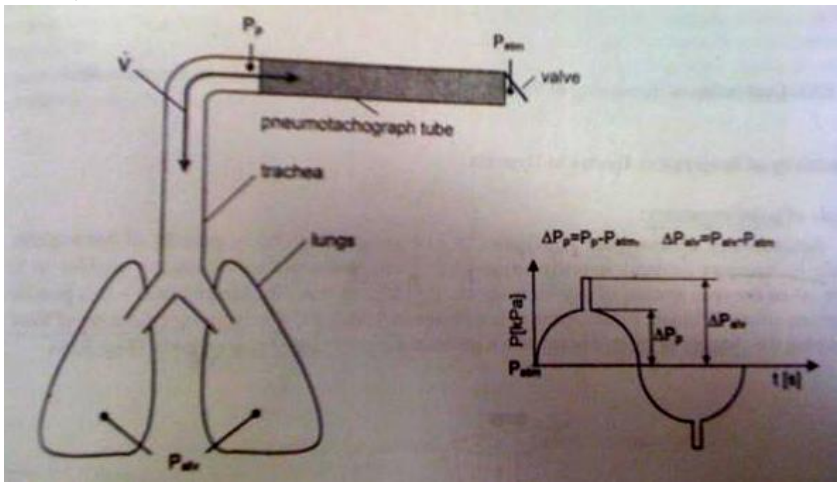
- **duration of inspiration ($T_i$)**
- **duration of expiration ($T_e$)**
- **respiratory intervals (BI=breathing interval)**
- **amplitude $V_t$**

## 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 trough the pneumotachograph, two resistances are connected in series: that of the pneumotachograph ($R_p$) and the airway resistance ($R_a$). If the alveolar pressure ($P_{alv}$), pressure at proximal end of the pneumotachograph ($P_p$), and resistance of the pneumotachograph ($R_p$) are known, then:



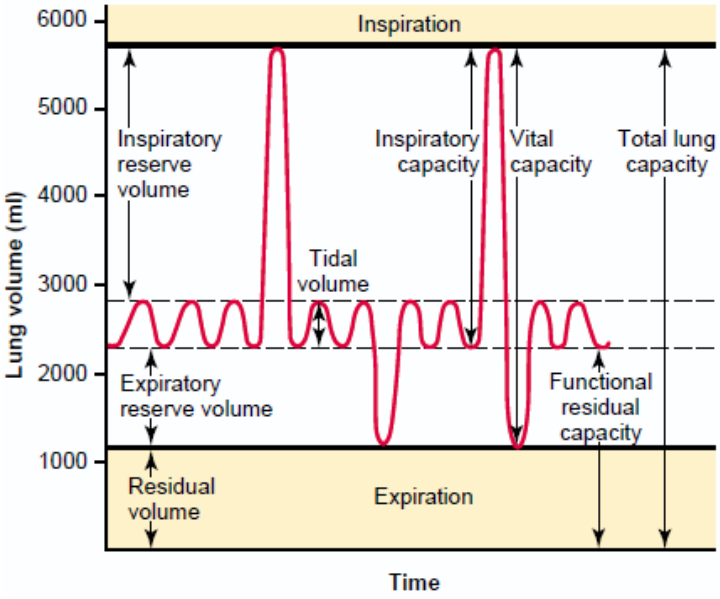

***Principle of pneumotachography***

The formula for calculation of airway resistance is:

$$R_d = R_p \times (\Delta P_{alv}/\Delta P_p - 1)$$

## 61. Maximum respiratory flow – volume curve (spirogram)

**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.*




*COMPLETE .. . specify !!*

## 62. pH measurement (Astrup method)

The **Astrup method** for determination of *arterial pH*, *$pCO_2$*, and *"base excess"* provides a simple and accurate means for quantitation of acid-base disorders. The "base excess" value, a measure of metabolic acidosis or alkalosis, gives the clinician a valuable tool with which to estimate electrolyte replacement. The $pCO_2$ is a measure of respiratory acidosis or alkalosis. The pH is used as a measure of the adequacy of compensation. Several representative cases illustrate the use and interpretation of the test.

"Base excess":
**1. Metabolic acidosis** – patients have a "base excess" less than zero (minus "base excess").
**2. Metabolic alkalosis** – the diagnostic feature seen is an elevated "base excess".

$pCO_2$: is a measure of **respiratory acidosis/alkalosis**.

pH: is used as a measure of the adequacy of compensation.

Astrup recommended that electrolyte deficits in the extracellular space be calculated using the formula: ***Total deficit mEq = "Base excess" X 0.3 X body weight Kg***

The advantages of the Astrup system are its technical simplicity and speed and the ability to graphically clarify complex chemical relationships.

## 63. Clearance

– indicates the volume of plasma cleared of a substance per unit time.

– The units of clearance are **mL/min** and **mL/24 hr**.

$$C = UV/P$$

where:

C = clearance (mL/min or mL/24 hr)

U = urine concentration (mg/mL)

V = urine volume/time (mg/min)

P = plasma concentration (mg/mL)

$$GFR = \frac{\dot{V}_U \cdot U_{In}}{P_{In}} [L/min]$$

The expression on the right of equation represents **clearance**, regardless of which substance is being investigated. Therefore, the *inulin or creatinine clearance represents the GFR*. (Although the plasma concentration of creatinine, $P_{cr}$, rises as the GFR falls, $P_{cr}$ alone is a quite unreliable measure of GFR.)

**Fractional excretion** (**FE**) is the ratio of clearance of a given substance X to inulin clearance ($C_X/C_{In}$) and defines which fraction of the filtered quantity of X was excreted. FE>1 if the substance is removed from the tubule by reabsorption (e.g. $Na^+$, $Cl^-$, amino acids, glucose, etc.), and FE<1 if the substance is subject to filtration plus tubular secretion. For PAH, tubular secretion is so effective that $FE_{PAH}$ ≈5 (500%).

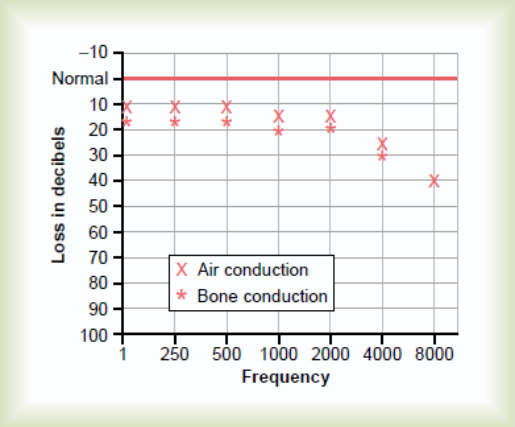
## 64. Audiometry

**Subjective hearing tests** are performed using an **audiometer**. The patient is presented sounds of various frequencies and routes of conduction (bone, air). The sound pressure is initially set at a level under the threshold of hearing and is raised in increments until the patient is able to hear the presented sound (*threshold audiogram*). If the patient is unable to hear the sounds at normal levels, he or she has an hearing loss, which is quantitated in decibels (dB). In **audiometry**, all frequencies at the normal threshold of hearing are assigned the value of 0 dB. Hearing loss can be caused by presbycusis, middle ear infection (impaired air conduction), and damage to the internal ear (impaired air and bone conduction) caused, for example, by prolonged exposure to excessive sound pressure, by ototoxic medication (blockage of stria vascularis by loop diuretics), or by defects of the KCNQ4 or KCC4 genes.

### Audiogram

In performing a hearing test using an audiometer, one tests about 8 to 10 frequencies covering the auditory spectrum, and the hearing loss is determined for each of these frequencies. Then the so-called *audiogram* is plotted, depicting hearing loss at each of the frequencies in the auditory spectrum.

The audiometer, in addition to being equipped with an earphone for testing air conduction by the ear, is equipped with a mechanical vibrator for testing bone conduction from the mastoid process of the skull into the cochlea.




Audiogram of the old-age type of nerve deafness.

## 65. Cardiovascular response to Valsalva manoeuvre

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.

| Effect of Valsalva | Cardiac Finding |
|---|---|
| Decreased | Aortic Stenosis |
| | Pulmonic Stenosis |
| | Tricuspid Regurgitation |
| Increased | Hypertrophic cardiomyopathy, mitral valve prolapse |

## 66. Examination of baroreflex sensitivity

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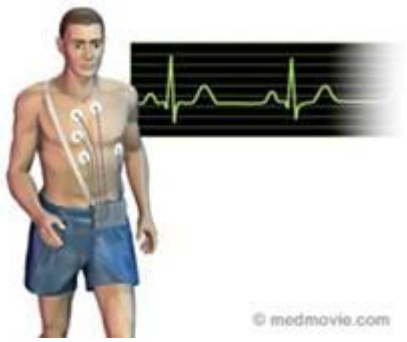
- When the person stops the maneuver, there is a rebound increase in venous return, cardiac output, and arterial pressure. The increase in arterial pressure is sensed by the baroreceptors, which direct a decrease in heart rate.

## 67. Examination of heart rate and blood pressure variability

*See Q. 43-45, 52, 68*

# 68. 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 instigate, 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.

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

## *Radioimmunoassay (RIA)*

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

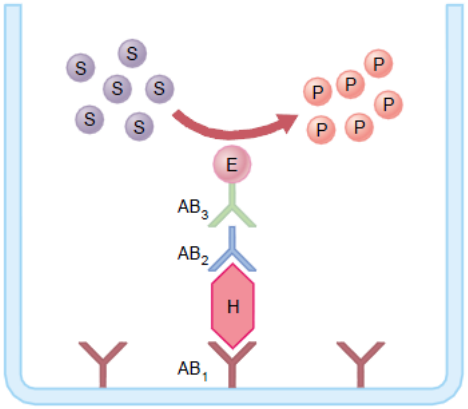
To perform a radioimmunoassay, a known quantity of an antigen is made radioactive, frequently by labeling it with gamma-radioactive isotopes of iodine attached to tyrosine. This radiolabeled antigen is then mixed with a known amount of antibody for that antigen, and as a result, the two chemically bind 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)*

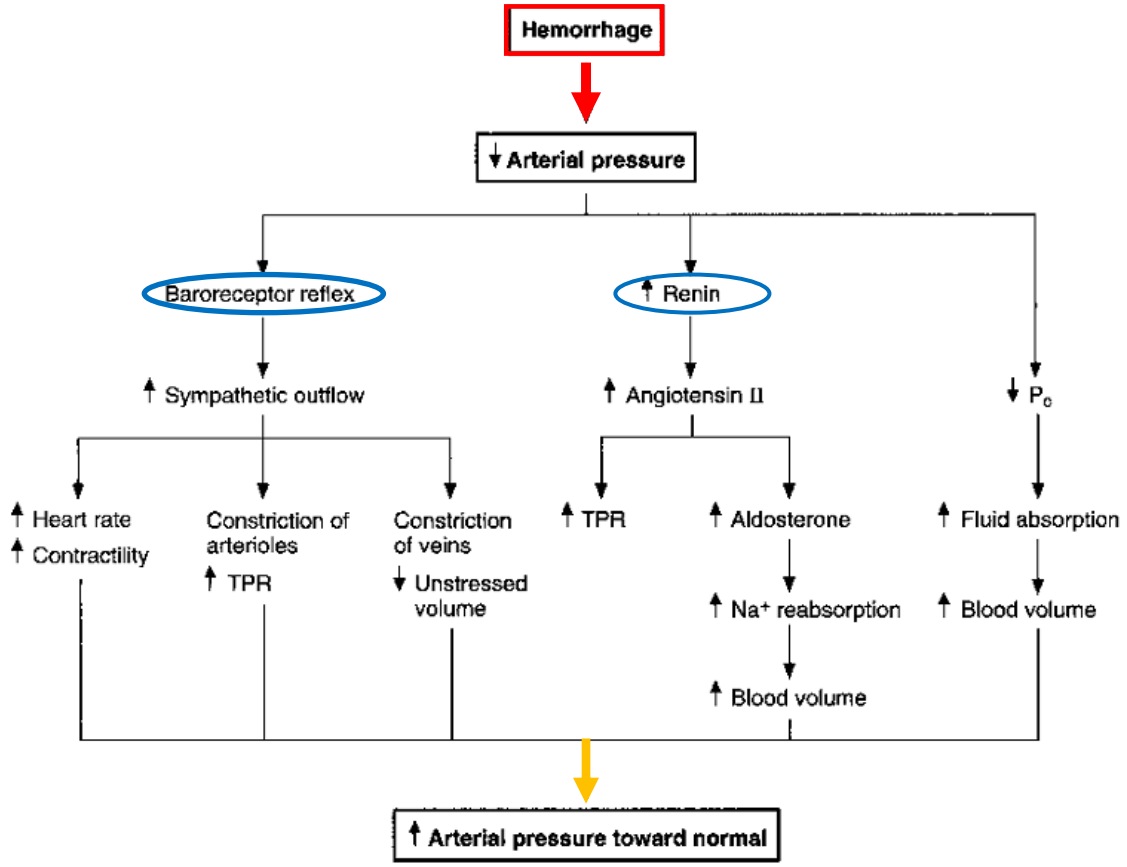
Also known as **Enzyme-Linked Immunosorbent Assay (ELISA)** can be used to measure almost any protein, including hormones. This test combines the specificity of antibodies with the sensitivity of simple enzyme assays. The figure on the right shows the basic elements of this method, which is often performed 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.




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.

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.

## 70. Reaction of circulatory system on bleeding




Cardiovascular responses to hemorrhage. $P_c$ = capillary hydrostatic pressure; *TPR* = total peripheral resistance.

– The **compensatory responses** to acute blood loss are as follows:

1. **A decrease in blood volume** produces a decrease in mean systemic pressure. As a result, there is a **decrease in both cardiac output** and **arterial pressure.**
2. The **carotid sinus baroreceptors** detect the decrease in arterial pressure. As a result of the baroreceptor reflex, there is **increased sympathetic outflow to the heart and blood vessels** and **decreased parasympathetic outflow to the heart,** producing:
   - **a.** ↑ heart rate
   - **b.** ↑ contractility
   - **c.** ↑ TPR (due to arteriolar constriction)
   - **d.** ↓ unstressed volume and ↑ stressed volume (due to venous constriction)

   – Vasoconstriction occurs in skeletal, splanchnic, and cutaneous vascular beds. However, it does not occur in coronary or cerebral vascular beds, ensuring that adequate blood flow will be maintained to the heart and brain.

   – These responses attempt to restore normal arterial blood pressure.
3. **Chemoreceptors in the carotid and aortic bodies** are very sensitive to hypoxia. They supplement the baroreceptor mechanism by increasing sympathetic outflow to the heart and blood vessels.
4. **Cerebral ischemia** (if present) causes an **increase in $P_{CO_2}$,** which activates chemoreceptors in the vasomotor center to increase sympathetic outflow.
5. **Arteriolar vasoconstriction** causes a **decrease in $P_c$.** As a result, **capillary absorption is favored,** which helps to restore circulating blood volume.
6. **The adrenal medulla releases epinephrine and norepinephrine,** which supplement the actions of the sympathetic nervous system on the heart and blood vessels.
7. **The renin-angiotensin-aldosterone system** is activated by the decrease in renal perfusion pressure. Because **angiotensin II** is a potent vasoconstrictor, it reinforces the stimulatory effect of the sympathetic nervous system on TPR. **Aldosterone** increases NaCl reabsorption in the kidney, increasing the circulating blood volume.
8. **ADH** is released when atrial receptors detect the decrease in blood volume. ADH causes both vasoconstriction and increased water reabsorption in the kidney, both of which will tend to increase blood pressure.

# 71. Reflex reactions of circulatory system (diving reflex, Valsalva manouvre, Müller manouvre)

## *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.

## *Müller's manoeuvre*

After a forced expiration, an attempt at inspiration is made with closed mouth and nose, whereby the negative pressure in the chest and lungs is made very subatmospheric; the reverse of Valsalva manoeuvre.

→Breathe in with mouth and nose closed
→Generation of a negative pressure in upper airway
→Results are monitored by echocardiogram of left ventricle
→End diastolic and end systolic dimension increases
→Obtained results show that lung volume affects left ventricle response due to reduced intrathoracic pressure changing afterload and filing.

## *Valsalva manouvre*

- 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.

| Effect of Valsalva | Cardiac Finding |
|---|---|
| Decreased | Aortic Stenosis |
| | Pulmonic Stenosis |
| | Tricuspid Regurgitation |
| Increased | Hypertrophic cardiomyopathy, mitral valve prolapse |

# 72. Respiratory quotient

**"Respiratory Quotient" Is the Ratio of CO2 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.

# 73. Cardiopulmonary response to exercise

## 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 is 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 relationship, IV D 5).
   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 muscle 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 $P_{O_2}$ and $P_{CO_2}$ do not change** during exercise.
   - **Arterial pH** does not change during moderate exercise, although it may decrease during strenuous exercise because of **lactic acidosis.**
3. On the other hand, **venous $P_{CO_2}$ 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.**

# 74. Autocrine, paracrine, and endocrine regulation

## Autocrine signaling

– Is a form of signaling in which a cell secretes a hormone or chemical messenger (called the autocrine agent) that binds to autocrine receptors *on the same cell*, leading to changes in the cells.
– An example of an autocrine agent is the **cytokine interleukin-1** in *monocytes*. When this is produced in response to external stimuli, it can bind to cell-surface receptors on the same cell that produced it.

## Paracrine signaling

– Is a form of cell signaling in which the target cell is near the signal-releasing cell.
– **Growth factor** and **clotting factors** are paracrine signaling agents. The local action of growth factor signaling plays an especially important role in the development of tissues. In insects, **Allatostatin** controls growth through paracrine action on the *corpora allata*.

## Endocrine signaling

– Is a system of glands, each of which secretes a type of hormone into the bloodstream to regulate the body. A number of glands that signal each other in sequence is usually referred to as an axis, for example, the ***hypothalamic-pituitary-adrenal axis***.
– Typical endocrine glands are the **pituitary**, **thyroid**, and **adrenal glands**.
– In addition to the specialized endocrine organs mentioned above, many other organs that are part of other body systems, such as the **kidney**, **liver**, **heart** and **gonads**, have secondary endocrine functions. For example the kidney secretes endocrine hormones such as ***erythropoietin*** and ***renin***.

# 75. Chemical characteristics of hormones

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

- **Endocrine hormones**, i.e., those transported in the bloodstream, are produced in *endocrine glands* such as the hypothalamus, thyroid, parathyroid glands, adrenal medulla, pancreatic islets, ovaries and testes. They are also synthesized in diffusely scattered *endocrine cells* of the CNS, in C cells of the thyroid, and in the thymus, atria, kidneys, liver, gastrointestinal tract, etc.
- **Paracrine hormones**, i.e., those that affect nearby cells only (tissue hormones or *mediators*; see below) are secreted by cells widely distributed throughout the body.

## 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.

## Hormone receptors

The receptors (docking sites) for glycoprotein hormones, peptide hormones and catecholamines are transmembrane proteins that bind to their specific hormone on the outer cell surface.
Many of these hormones induce the release of intracellular **second messengers** that transmit the hormone signal inside the cell.

Some peptide hormones like **insulin**, **prolactin**, **atriopeptin** and numerous growth factors bind to cell surface receptors with cytosolic domains with *enzymatic activity*. Steroid hormones, on the other hand, enter the cells themselves. Once they bind to ***cytosolic receptor proteins***, steroid hormones (as well as calcitriol, T3 and T4) are transported to the cell nucleus, where they influence transcription (genomic action).

A target cell can have different receptors for different hormones (e.g., insulin and glucagon) or different receptors for a single hormone (e.g., $\alpha_1$ and $\beta_2$ adrenoceptors for epinephrine).

The secretion of hormones is often triggered by neural impulses from the CNS. The *hypothalamus* is the main neurohormonal control center. Hypothalamic neurons extend to the posterior pituitary (neurohypophysis). The hormones are secreted either by the hypothalamus itself or by the posterior pituitary. Hypothalamic hormones also control hormone release from the *anterior pituitary* (adenohypophysis). Anterior pituitary *Glandotropic hormones* control *peripheral endocrine glands*, which release the endhormone. The original signal can be *amplified* or *modulated* at these relay sites.

# 76. Sympathetic alpha- and beta-receptors

## Adrenergic receptors (adrenoreceptors)

### $\alpha_1$ Receptors

- are located on vascular smooth muscle of then skin and splanchnic regions, the gastrointestinal (GI) and bladder sphincters, and the radial muscle of the iris.
- produce **excitation** (e.g., contraction or constriction).
- Are equally sensitive to norepinephrine and epinephrine. However, only norepinephrine released from adrenergic neurons is present in high enough conc. to activate $\alpha_1$ receptors.
- **Mechanism of action: $G_q$ protein;** stimulation of phospholipase C, and increase in inositol 1,4,5-triphosphate **($IP_3$)** and intracellular [$Ca^{2+}$].

### $\alpha_2$ Receptors

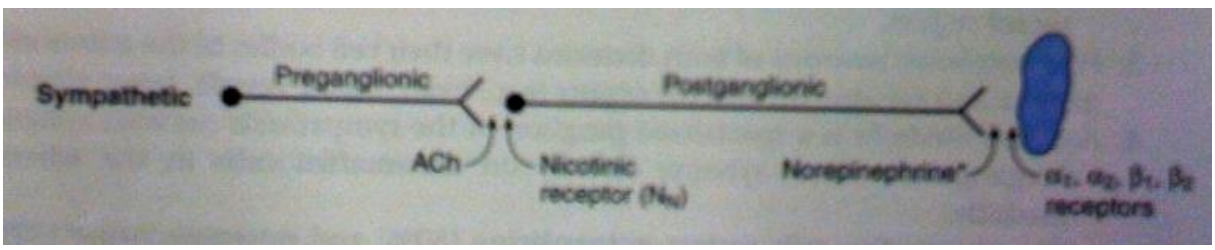
- are located in presynaptic nerve terminals, platelets, fat cell, and the walls of the GI tract.
- often produce inhibition (e.g., relaxation or dilation).
- **Mechanism of action: $G_i$ protein** inhibition of adenylate cyclase and **decrease in cyclic adenosine monophosphate (cAMP)**.

### $\beta_1$ Receptors

- are located in the sinoatrial (SA) node, atrioventricular (AV) node, and ventricular muscle of the **heart**.
- produce excitation (e.g., increased heart rate, increased conduction velocity, increased contractility).
- are sensitive to both norepinephrine and epinephrine, and are more sensitive than the $\alpha_1$ receptors.
- **Mechanism of action: $G_s$ protein,** stimulation of adenylate cyclase and increas in cAMP.

### $\beta_2$ Receptors

- are located on vascular smooth muscle of skeletal muscle, bronchial smooth muscle, and in the walls of the GI tract and bladder.
- produce **relaxation** (e.g., dilation of vascular smooth muscle, dilation of bronchioles, relaxation of the bladder wall).
- are more sensitive to epinephrine than to norepinephrine.
- are more sensitive to epinephrine than $\alpha_1$ receptors.
- **Mechanism of action: $G_s$ protein,** stimulation of adenylate cyclase and increas in cAMP.



## 77. 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.

## 78. Oogenesis

The development of the female gametes (ova) extends from the oogonium stage to the primary oocyte stage (in the primordial follicle), starting long before birth. Oogenesis therefore occurs much sooner than the corresponding stages of spermatogenesis. The fetal phase of oogenesis is completed by the first week of gestation; these oocytes remain latent until puberty. In the sexually mature female, a fertilizable ovum develops in the graafian follicles approximately every28 days.

2 phases: **oocytogenesis**
**Meiosis**

**oocytogenesis -** mitotic division of oogonia - begins during the fetal period
the oogonia enlarge to form **primary oocytes**, they enter the first meiotic division that is stopped in the prophase, the cell nucleus is then transformed into the interphase form in which is to stay to the beginning of reproductive life of females

the first meiotic division is completed shortly before the ovulation - the primary oocyte divides unequal and gives rise to large **secondary oocyte** and the **first polar body** (polar body is nonfunctional and soon degenerates)
in time of ovulation the secondary oocyte enters the second meiotic division that progresses only to metaphase, in which division is arrested
completion of the second meiotic division is closely connected with penetration of the sperm into the oocyte: the division becomes again to continue and developed daughter cells are the **mature ovum** and the **secondary polar body**

# 79. Hormonal contraception

## Hormonal contraception

The term refers to birth control methods that act on the endocrine system.

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.

### Mechanism of action

Combined hormonal contraceptives

Prevent ovulation by suppressing the release of gonadotropins. They inhibit follicular development and prevent ovulation as their primary mechanism of action.

***Progestin*** negative feedback decreases the pulse frequency of gonadotropin-releasing hormone (GnRH) release by the hypothalamus, which decreases the release of follicle-stimulating hormone (FSH) and greatly decreases the release of luteinizing hormone (LH) by the anterior pituitary. Decreased levels of FSH inhibit follicular development, preventing an increase in estradiol levels. Progestin negative feedback and the lack of estrogen positive feedback on LH release prevent a mid-cycle LH surge. Inhibition of follicular development and the absence of a LH surge prevent ovulation.

***Estrogen*** was originally included in oral contraceptives for better cycle control (to stabilize the endometrium and thereby reduce the incidence of breakthrough bleeding), but was also found to inhibit follicular development and help prevent ovulation. Estrogen negative feedback on the anterior pituitary greatly decreases the release of FSH, which inhibits follicular development and helps prevent ovulation.

A secondary mechanism of action of all progestin-containing contraceptives is *inhibition of sperm penetration through the cervix* into the upper genital tract, by decreasing the amount of and increasing the viscosity of the cervical mucus.

Progestin-only

The mechanism of action of progestogen-only contraceptives depends on the progestogen activity and dose.

**Low dose progestin-only** contraceptives inhibit ovulation in ~50% of cycles and rely mainly on their progestin effect of thickening the cervical mucus and thereby reducing sperm viability and penetration.

**Intermediate dose progestogen-only** allow some follicular development but much more consistently inhibit ovulation in 97–99% of cycles.

**High dose progestogen-only** contraceptives, such as the **injectables** *Depo-Provera* and *Noristerat*, completely inhibit follicular development and ovulation.

# 80. 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.

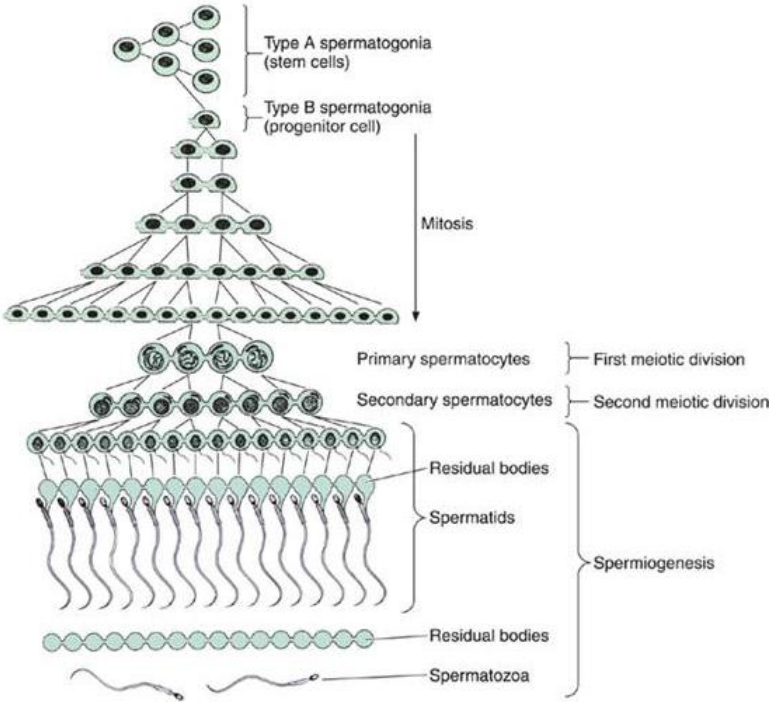
## Spermatogenesis

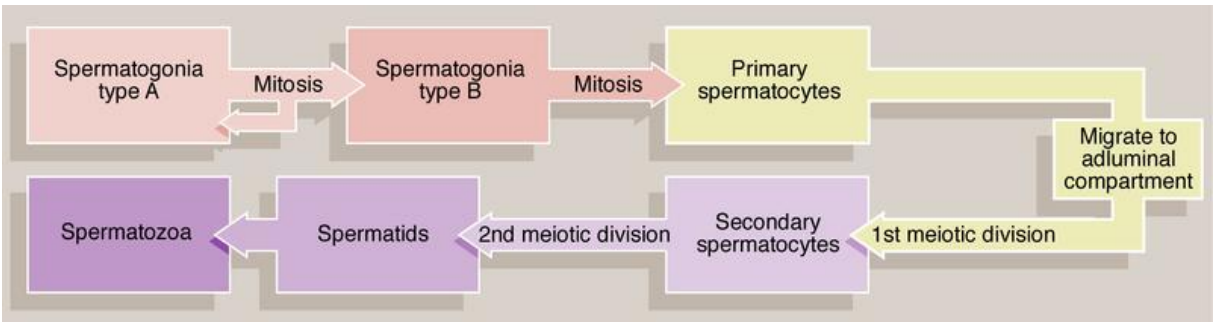
It begins with a primitive germ cell, the **spermatogonium**. At sexual maturity, spermatogonia begin dividing by mitosis, producing successive generations of cells. The newly formed cells can follow one or two paths: they can continue dividing as stem cells, also called **type A spermatogonia**, or 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**.



# 81. Puberty and menopause

## Puberty and Menarche

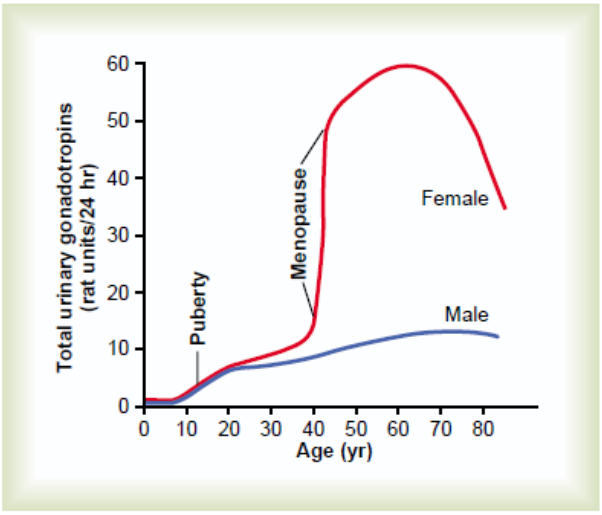
*Puberty* means the onset of adult sexual life, and *menarche* means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, as shown in figure below, and usually 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, and for reasons not understood, the hypothalamus does not secrete significant quantities of GnRH during childhood. Experiments have shown that the hypothalamus itself is capable of secreting this hormone, but the appropriate signal from some other area of brain to cause the secretion is lacking. Therefore, it is now believed that the onset of puberty is initiated by some maturation process that occurs elsewhere in the brain, perhaps somewhere in the limbic system.

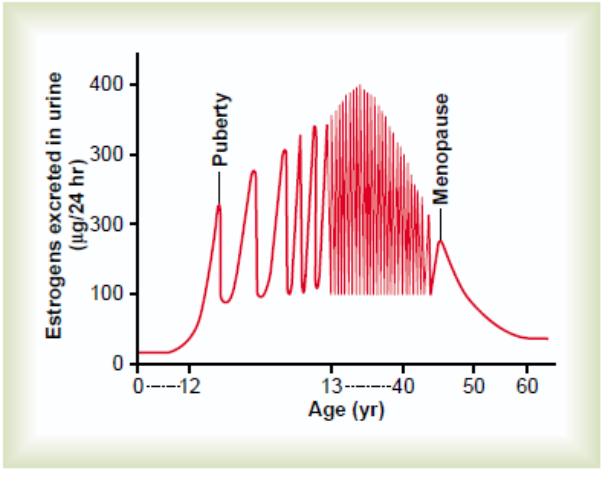
## Menopause

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. Throughout a woman's reproductive life, about 400 of the primordial follicles grow into mature follicles and ovulate, and hundreds of thousands of ova degenerate. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH, and, as shown in the figure below, 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.




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.




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

# 82. Physiological significance of positive and negative feed-back

### *Negative Feedback Nature of Most Control Systems*

Most control systems of the body act by *negative feedback.* 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*

If one considers the nature of positive feedback, one immediately sees that positive feedback does not lead to stability but to instability and often death. For example, if a healthy person with a heart that pumps about 5 liters of blood per minute, 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 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.

**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. If it is not powerful enough, the contractions usually die out, and a few days pass before they begin again.

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.

# 83. Physiological regulations (overview) ⟹ see Q. 84 (94, 74, 82, 100)

# 84. 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. For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the liver is responsible for metabolizing toxic substances and maintaining carbohydrate metabolism, the kidneys are responsible for regulating blood water levels, re-absorption of substances into the blood, maintenance of salt and ion levels in the blood, regulation of blood pH, and excretion of urea and other wastes.

An inability to maintain homeostasis may lead to death or a disease, a condition known as *homeostatic imbalance*. For instance, heart failure may occur when negative feedback mechanisms become overwhelmed and destructive positive feedback mechanisms take over. Other diseases which result from a homeostatic imbalance include diabetes, dehydration, hypoglycemia, hyperglycemia, gout and any disease caused by the presence of a toxin in the bloodstream. Medical intervention can help restore homeostasis and possibly prevent permanent damage to the organs.

### *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 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.

# 85. 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<br>$HCO_3^-$ resorption | days |

**Buffer bases in (arterial) plasma**

| Buffer base | mmol/l |
|---|---|
| $HCO_3^-$ | 24 |
| Protein-His | 17* |
| $HPO_4^{2-}$ | 1 |
| --- | --- |
| **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).

**1.** ***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 $H_2PO_4^-$/$HPO_4^{2-}$ buffer pair is 6.8.
– Phosphate is most important as **urinary buffer**; excretion of $H^+$ as $H_2PO_4^-$ is called **titratable acid**.

**2.** ***Intracellular buffers***

**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**.

# 86. 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:

- Excretion of metabolic waste products and foreign chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Secretion, metabolism, and excretion of hormones
- 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 $D_3$ Production.** The kidneys produce the active form of vitamin D, 1,25-dihydroxyvitamin $D_3$ (*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.

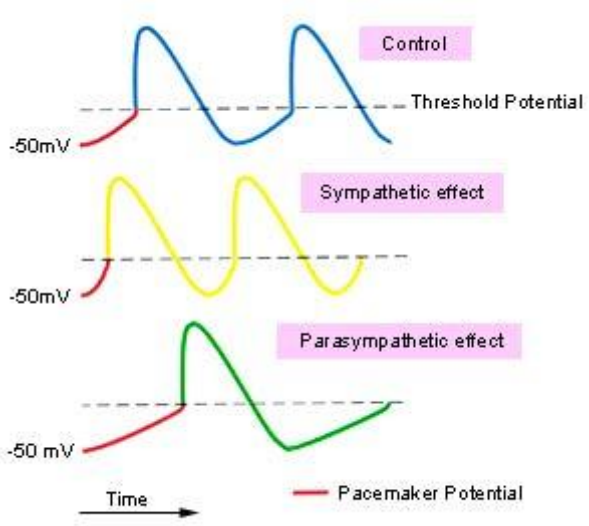
## 87. Regulation of cardiac output

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 enervated 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

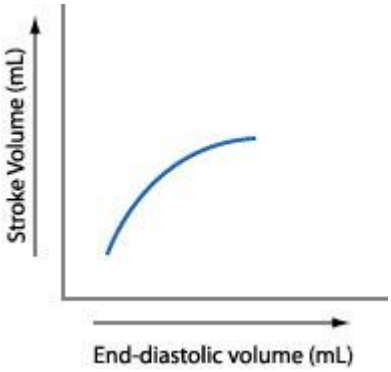
**End-diastolic Volume**

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.

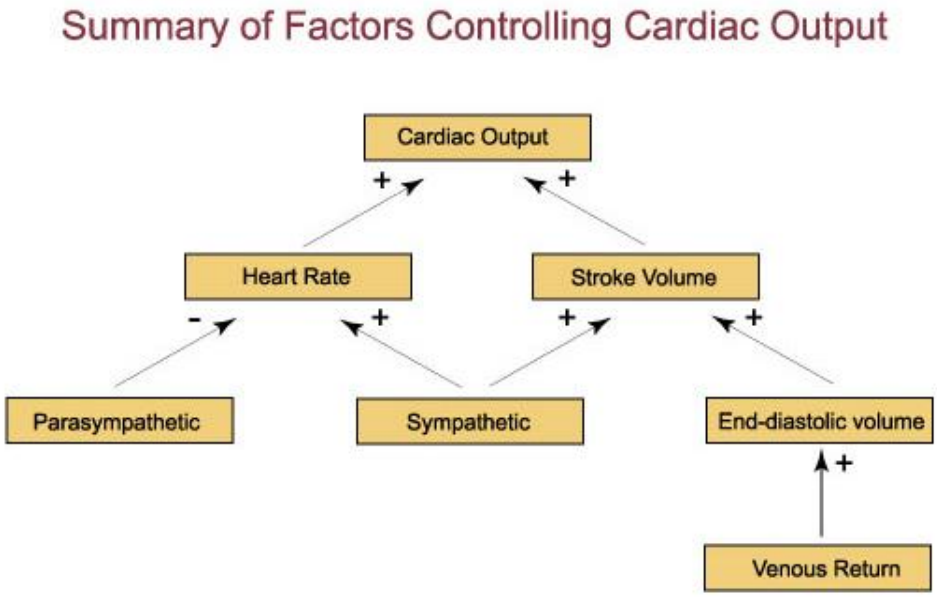
**Starling's Law**

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 enervated 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.



## 88. Regulation of blood circulation upon orthostasis

– The following changes occur when an individual **moves from a supine position 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, $P_c$ 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 to 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 relationship, IV D 5).
4. Initially, arterial pressure decreases because of the reduction in cardiac output. If cerebral blood pressure becomes low enough, fainting 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 on standing) may occur in individuals whose baroreceptor reflex mechanism is impaired (e.g., individuals treated with sympatholytic 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.

# 89. Regulation of ventilation

## Innervations and control centres

The respiratory muscles are innervated by nerve fibers extending from the cervical and thoracic medulla (C4 – C8 and T1 –T7). The most important **control centers** are located in the ***medulla oblongata*** and cervical *medulla* (**C1–C2**), where interactive *inspiratory and expiratory neurons* exist on different levels. The network of these spatially separate neuron groups form a **rhythm generator (respiratory "center")** where respiratory rhythm originates. The neuron groups are triggered alternately, resulting in rhythmic inspiration and expiration. They are activated in a tonic (nonrhythm- dependent) manner by the *formation reticularis*, which receives signals from *respiratory stimulants* in the periphery and higher centers of the brain.

### **Respiratory sensors** or receptors are involved in respiratory control circuits

*Central* and *peripheral chemosensors* on the medulla oblongata and in the arterial circulation continuously register gas partial pressures in cerebrospinal fluid (CSF) and blood, respectively, and *mechanosensors* in the chestwall respond to stretch of intercostal muscles to modulate the depth of breathing. *Pulmonary stretch sensors* in the tracheal and bronchial walls respond to marked increases in lung volume, thereby limiting the depth of respiration in humans (*Hering–Breuer reflex*). *Muscle spindles* in the respiratory muscles also respond to changes in airway resistance in the lung and chest wall.

The extent of involuntary ventilation is mainly determined by the partial pressures of $O_2$ and $CO_2$ and the pH of blood and CSF. Chemosensors respond to any changes in these variables.

- **Peripheral chemosensors** in the glomera aortica and carotica register changes in the arterial $Po_2$. If it falls, they stimulate an increase in ventilation via the vagus (X) and glossopharyngeal nerves (IX) until the arterial $Po_2$ rises again. This occurs, for example, at high altitudes. The impulse frequency of the sensors increases sharply when the $Po_2$ drops below 13 kPa or 97mmHg (**peripheral ventilatory drive**). These changes are even stronger when $Pco_2$ and/or the $H^+$ concentration in blood also increase.
- **The central chemosensors**, in particular, in the medulla react to $Co_2$ and $H^+$ increases (=pH decrease) in the CSF. Ventilation is then increased until $Pco_2$ and the $H^+$ concentration in blood and CSF decrease to normal values. This mostly **central respiratory drive** is very effective in responding to acute changes. An increase in arterial $Pco_2$ from, say, 5 to 9 kPa increases the total ventilation $V_E$ by a factor often.

### Exercise

During **physical work**, the total ventilation increases due to (a) co-innervation of the respiratory centers (by collaterals of cortical efferent motor fibers) and (b) through impulses transmitted by proprioceptive fibers from the muscles.

### Non-feedback sensors and stimulants

Also play an important role in modulating the basic rhythm of respiration. They include:

- ***Irritant sensors*** in the bronchial mucosa, which quickly respond to lung volume decreases by increasing the respiratory rate (deflation reflex or Head's reflex), and to dust particles or irritating gases by triggering the cough reflex.
- ***J sensors*** of free C fiber endings on alveolar and bronchial walls; these are stimulated in pulmonary edema, triggering symptoms such as apnea and lowering the blood pressure.
- ***Higher central nervous centers*** such as the cortex, limbic system, hypothalamus or pons. They are involved in the expression of emotions like fear, pain and joy; in reflexes such as sneezing, coughing, yawning and swallowing; and in voluntary control of respiration while speaking, singing, etc.
- ***Pressosensors***, which are responsible for increasing respiration when the blood pressure decreases.
- ***Heat and cold sensors*** in the skin and thermoregulatory center. Increases (fever) and decreases in body temperature lead to increased respiration.
- ***Certain hormones*** also help to regulate respiration. Progesterone, for example, increases respiration in the second half of the menstrual cycle and during pregnancy.

# 90. Regulation of gastric and pancreatic secretion

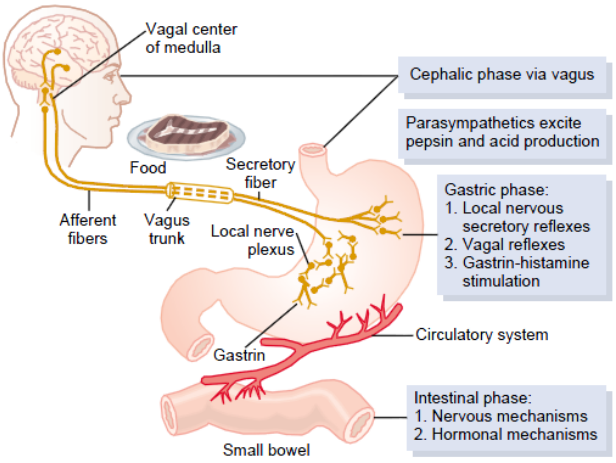
## *Stimulation of Gastric Acid Secretion*

The ***parietal cells***, located deep in the *oxyntic glands* of the main body of the stomach, are the only cells that secrete *hydrochloric acid*. As noted earlier in the chapter, 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 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.




## *Regulation of Pepsinogen Secretion*

*Pepsinogen* secretion by the peptic cells in the oxyntic glands 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 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*

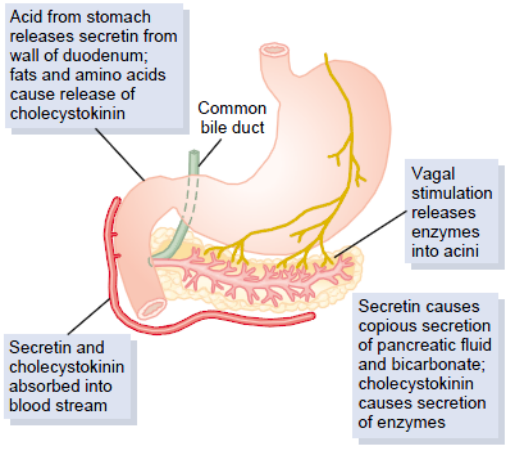
Three basic stimuli are important in causing pancreatic secretion:

**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.




Regulation of pancreatic secretion.

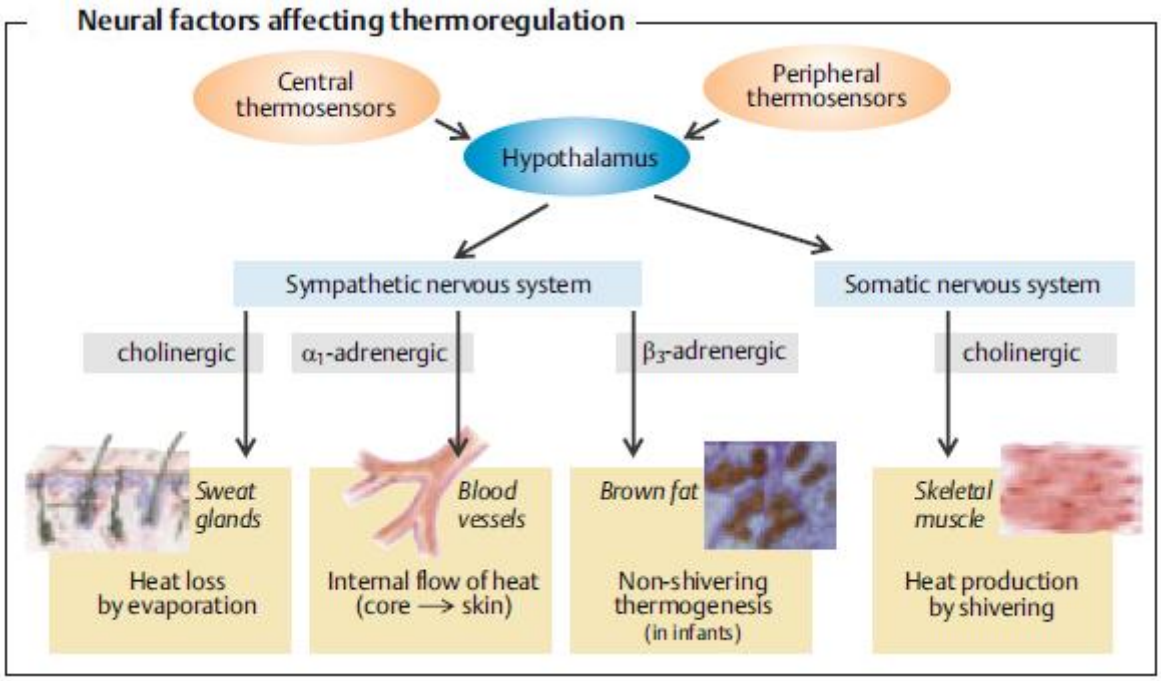
## 92. Thermoregulation

Thermoregulation maintains the **core temperature** at a constant **set point** (≈**37°C**) despite fluctuations in heat absorption, production, and loss. The core temperature exhibits *circadian variation*. It fluctuates by about 0.6 °C and is lowest around 3 a.m., and highest around 6 p.m..
The set point changes are controlled by an intrinsic *biological clock*. Extended set-point fluctuations happen during the menstrual cycle and fever.

The *control center* for body temperature and *central thermosensors* are located in the **hypothalamus**. Additional thermosensors are located in the spinal cord and skin. The control center compares the actual core temperature with the set-point value and initiates measures to counteract any deviations.

When the **core temperature rises** above the set point (e.g., during exercise), the body increases the internal heat flow by *dilating the blood vessels* of the skin. Moreover, arteriovenous anastomoses open in the periphery, especially in the fingers. The blood volume transported per unit time then not only conveys more heat, but also reduces the countercurrent exchange of heat between the arteries and their accompanying veins. In addition, venous return in the extremities is *re-routed* from the deep, accompanying veins to the superficial veins. **Sweat secretion** also increases. The evaporation of sweat cools the skin, thereby creating the core/skin temperature gradient needed for the internal heat flow. *Centralwarm sensors* emit the signals that activate the sweat glands. The efferent nerve fibers to the sweat glands are cholinergic fibers of the sympathetic nervous system.

When the **core temperature falls** below set point, the body checks heat loss by constricting the blood vessels in the shell and increases heat production by generating voluntary and involuntary (*shivering*) muscle activity. Although infants can quickly become hypothermic because of their high surface/volume ratio, their *brown fat* allows them to produce additional heat (*non-shivering thermogenesis*). Upon exposure to low ambient temperatures, these three mechanisms are activated by the cold receptors of the skin *before* the core temperature falls.



# 93. Regulation of renal functions

## Nervous and Hormonal Factors Increase the Effectiveness of Renal-Body Fluid Feedback Control

### *Sympathetic Nervous System Control of Renal Excretion: Arterial Baroreceptor and Low-Pressure Stretch Receptor Reflexes*

Because the kidneys receive extensive sympathetic innervation, changes in sympathetic activity can alter renal sodium and water excretion as well as regulation of extracellular fluid volume under some conditions. For example, when blood volume is reduced by hemorrhage, the pressures in the pulmonary blood vessels and other low-pressure regions of the thorax decrease, causing reflex activation of the sympathetic nervous system. This in turn increases renal sympathetic nerve activity, which has several effects to decrease sodium and water excretion: **(1)** constriction of the renal arterioles, with resultant decreased GFR; **(2)** increased tubular reabsorption of salt and water; and **(3)** stimulation of ***renin*** release and increased ***angiotensin II*** and ***aldosterone*** formation, both of which further increase tubular reabsorption.
Also, reflex inhibition of renal sympathetic activity may contribute to the rapid elimination of excess fluid in the circulation that occurs after eating a meal that contains large amounts of salt and water.

### *Role of Angiotensin II in Controlling Renal Excretion*

When sodium intake is elevated above normal, renin secretion is decreased, causing decreased angiotensin II formation. Because angiotensin II has several important effects in increasing tubular reabsorption of sodium, a reduced level of angiotensin II decreases tubular reabsorption of sodium and water, thus increasing the kidneys' excretion of sodium and water.

Conversely, when sodium intake is reduced below normal, increased levels of angiotensin II cause sodium and water retention and oppose reductions in arterial blood pressure that would otherwise occur.
Thus, changes in activity of the renin-angiotensin system act as a powerful amplifier of the pressure natriuresis mechanism for maintaining stable blood pressures and body fluid volumes.

### *Role of Aldosterone in Controlling Renal Excretion*

Aldosterone increases sodium reabsorption, especially in the cortical collecting tubules. The increased sodium reabsorption is also associated with increased water reabsorption and potassium secretion. Therefore, the net effect of aldosterone is to make the kidneys retain sodium and water but to increase potassium excretion in the urine.

The function of aldosterone in regulating sodium balance is closely related to that described for angiotensin II. That is, with reduction in sodium intake, the increased angiotensin II levels that occur stimulate aldosterone secretion, which in turn contributes to the reduction in urinary sodium excretion and, therefore, to the maintenance of sodium balance.

### *Role of ADH in Controlling Renal Water Excretion*

ADH plays an important role in allowing the kidneys to form a small volume of concentrated urine while excreting normal amounts of salt. This effect is especially important during water deprivation, which strongly elevates plasma levels of ADH that in turn increase water reabsorption by the kidneys and help to minimize the decreases in extracellular fluid volume and arterial pressure that would otherwise occur.

### *Role of Atrial Natriuretic Peptide in Controlling Renal Excretion*

Once released by the cardiac atria, ANP enters the circulation and acts on the kidneys to cause small increases in GFR and decreases in sodium reabsorption by the collecting ducts.

# 94. General principle of endocrine regulation

## Endocrine signaling

– Is a system of glands, each of which secretes a type of hormone into the bloodstream to regulate the body. A number of glands that signal each other in sequence is usually referred to as an axis, for example, the ***hypothalamic-pituitary-adrenal axis***.

– Typical endocrine glands are the **pituitary**, **thyroid**, and **adrenal glands**.

– In addition to the specialized endocrine organs mentioned above, many other organs that are part of other body systems, such as the **kidney**, **liver**, **heart** and **gonads**, have secondary endocrine functions. For example the kidney secretes endocrine hormones such as ***erythropoietin*** and ***renin***.

| Hormone | Abbreviation | Gland of Origin | Major Actions* |
|---|---|---|---|
| Thyrotropin-releasing hormone | TRH | Hypothalamus | Stimulates secretion of TSH and prolactin |
| Corticotropin-releasing hormone | CRH | Hypothalamus | Stimulates secretion of ACTH |
| Gonadotropin-releasing hormone | GnRH | Hypothalamus | Stimulates secretion of LH and FSH |
| Growth hormone releasing hormone | GHRH | Hypothalamus | Stimulates secretion of growth hormone |
| Somatotropin release-inhibiting hormone (somatostatin) | SRIF | Hypothalamus | Inhibits secretion of growth hormone |
| Prolactin-inhibiting factor (dopamine) | PIF | Hypothalamus | Inhibits secretion of prolactin |
| Thyroid-stimulating hormone | TSH | Anterior pituitary | Stimulates synthesis and secretion of thyroid hormones |
| Follicle-stimulating hormone | FSH | Anterior pituitary | Stimulates growth of ovarian follicles and estrogen secretion<br>Promotes sperm maturation (testes) |
| Luteinizing hormone | LH | Anterior pituitary | Stimulates ovulation, formation of corpus luteum, and synthesis of estrogen and progesterone (ovary)<br>Stimulates synthesis and secretion of testosterone (testes) |
| Growth hormone | GH | Anterior pituitary | Stimulates protein synthesis and overall growth |
| Prolactin | | Anterior pituitary | Stimulates milk production and breast development |
| Adrenocorticotropic hormone | ACTH | Anterior pituitary | Stimulates synthesis and secretion of adrenal cortical hormones |
| β-lipotropin | | Anterior pituitary | ? in human |
| Melanocyte-stimulating hormone | MSH | Anterior pituitary | Stimulates melanin synthesis (? humans) |
| Oxytocin | | Posterior pituitary | Milk ejection; uterine contraction |
| Antidiuretic hormone (vasopressin) | ADH | Posterior pituitary | Stimulates $H_2O$ reabsorption by renal collecting ducts |
| L-thyroxine<br>Triiodothyronine | $T_4$<br>$T_3$ | Thyroid gland | Skeletal growth; ↑ $O_2$ consumption; heat production; ↑ protein, fat, and carbohydrate use; maturation of nervous system (perinatal) |
| Glucocorticoids (cortisol) | | Adrenal cortex | Stimulates gluconeogenesis; anti-inflammatory; immunosuppression |
| Estradiol | | Ovary | Growth and development of female reproductive organs; follicular phase of menstrual cycle |
| Progesterone | | Ovary | Luteal phase of menstrual cycle |
| Testosterone | | Testes | Spermatogenesis; male secondary sex characteristics |
| Parathyroid hormone | PTH | Parathyroid gland | ↑ serum [$Ca^{2+}$]; ↓ serum [phosphate] |
| Calcitonin | | Thyroid gland (parafollicular cells) | ↓ serum [$Ca^{2+}$] |
| Aldosterone | | Adrenal cortex | ↑ renal $Na^+$ reabsorption<br>↑ renal $K^+$ secretion; ↑ renal $H^+$ secretion |
| 1,25-dihydroxycholecalciferol | | Kidney (activation site) | ↑ intestinal $Ca^{2+}$ absorption; ↑ bone mineralization |
| Insulin | | Pancreas (beta cells) | ↓ blood [glucose]; ↓ blood [amino acid]; ↓ blood [fatty acid] |
| Glucagon | | Pancreas (alpha cells) | ↑ blood [glucose]; ↑ blood [fatty acid] |
| Human chorionic gonadotropin | HCG | Placenta | ↑ estrogen and progesterone synthesis in corpus luteum of pregnancy |
| Human placental lactogen | HPL | Placenta | Same actions as growth hormone and prolactin during pregnancy |

# 95. Sympathetic nervous system (overview)

- Part of the autonomic nervous system

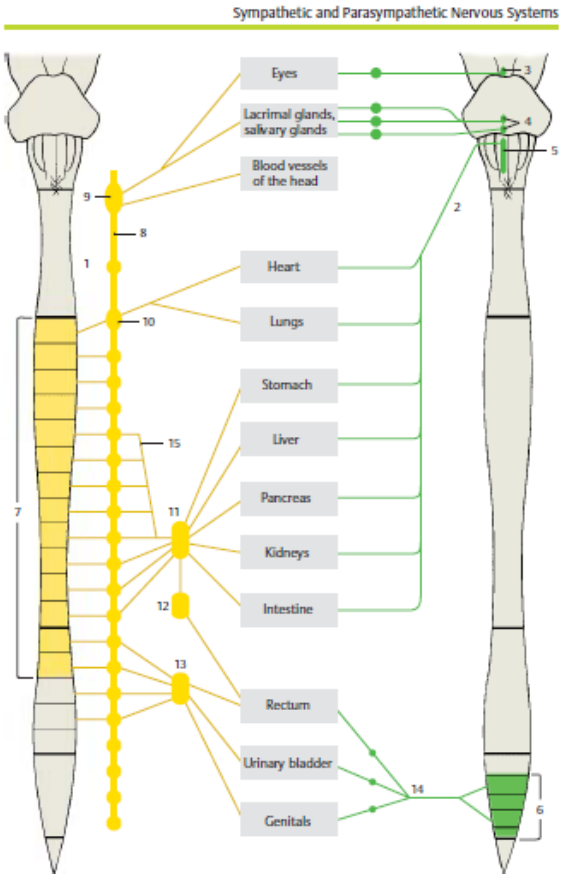
The **vegetative** or **autonomic nervous system** supplies the internal organs and their coverings.

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.

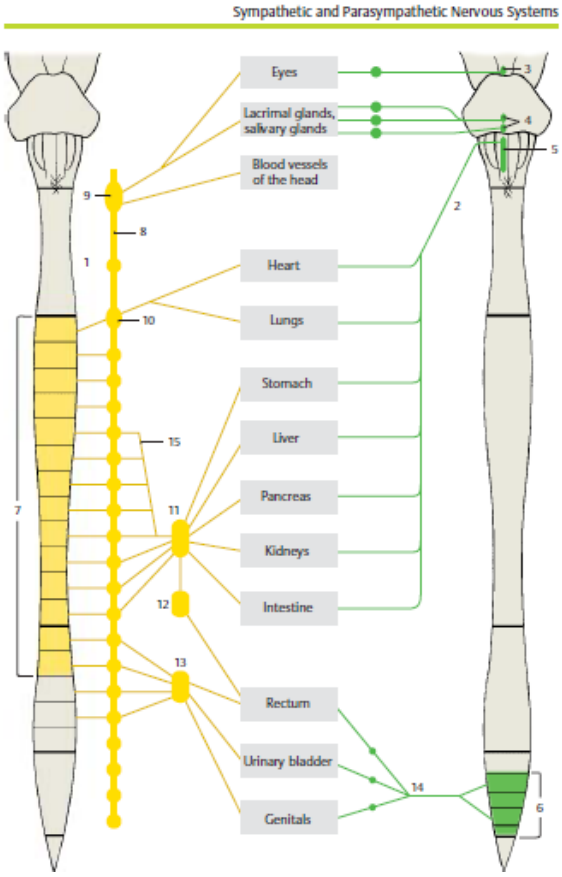
> The *middle cervical ganglion* may be absent, and the *inferior cervical ganglion* has in most cases fused with the first thoracic ganglion to form the **stellate ganglion**. Its postganglionic fibers form plexuses around the subclavian artery and around the vertebral artery. Fiber bundles connecting 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.*

# 96. 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.

# 97. Adaptations to extreme environmental conditions

## Respiratory system

**Adaptation to high altitude**

1. **Alveolar $P_{O_2}$** is decreased at high altitude because the barometric pressure is decreased. As a result, arterial $P_{O_2}$ is also decreased **(hypoxemia).**
2. Hypoxemia stimulates the peripheral chemoreceptors and increases the ventilation rate **(hyperventilation).** This hyperventilation produces **respiratory alkalosis,** which can be treated by administering **acetazolamide.**
3. Hypoxemia also stimulates renal production of **erythropoietin,** which increases the production of RBCs. As a result, there is **increased hemoglobin concentration**, increased $O_2$-carrying capacity of blood, and increased $O_2$ content of blood.
4. **2,3-DPG concentrations are increased,** shifting the hemoglobin–$O_2$ dissociation curve to the right. There is a resulting decrease in affinity of hemoglobin for $O_2$ that facilitates unloading of $O_2$ in the tissues.
5. **Pulmonary vasoconstriction** is another result of hypoxemia (hypoxic vasoconstriction). Consequently, there is an increase in pulmonary arterial pressure, increased work of the right side of the heart against the higher resistance, and hypertrophy of the right ventricle.

### *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.

### *Thermorgulation*

The *control center* for body temperature and *central thermosensors* are located in the **hypothalamus**. Additional thermosensors are located in the spinal cord and skin. The control center compares the actual core temperature with the set-point value and initiates measures to counteract any deviations.

When the **core temperature rises** above the set point (e.g., during exercise), the body increases the internal heat flow by *dilating the blood vessels* of the skin. Moreover, arteriovenous anastomoses open in the periphery, especially in the fingers. The blood volume transported per unit time then not only conveys more heat, but also reduces the countercurrent exchange of heat between the arteries and their accompanying veins. In addition, venous return in the extremities is *re-routed* from the deep, accompanying veins to the superficial veins. **Sweat secretion** also increases. The evaporation of sweat cools the skin, thereby creating the core/skin temperature gradient needed for the internal heat flow. *Centralwarm sensors* emit the signals that activate the sweat glands. The efferent nerve fibers to the sweat glands are cholinergic fibers of the sympathetic nervous system.

When the **core temperature falls** below set point, the body checks heat loss by constricting the blood vessels in the shell and increases heat production by generating voluntary and involuntary (*shivering*) muscle activity. Although infants can quickly become hypothermic because of their high surface/volume ratio, their *brown fat* allows them to produce additional heat (*non-shivering thermogenesis*). Upon exposure to low ambient temperatures, these three mechanisms are activated by the cold receptors of the skin *before* the core temperature falls.

# 98. Adaption to exercise

## 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 is 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 relationship, IV D 5).
   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 muscle 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 $P_{O_2}$ and $P_{CO_2}$ do not change** during exercise.
   - **Arterial pH** does not change during moderate exercise, although it may decrease during strenuous exercise because of **lactic acidosis.**
3. On the other hand, **venous $P_{CO_2}$ 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.**

## *Sources of ATP during muscular work*

- **in the first 10 sec** – ATP itself and 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 pyruvate → 2 acetyl-CoA → **38 ATP**
- **After 2 hours** – aerobic oxidation of FA
  stearic acid → 9 acetyl-CoA → **146 ATP**
  palmitic acid → 8 acetyl-CoA → **129 ATP**

# 99. Integration of nervous and hormonal regulation

Unlike unicellular organisms, multicellular organisms have numerous specialized groups of cells and organs, the many different functions of which must be expediently *integrated* and *coordinated*. In mammals, the **nervous system** and **endocrine system** are chiefly responsible for control and integration, while the **immune system** serves as an information system for corporal immune defense. These systems communicate by way of *electrical and/or chemical* **signals**.

Nerve impulses and hormonal signals serve to **control and regulate** the metabolism and internal milieu (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.

**Nerve fibers** are specifically adapted for rapid transmission of finely graded signals.

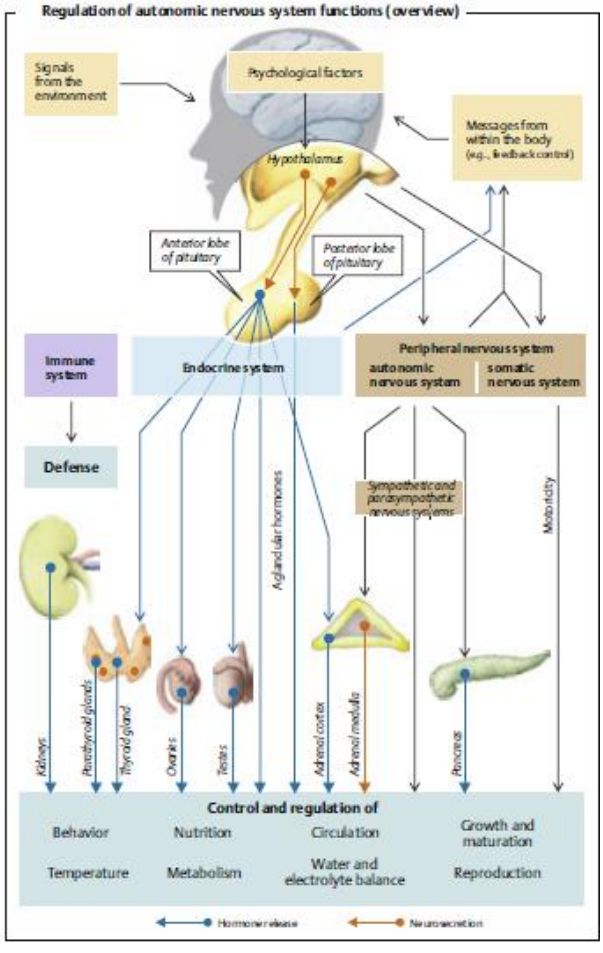
The nervous system consists of the **central nervous system** (CNS) and **peripheral nervous system** . The latter consists of:

- The **somatic nervous system**, which conducts impulses from non-visceral sensors to a center (afferent neurons) and controls the skeletal musculature (efferent neurons).
- The **peripheral autonomic nervous system**, which consists of efferent neurons and mainly functions to control the circulatory system, inner organs and sexual functions. It is supplemented by:
  - **Visceral afferent neurons**, i.e., nerve fibers that conduct signals from inner organs to a center. They are usually located in the same nerves as autonomous fibers (e.g., in vagus nerve); and the
  - **Enteric nervous system**, which integrates the local functions of the esophagus, stomach and gut.

## Hormones

Like neurotransmitters and the immune system's cytokines and chemokines, hormones serve as *messenger substances* that are mainly utilized for *slower, long-term* transmission of signals.

- **Endocrine hormones** are carried by the blood to target structures great distances away.
- **Paracrine hormones** (and other paracrine transmitters) only act on cells in the immediate vicinity of the cells from which they are released.
- Hormones that act on the cells that produced the messenger substance are referred to as **autocrine hormones**.




Hormones work closely with the nervous system to regulate *digestion, metabolism, growth, maturation, physical* and *mental development, maturation, reproduction, adaptation,* and the internal milieu of the body (*homeostasis*). Most of these actions are predominately autonomous functions subject to central control by the **hypothalamus**, which is controlled by higher centers of the brain

## Neurotransmitters

Are released at chemical **synapses** of nerve endings transmit signals to postsynaptic nerve fibers, muscles or glands. Some neuropeptides released by presynaptic neurons also exert their effects in neighboring synapses, resulting in a kind of "paracrine" action.

Neurons can also secrete hormones, e.g., epinephrine, oxytocin and antidiuretic hormone. Some transmitter substances of the immune system, e.g. thymosin and various cytokines, also have endocrine effects.

# Part B

## 1. Blood composition – values.

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 called **formed elements**.

***THE 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.

**Hematocrit:**
the volume of blood cells per unit volume of blood - cca 45 % of blood cells

Blood cells (formed elements)
- Red blood cells – **erythrocytes** 4 – 6 millions/ 1 µl **of blood**
- White blood cells – **leukocytes** 5,000 – 9,000 / 1 µl
- Platelets – **thrombocytes** 150,000 – 250,000/ 1 µl

ERYTHROCYTES
- 4 – 6 million/µl
- Shape: biconcave disc, dumble-shaped *(in cross section)*
- Size: 7.4 µm in diameter (= normocyte)
- Lifespan: 120 days

LEUKOCYTES

| Granulocytes: | Agranulocytes |
|---|---|
| - neutrophils<br>- eosinophils<br>- basophils | - lymphocytes<br>- monocytes |

Neutrophil granulocytes (neutrophils)
- 71 % of all white blood cells (DWCC)
- Ø 10 – 12 µm

Eosinophil granulocytes (eosinophils)
- 1– 4 % of all white blood cells (DWCC)
- Ø 12 – 14 µm

Basophil granulocytes (basophils)
- up to 1 % of all white blood cells (DWCC)
- Ø up to 10 µm

LYMPHOCYTES ***20% of all WBCs***
- Classification:
  - according to origin – T-Ly (*thymus*), B-Ly (bone marrow ≅ bursa of Fabricius in birds)
  - according to the size – small (Ø 8 µm), middle-sized (Ø 10-12 µm), large (Ø 16-18 µm),

MONOCYTES ***5 % of all WBCs***
- Ø 15 – 20 µm

THROMBOCYTES (blood platelets)
- 150,000 – 300,000 / 1 µl of blood
- thrombocytosis X thrombocytopenia
- - are not cells, but cytoplasmic fragments of large cell (megakaryocyte) in bone marrow
- shape: flattened discoid plate
- size: 2 – 4 µm

# 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. In some lower animals, hemoglobin circulates as free protein in the plasma, not enclosed in red blood cells. When it is free in the plasma of the human being, about 3 per cent of it leaks through the capillary membrane into the tissue spaces or through the glomerular membrane of the kidney into the glomerular filtrate each time the blood passes through the capillaries. Therefore, for hemoglobin to remain in the human blood stream, it must exist inside red blood cells.

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 several thousand fold. 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 and a thickness of 2.5 micrometers at the thickest point and 1 micrometer or less in the center. The average volume of the red blood cell is 90 to 95 cubic micrometers.

The shapes of red blood cells can change remarkably as the cells squeeze through capillaries.

### *Concentration of Red Blood Cells in the Blood*

In normal men, the average number of red blood cells per cubic millimeter is 5,200,000 (±300,000); in normal women, it is 4,700,000 (±300,000). Persons living at high altitudes have greater numbers of red blood cells.

### *Quantity of Hemoglobin in the Cells*

Red blood cells have the ability to concentrate hemoglobin in the cell fluid up to about 34 grams in each 100 milliliters of cells.

**RETICULOCYTES** are immature erythrocytes released from the bone marrow into the peripheral blood. They contain some rests of organelles (mainly ribosomes, but not nucleus) which are loosed during maturation (24 – 48 hours) and reticulocytes transform into mature erythrocytes. Reticulocytes represent 0.5 – 1.5 % of all erytrhocytes in peripheral blood. Reticulocytosis – increased number of reticulocytes, a sign of increased releasing of these immature cells from bone marrow. Anemia – decreased number of erythrocytes, polyglobulia or polycythemia – increased number of erythrocytes.

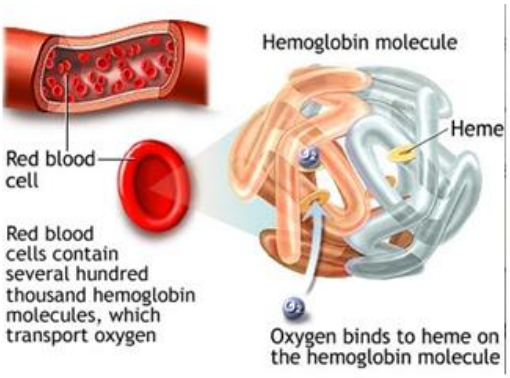
## *Haemolysis*

Is the breaking open of red blood cells and the release of hemoglobin into the surrounding fluid (plasma, *in vivo*).

***In vivo*** (inside the body): hemolysis, which can be caused by a large number of conditions, can lead to anemia.

***In vitro*** (outside the body): hemolysis can be an important unwanted effect in medical tests and can cause inaccurate results, because the contents of hemolysed red blood cells are included with the plasma. The concentration of potassium inside red blood cells is much higher than in the plasma and so an elevated potassium is usually found in biochemistry tests of hemolysed blood. If as little as 0.5% of the red blood cells are hemolysed the serum will have a visually obvious pinkish colour, due to hemoglobin.

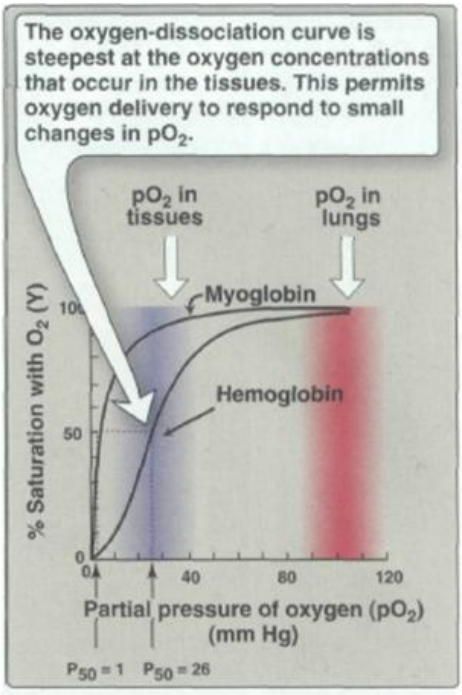
## 3. Haemoglobin and its derivates




### Hemoglobin

- is a globular protein of four subunits
- each subunit contains a heme portion, which is a complex of **protoporphyrin IX** and **ferrous iron ($Fe^{2+}$)**.
- each subunit is a polypeptide chain. The hemoglobin tetramer can be envisioned as being composed of two identical dimers, $(\alpha\beta)_1$ and $(\alpha\beta)_2$.

**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 group increases the oxygen affinity of the remaining 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, as shown by the steep upward curve in the region near 20 to 30 mm Hg.




**Shift of the oxygen-dissociation curve:**
Hemoglobin from which 2,3-BPG has been removed has a high affinity for oxygen. However, as seen in the red blood cell, the presence of 2,3-BPG significantly reduces the affinity of hemoglobin for oxygen, shifting the oxygen-dissociation curve to the right (Figure This reduced affinity enables hemoglobin to release oxygen efficiently at the partial pressures found in the tissues.

### Minor hemoglobins

It is important to remember that human hemoglobin A **(HbA)** is just one member of a functionally and structurally related family of proteins, the hemoglobins (table on the right) 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 **$HbA_2$**, 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, **$HbA_{1c}$**.

| Form | Chain composition | Fraction of total hemoglobin |
|---|---|---|
| HbA | $\alpha_2\beta_2$ | 90% |
| HbF | $\alpha_2\gamma_2$ | <2% |
| $HbA_2$ | $\alpha_2\delta_2$ | 2–5% |
| $HbA_{1c}$ | $\alpha_2\beta_2$-glucose | 3–9% |

### Fetal hemoglobin [hemoglobin F (HbF)]

- in **fetal hemoglobin**, the **B chains are replaced by γ chains.**
- the $O_2$ affinity of fetal hemoglobin is higher than the $O_2$ affinity of adult hemoglobin (left-shift) because 2,3-diphosphoglycerate (DPG) binds less avidly.
- because the $O_2$ affinity fo fetal hemoglobin is higher than the $O_2$ affinity of adult hemoglobin, $O_2$ movement from mother to fetus is facilitated.

# 4. Erytropoesis

## *Erythropoesis*

- **Proerythroblast**
- **Basophilic erythroblast**
- **Polychromatophilic erythroblast**
- **Ortochromatic erythroblast**
- **Reticulocyte**

**Process - during repeated mitoses:**

☞ cell size decreases from 20 μm to 8 μm 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)


Proerythroblast

**Proerythroblast**

- ∅ 15 – 20 μm
- basophilic cytoplasm forms iregular, „ear-shaped" projections from the surface of the cell
- spherical nucleus contains 2 – 3 nucleoli


Basophilic erythroblast

**Basophilic erythroblast**

- ∅ 16 μm
- basophilic cytoplasm
- condensation of nuclear chromatin begins
- absence of nucleoli


Polychromatophilic erythroblast

**Polychromatophilic erythroblast**

- ∅ 12 μm
- production of hemoglobin begins and causes irregular staining of cytoplasm – partly basophilic, partly acidophilic
- condensed chromatin


Orthochromatophilic erythroblast

**Ortochromatophilic erythroblast**

- ∅ 9 – 10 μm
- acidophilic cytoplasm with hemoglobin
- pycnotic nucleus in excentric position before enucleation


Reticulocyte

**Reticulocyte**

- ∅ 8 μm
- acidophilic cytoplasm with hemoglobin
- without nucleus, but with the rests of some organelles – substantia reticulofilamentosa


Erythrocyte

## 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

## 10. Blood groups antigens

A person's blood group is determined by the type of antigen (certain glycolipids) present on the red blood cells (RBCs).

In the **AB0 system**, the antigens are A and B. In blood type A, antigen A (on RBC) and anti-B antibody (in serum) are present; in type B, B and anti-A are present; in type AB, A and B are present, no antibody; in type 0 (zero), no antigen but anti-A and anti-B are present.

When giving a **blood transfusion**, it is important that the blood groups of donor and recipient match, i.e. that the RBCs of the donor (e.g. A) do not come in contact with the respective antibodies (e.g. anti-A) in the recipient. If the donor's blood is the wrong type, *agglutination* (cross-linking by IgM) and *hemolysis* (bursting) of the donor's RBCs will occur. Donor and recipient blood types must therefore be determined and *cross-matched* prior to a blood transfusion.

Since AB0 antibodies belong to the IgM class, they usually do not cross the placenta.

In the **Rh system**, antibodies against rhesus antigens (C, D, E) on RBCs do not develop unless *prior sensitization* has occurred. D is by far the most antigenic. A person is Rh-positive ($Rh^+$) when D is present on their RBCs (most people), and Rh-negative ($Rh^-$) when D is absent. Anti-D antibodies belong to the IgG class of immunoglobulins, which are capable of crossing the placenta.

$Rh^-$ individuals can form anti-$Rh^+$ (= anti-D) antibodies, e.g., after sensitization by a mismatched blood transfusion or of an $Rh^-$mother by an $Rh^+$ fetus. Subsequent exposure to the mismatched blood leads to a severe antigen-antibody reaction characterized by intravascular agglutination and hemolysis.

**Blood Types with Their Genotypes and Their Constituent Agglutinogens and Agglutinins**

| Genotypes | Blood Types | Agglutinogens | Agglutinins |
|---|---|---|---|
| OO | O | — | Anti-A and Anti-B |
| OA or AA | A | A | Anti-B |
| OB or BB | B | B | Anti-A |
| AB | AB | A and B | — |

**Blood Typing, Showing Agglutination of Cells of the Different Blood Types with Anti-A or Anti-B Agglutinins in the Sera**

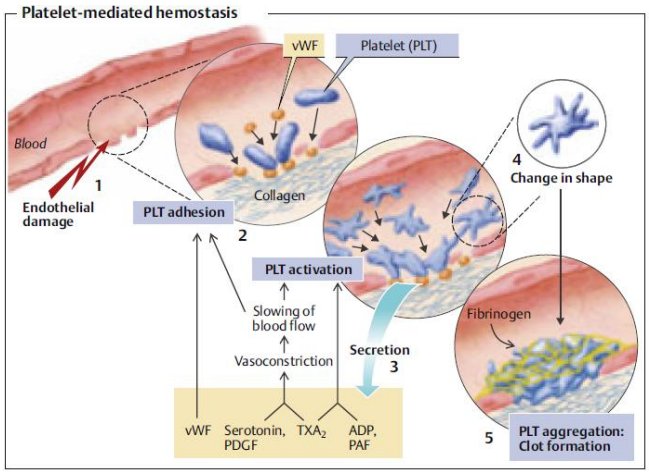
| Red Blood Cell Types | Sera | |
|---|---|---|
| | *Anti-A* | *Anti-B* |
| O | – | – |
| A | + | – |
| B | – | + |
| AB | + | + |

## 11. Function of platelets

**Platelets**, or **thrombocytes** are small, irregularly-shaped anuclear cell fragments which are derived from fragmentation of precursor megakaryocytes. 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*, which we discuss later in relation to blood coagulation; 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.

When an endothelial injury occurs, platelets adhere to subendothelial collagen fibers bridged by **von Willebrand's factor** (vWF), which is formed by endothelial cells and circulates in the plasma complexed with **factor VIII**. Glycoprotein complex **GP Ib/IX** on the platelets are *vWF receptors*. This ***adhesion*** activates platelets. They begin to release substances, some of which promote platelet adhesiveness (vWF). Others like **serotonin**, **platelet-derived growth factor (PDGF)** and **thromboxane $A_2$ ($TXA_2$)** promote vasoconstriction. Vasoconstriction and platelet *contraction* slow the blood flow. Mediators released by platelets enhance platelet activation and attract and activate more platelets: **ADP**, $TXA_2$, **platelet-activating factor (PAF)**. The shape of activated platelets changes drastically. Discoid platelets become spherical and exhibit pseudopodia that intertwine with those of other platelets. This ***platelet aggregation*** is further enhanced by **thrombin** and stabilized by **GP IIb/IIIa**. Once a platelet changes its shape, GP IIb/IIIa is expressed on the platelet surface, leading to fibrinogen binding and platelet aggregation. GP IIb/IIIa also increases the adhesiveness of platelets, which makes it easier for them to stick to subendothelial *fibronectin*.



# 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 vasoconstriction 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 $A_2$***.

## Formation of the Platelet Plug

When an endothelial injury occurs, platelets adhere to subendothelial collagen fibers bridged by **von Willebrand's factor** (vWF), which is formed by endothelial cells and circulates in the plasma complexed with **factor VIII**. Glycoprotein complex **GP Ib/IX** on the platelets are *vWF receptors*. This ***adhesion*** activates platelets. They begin to release substances, some of which promote platelet adhesiveness (vWF). Others like **serotonin**, **platelet-derived growth factor (PDGF)** and **thromboxane $A_2$ ($TXA_2$)** promote vasoconstriction. Vasoconstriction and platelet *contraction* slow the blood flow. Mediators released by platelets enhance platelet activation and attract and activate more platelets: **ADP**, $TXA_2$, **platelet-activating factor (PAF)**. The shape of activated platelets changes drastically. Discoid platelets become spherical and exhibit pseudopodia that intertwine with those of other platelets. This ***platelet aggregation*** is further enhanced by **thrombin** and stabilized by **GP IIb/IIIa**. Once a platelet changes its shape, GP IIb/IIIa is expressed on the platelet surface, leading to fibrinogen binding and platelet aggregation. GP IIb/IIIa also increases the adhesiveness of platelets, which makes it easier for them to stick to subendothelial *fibronectin*.

## 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.

## Fibrous Organization or Dissolution of the Blood Clot

Once a blood clot has formed, it can follow one of two courses: **(1)** It can become invaded by *fibroblasts*, which subsequently form connective tissue all through the clot, or **(2)** it can dissolve. The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed (which is promoted at least partially by *growth factor* secreted by platelets). This continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.

Conversely, when excess blood has leaked into the tissues and tissue clots have occurred where they are not needed, special substances within the clot itself usually become activated. These function as enzymes to dissolve the clot.

## 13. Anticlotting mechanism

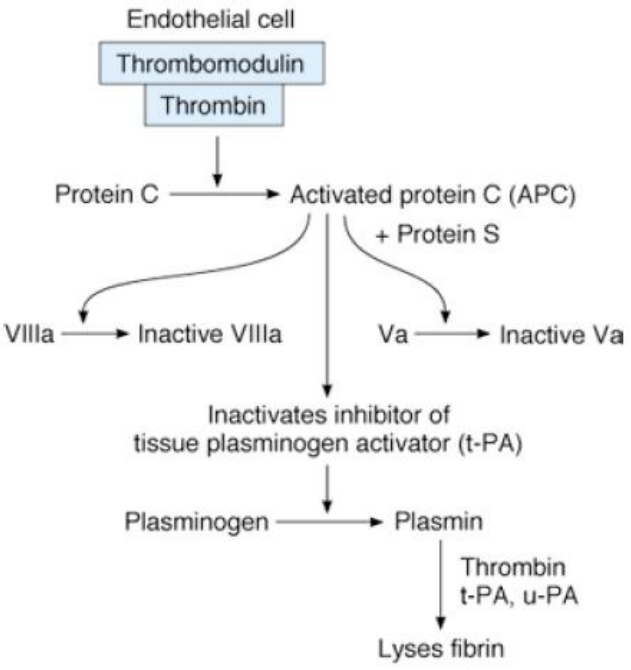
The tendency of blood to clot is balanced in vivo by limiting reactions that tend to prevent clotting inside the blood vessels and to break down any clots that do form. These reactions include the interaction between the platelet-aggregation effect of ***thromboxane $A_2$*** and the antiaggregation effect of **prostacyclin**, which causes clots to form at the site when a blood vessel is injured but keeps the vessel lumen free of clot.

**Antithrombin III** is a circulating protease inhibitor that binds to the serine proteases in the coagulation system, blocking their activity as clotting factors. This binding is facilitated by **heparin**, a naturally occurring anticoagulant that is a mixture of sulfated polysaccharides. The clotting factors that are inhibited are the active forms of factors IX, X, XI, and XII.

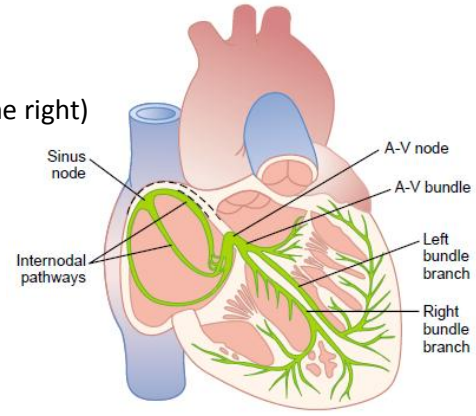
The endothelium of the blood vessels also plays an active role in preventing the extension of clots into blood vessels. All endothelial cells except those in the cerebral microcirculation produce **thrombomodulin**, a thrombin-binding protein, and express it on their surface. In the circulating blood, thrombin is a procoagulant that activates factors V and VIII, but when it binds to thrombomodulin, it becomes an anticoagulant in that the thrombomodulin-thrombin complex activates protein C. **Activated protein C (APC)**, along with its cofactor protein S, inactivates factor V and VII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin.

**Plasmin (fibrinolysis)** is the active component of the **plasminogen (fibrinolytic) system**. This enzyme lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDP) that inhibit thrombin. Plasmin is formed from its inactive precursor, plasminogen, by the action of thrombin and **tissue-type plasminogen activator (t-PA)**. It is also activated by **urokinase-type plasminogen activator (u-PA)**.

Plasminogen receptors are located on the surface of many different types of cells and are plentiful on endothelial cells. When plasminogen binds to its receptors, it becomes activated, so intact blood vessel walls are provided with a mechanism that discourages clot formation.



# 14. Conducting system of the heart

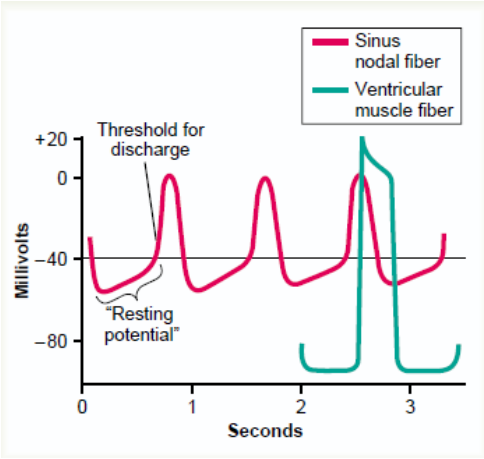



## Specialized Excitatory and Conductive System of the Heart (figure on the right)

### *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.

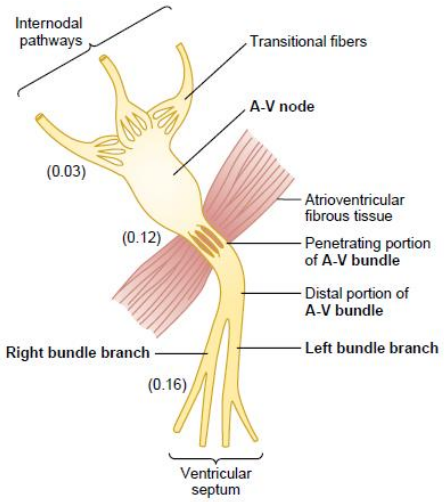
### Automatic Electrical Rhythmicity of the Sinus Fibers




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.

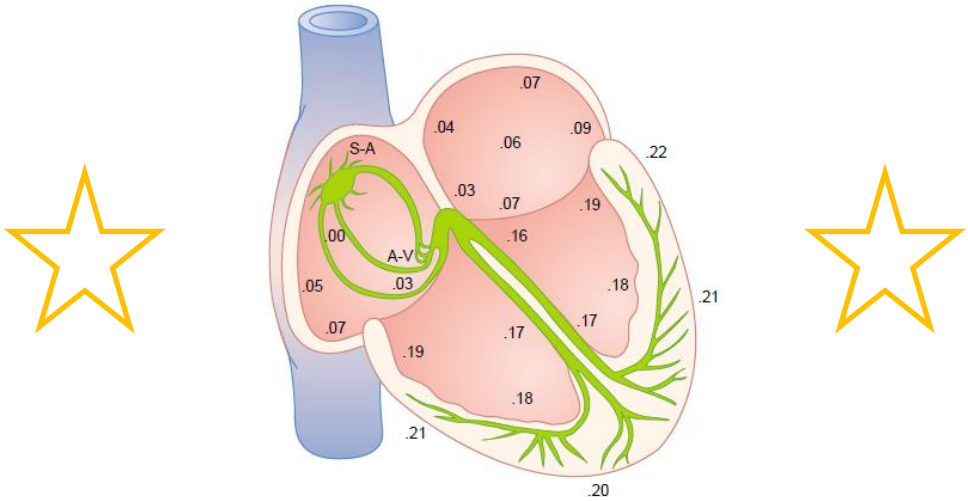



### *Self-Excitation of Sinus Nodal Fibers*

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.*

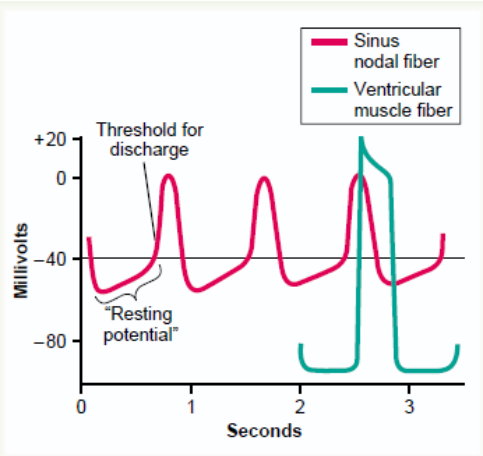
Last, we must explain why this new state of hyperpolarization is not maintained forever. The reason is that during the next few tenths of a second after the action potential is over, progressively more and more potassium channels close. The inward-leaking sodium and calcium ions once again overbalance 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.




**IMPORTANT! → Know by heart !!**

## 15. Cardiac automaticity (prefer to q. 14)

Some cardiac fibers have the capability of *self-excitation*.




***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.

# 16. Spread and retreat of excitation wavefront

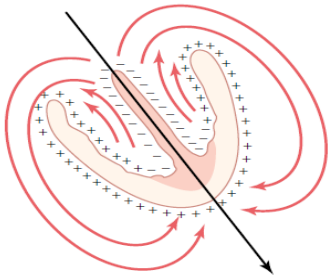
### Spread of Cardiac Excitation

Depolarization initiated in the SA node spreads radially through the atria, then converges on the AV node. Atrial depolarization is complete in about 0.1 s. Because conduction in the AV node is slow there is a delay of about 0.1 s (AV nodal delay) before excitation spreads to the ventricles. This delay is shortened by stimulation of the sympathetic nerves to the heart and lengthened by stimulation of the vagi. From the top of the septum, the wave of depolarization spreads in the rapidly conducting Purkinje fibers to all parts of the ventricles in the 0.08-0.1 s. In humans, depolarization of the ventricular muscle starts at the left side of the interventricular septum and moves first to the right across the midportion of the septum. The wave of depolarization then spreads down the septum to the apex of the heart. It returns along the ventricular walls to the AV groove, proceeding from the endocardial to the epicardial surface. The last parts of the heart to be depolarized are the posterobasal portion of the left ventricle, the pulmonary conus, and the uppermost portion of the septum.

# 17. Electric vector of the heart. Vectocardiography. (Guyton chap. 12)

### Use of Vectors to Represent Electrical Potentials

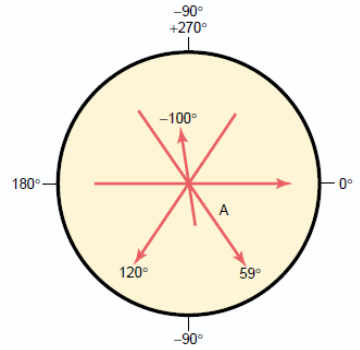
A vector is an arrow that points in the direction of the electrical potential generated by the current flow, *with the arrowhead in the positive direction.* Also, by convention, the length of the arrow is drawn *proportional to the voltage of the potential.*



Mean vector through the partially depolarized ventricles.

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.




### Vectocardigram

The so-called *vectorcardiogram* depicts these changes at different times during the cardiac cycle, as shown in Figure 12–10.

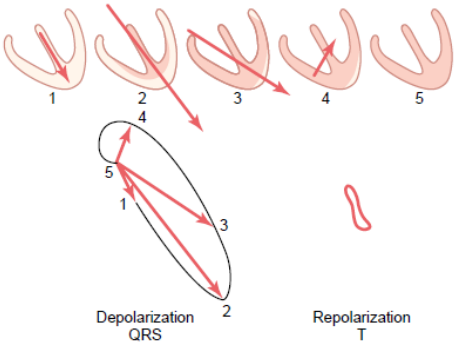
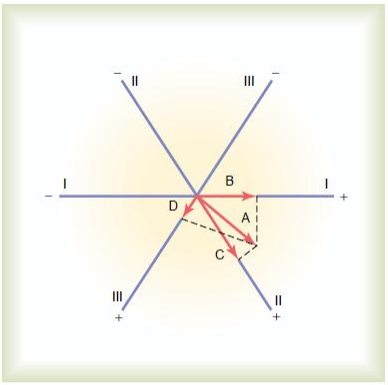



**Figure 12–10**

QRS and T vectorcardiograms.




**Vectorial Analysis of Potentials in the Three Standard Bipolar Limb Leads**

# 18. Specific features of cardiac metabolism

Most important, 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

The heart, is actually two separate pumps: a ***right heart*** that pumps blood through the lungs, and a ***left heart*** that pumps blood through the peripheral organs. In turn, each of these hearts is a pulsatile two-chamber pump composed of an *atrium* and a *ventricle.* Each atrium is a weak primer pump for the ventricle, helping to move blood into the ventricle. The ventricles then supply the main pumping force that propels the blood either (1) through the pulmonary circulation by the right ventricle or (2) through the peripheral circulation by the left ventricle.

## Physiology of Cardiac Muscle

The heart is composed of three major types of cardiac muscle: ***atrial muscle, ventricular muscle,*** and specialized ***excitatory*** and ***conductive muscle*** fibers. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer. Conversely, the specialized excitatory and conductive fibers contract only feebly because they contain few contractile fibrils; instead, they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart.

### *Cardiac Muscle as a Syncytium*

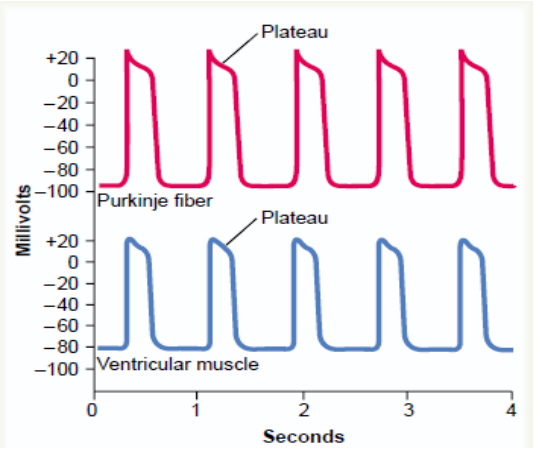
At each intercalated disc the cell membranes fuse with one another in such a way that they form permeable "communicating" junctions (gap junctions) that allow almost totally free diffusion of ions.

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 throughout the latticework interconnections.

The heart actually is composed of two syncytiums: the ***atrial syncytium*** and the ***ventricular syncytium.*** This division of the muscle of the heart into two functional syncytiums allows the atria to contract a short time ahead of ventricular contraction, which is important for effectiveness of heart pumping.

### ! Action Potentials in Cardiac Muscle

The *action potential* recorded in a ventricular muscle fiber, averages about 105 millivolts, which means that the intracellular potential rises from a very negative value, about -85 millivolts, 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*** as shown in the figure, 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.




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 and **(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.

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. 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 do close at the end of 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions 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.

> 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. Also, inside the T tubules is a large quantity of *mucopolysaccharides* that are *electronegatively* charged and bind an abundant store of calcium ions, keeping these always available for diffusion to the interior of the cardiac muscle fiber when a T tubule action potential appears.

## 20. Difference 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***

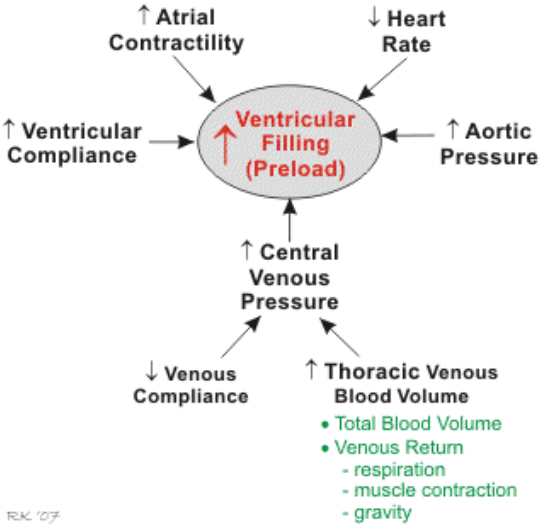
Physical examination can reveal pitting peripheral ***edema***, ascites, and hepatomegaly. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by the hepatojugular reflux. If the right ventriclar pressure is increased, a *parasternal heave* may be present, signifying the compensatory increase in contraction strength.

# 21. Determinants of cardiac performance: preload, afterload, inotropy

The heart *autonomously* responds to changes in ventricular volume load or aortic pressure load by adjusting the stroke volume (SV) in accordance with the myocardial *preload* (resting tension). The FSM also functions to maintain an equal SV in both ventricles to prevent congestion in the pulmonary or systemic circulation.

### Preload change

When the volume load (preload) *increases*, the start of isovolumic contraction shifts to the right along the passive P–V curve. This increases end-diastolic volume (EDV), stroke volume (SV), cardiac work and end-systolic volume (ESV).



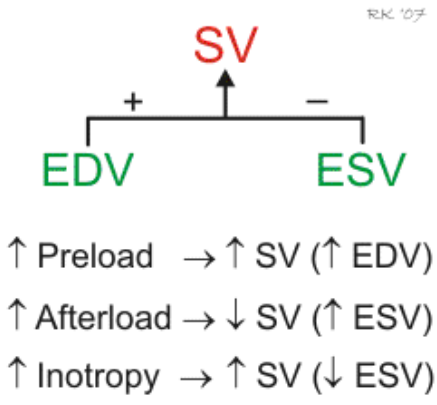

### Afterload change

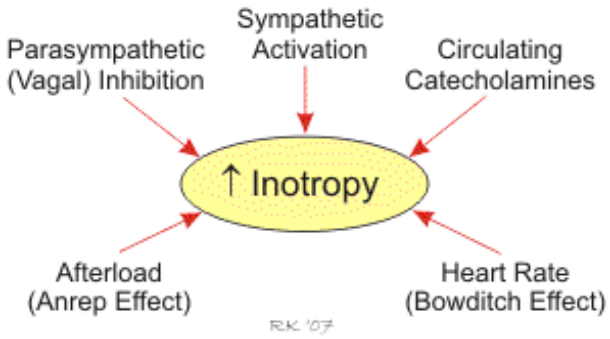
When the aortic pressure load (afterload) *increases*, the aortic valve will not open until the pressure in the left ventricle has risen accordingly. Thus, the SV in the short transitional phase ($SV_t$) will decrease, and ESV will rise ($ESV_t$). Consequently, the start of the isovolumic contraction shifts to the right along the passive P–V curve. SV will then normalize despite the increased aortic pressure, resulting in a relatively large increase in ESV.

### 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 ($\beta_1$-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.




**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.

# 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. As an example of normal reserve, during severe exercise the cardiac output of a healthy young adult can rise to about five times normal; this is an increase above normal of 400 per cent—that is, *a cardiac reserve of 400 per cent*.

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*

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.

## Cardiac failure ("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 **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 lead 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. When a larger arterior venous fistula is present, in *thyrotoxicosis*, and in thiamine deficiency, cardiac output may be elevated in absolute terms but still be inadequate to meet the needs of the tissues **(high-output failure).**

### 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 positively 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.

## Cardiac Cycle

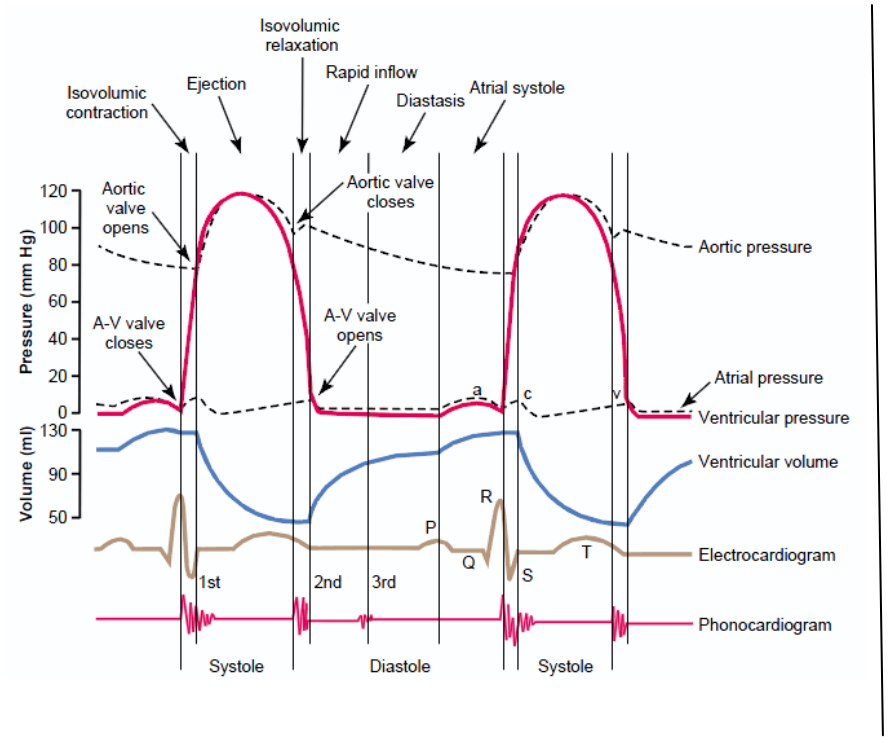
The cardiac events that occur from the beginning of one heartbeat to the beginning of the next are called the *cardiac cycle.* Each cycle is initiated by spontaneous generation of an action potential in the *sinus node*. This node is located in the superior lateral wall of the right atrium near the opening 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.

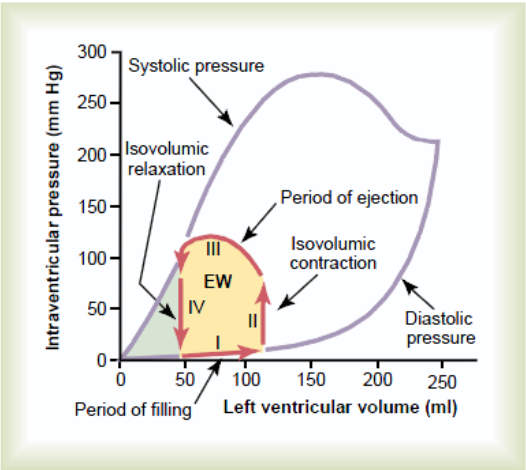
## Diastole and Systole

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***.

The figure below (left) shows the different events during the cardiac cycle for the left side of the heart. The top three curves show the pressure changes in the aorta, left ventricle, and left atrium, respectively. The fourth curve depicts the changes in left ventricular volume, the fifth the *electrocardiogram*, and the sixth a *phonocardiogram*, which is a recording of the sounds produced by the heart—mainly by the heart valves—as it pumps.




### *Pressure-volume loop*




### *Relationship of the Electrocardiogram to the Cardiac Cycle*

The ***P wave*** is caused by *spread of depolarization* through the atria, and this is followed by atrial contraction, which causes a slight rise in the atrial pressure curve immediately after the electrocardiographic P wave.

About 0.16 second after the onset of the P wave, the ***QRS waves*** appear as a result of electrical depolarization of the ventricles, which initiates contraction of the ventricles and causes the ventricular pressure to begin rising (as also shown in the figure). Therefore, the QRS complex begins slightly before the onset of ventricular systole.

Finally, one observes the ***ventricular T wave*** in the electrocardiogram. This represents the stage of repolarization of the ventricles when the ventricular muscle fibers begin to relax. Therefore, the T wave occurs slightly before the end of ventricular contraction.

# 24. Stroke volume and cardiac output

**Stroke volume**

– is the volume ejected from the ventricle on each beat.
– is expressed by the following equation:

$$\text{Stroke volume} = \text{End-diastolic volume} - \text{End-systolic volume}$$

**Cardiac output**

– is expressed by the following equation:

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$

**Ejection fraction**

– is the fraction of the end-diastolic volume ejected in each stroke volume.
– is normally 0.55, or **55%.**
– is expressed by the following equation:

$$\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}$$

**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

## Relationship of the Heart Sounds to Heart Pumping

When listening to the heart with a stethoscope, one does not hear the opening of the valves because this is a relatively slow process that normally makes no noise. However, when the valves close, the vanes of the valves and the surrounding fluids vibrate under the influence of sudden pressure changes, giving off sound that travels in all directions through the chest.

When the ventricles contract, one first hears a sound caused by closure of the A-V valves. The vibration is low in pitch and relatively long-lasting and is known as the ***first heart sound***. When the aortic and pulmonary valves close at the end of systole, one hears a rapid snap because these valves close rapidly, and the surroundings vibrate for a short period. This sound is called the ***second heart sound***.

## Heart Sounds Normal Heart Sounds

Listening with a stethoscope to a normal heart, one hears a sound usually described as "lub, dub, lub, dub". The "lub" is associated with closure of the atrioventricular (A-V) valves at the beginning of systole, and the "dub" is associated with closure of the semilunar (aortic and pulmonary) valves at the end of systole. The "lub" sound is called the *first heart sound,* and the "dub" is called the *second heart sound,* because the normal pumping cycle of the heart is considered to start when the A-V valves close at the onset of ventricular systole.

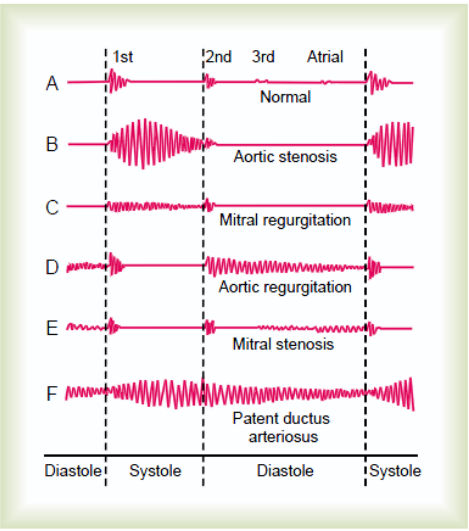
## Causes of the First and Second Heart Sounds

The earliest explanation for the cause of the heart sounds was that the "slapping" together of the valve leaflets sets up vibrations. However, this has been shown to cause little, if any, of the sound, because the blood between the leaflets cushions the slapping effect and prevents significant sound. Instead, the cause 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 vibrations travel through the adjacent tissues to the chest wall, where they can be heard as sound by using the stethoscope.

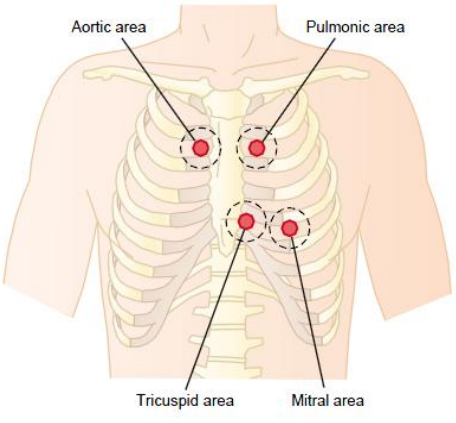
The **second heart sound** results from sudden closure of the semilunar valves at the end of systole. When the semilunar valves close, they bulge backward toward the ventricles, and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the walls of the arteries and the semilunar valves, as well as between these valves and the ventricular walls. The vibrations occurring in the arterial walls are then transmitted mainly along the arteries. When the vibrations of the vessels or ventricles come into contact with a "sounding board," such as the chest wall, they create sound that can be heard.

## Phonocardiogram

If a microphone specially designed to detect low-frequency sound is placed on the chest, the heart sounds can be amplified and recorded by a high-speed recording apparatus. The recording is called a *phonocardiogram,* and the heart sounds appear as waves.




Phonocardiograms from normal and abnormal hearts.




Chest areas from which sound from each valve is best heard.

# 26. Autoregulation of cardiac contraction: Starling principle

### Intrinsic Regulation of Heart Pumping—The Frank-Starling Mechanism

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.

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.

# 27. Autoregulation of cardiac contraction: frequency effect

**Parasympathetic effects on heart rate and conduction velocity**

– The SA node, atria, and AV node have parasympathetic vagal innervation, but the ventricles do not. The neurotransmitter is **acetylcholine** (ACh), which acts at **muscarinic receptors.**

**a. Negative chronotropic effect**

– **decreases heart rate** by decreasing the rate of phase 4 depolarization.
– Fewer action potentials occur per unit time because threshold potential is reached more slowly.
– The mechanism is **decreased $I_f$,** the inward $Na^+$ current that is responsible for phase 4 depolarization in the SA node.

**b. Negative dromotropic effect**

– **decreases conduction velocity through the AV node.**
– **increases the PR interval.**
– Action potentials are conducted more slowly from the atria to the ventricles.
– The mechanism is **decreased inward $Ca^{2+}$ current** and increased inward $K^+$ current.

**Sympathetic effects on heart rate and conduction velocity**

– **Norepinephrine** is the neurotransmitter, acting at **$\beta_1$ receptors.**

**a. Positive chronotropic effect**

– **increases heart rate** by increasing the rate of phase 4 depolarization.
– More action potentials occur per unit time because threshold potential is reached more quickly and more frequently.
– The mechanism is **increased $I_f$,** the inward $Na^+$ current that is responsible for phase 4 depolarization in the SA node.

**b. Positive dromotropic effect**

– **increases conduction velocity through the AV node.**
– **decreases the PR interval.**
– Action potentials are conducted more rapidly from the atria to the ventricles, and ventricular filling may be compromised.
– The mechanism is **increased inward $Ca^{2+}$ current.**

# 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 ($HR_{rest}$)

Is 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. Arrythmias

Pathological changes in cardiac *impulse generation or conduction* that can be visualized by ECG.

**Disturbances of impulse generation** change the sinus rhythm.

- ***Sinus tachycardia*:** The sinus rhythm rises to 100 $min^{-1}$ or higher e.g., due to physical exertion, anxiety, fever (rise of about 10 beats/min for each 1 °C) or hyperthyroidism.
- ***Sinus bradycardia:*** The heart rate falls below60 $min^{-1}$ (e.g., due to hypothyroidism).
  In both cases the rhythm is regular whereas in *sinus arrhythmias* the rate varies. In adolescents, sinus arrhythmias can be physiological and respiration-dependent (heart rate increases during inspiration and decreases during expiration).

## Ectopic pacemakers

Foci in the atrium, AV node or ventricles can initiate abnormal *ectopic* (heterotopic) impulses, even when normal (*nomotopic*) stimulus generation by the SA node is taking place. The rapid discharge of impulses from an atrial focus can induce **atrial tachycardia** (serrated baseline instead of normal P waves), which triggers a ventricular response rate of up to 200 $min^{-1}$. Fortunately, only every second or third stimulus is transmitted to the ventricles because part of the impulses arrive at the Purkinje fibers (longest APs) during their refractory period. Thus, Purkinje fibers act as impulse *frequency filters*. Elevated atrial contraction rates of up to 350 $min^{-1}$ are defined as **atrial flutter**, and all higher rates are defined as **atrial fibrillation** (up to 500 min–1).

**Ventricular tachycardia** is a rapid train of impulses originating from a ventricular (ectopic) focus, starting with an ***extrasystole (ES)***. The heart therefore fails to fill adequately, and the stroke volume decreases. A ventricular ES can lead to **ventricular fibrillation** (extremely frequent and uncoordinated contractions). Because of failure of the ventricle to transport blood, ventricular fibrillation can be fatal.

## Disturbances of impulse conduction → AV block

- ***First-degree* AV block**: prolonged but otherwise normal impulse conduction in the AV node (PQ interval >0.2 sec).
- ***Second-degree* AV block**: only every second (2:1 block) or third (3:1 block) impulse is conducted.
- ***Third-degree* AV block**: no impulses are conducted; sudden cardiac arrest may occur (*Adam–Stokes attack* or *syncope*). Ventricular atopic pacemakers then take over (ventricular bradycardia with normal atrial excitation rate), resulting in partial or total disjunction of QRS complexes and P waves. The heart rate drops to 40 to 55 $min^{-1}$ when the AV node acts as the pacemaker, and to a mere 25 to 40 $min^{-1}$ when tertiary (ventricular) pacemakers take over. Artificial pacemakers are then used.

## Bundle branch block

Disturbance of conduction in a branch of the bundle of His. Severe QRS changes occur because the affected side of the myocardium is activated by the healthy side via abnormal pathways.

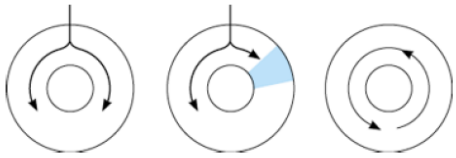
## 30. Mechanism of re-entry

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.

A common cause of paroxysmal arrhythmias is a defect in conduction that permits a wave of excitation to propagate continuously within a closed circuit (**circus movement**).
For example, if a transient block is present on one side of a portion of the conducting system, the impulse can go down the other side. If the block then wears off, the impulse may conduct in a retrograde direction in the previously blocked side back to the origin and then descend again, establishing a circus movement.

If the reentry is in the AV node, the reentrant activity depolarizes the atrium, and the resulting atrial beat is called en echo beat. In addition, the reentrant activity in the node propagates back down to the ventricle, producing paroxysmal nodal tachycardia.



Depolarization of a ring of cardiac tissue. Normally, the impulse spreads in both directions in the ring **(left)** and the tissue immediately behind each branch of the impulse is refractory. When there is a transient block on one side **(center),** the impulse on the other side goes around the ring, and if the transient block has now worn off **(right),** the impulse passes this area and continues to circle indefinitely (circus movement).

## 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.

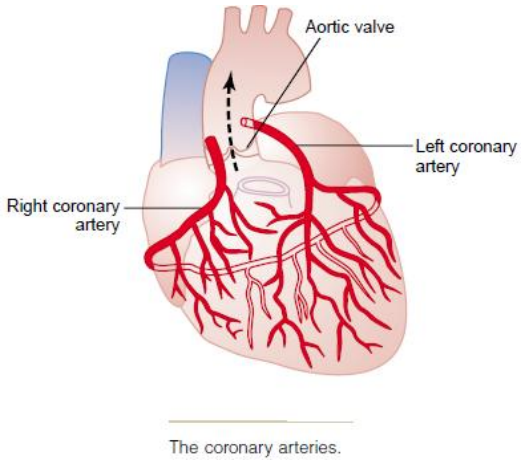
A larger heart results in *higher cardiac output*, or, in other words, more blood is being pumped out with each beat. With high cardiac output, the heart can allow itself to beat less, thus the *bradycardia* occurs.

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



The coronary arteries.

## *Coronary blood supply*

The blood flow to the myocardium is supplied by the two coronary arteries that arise from the aortic root. The right coronary artery (approx. 1/7th of the blood) usually supplies the greater portion of the right ventricle, while the left coronary artery (6/7th of the blood) supplies the left ventricle.

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.

### Coronary blood flow ($Q_{cor}$)

Is phasic, i.e., the amount of blood in the coronary arteries fluctuates during the cardiac cycle due to extremely high rises in extravascular tissue pressure during systole. The blood flow in the epicardial coronary artery branches and subepicardial vessels remains largely unaffected by these pressure fluctuations.
However, the *subendocardial vessels* of the *left ventricle* are compressed during systole when the extravascular pressure in that region (≈pressure in left ventricle, PLV) exceeds the pressure in the lumen of the vessels. Consequently, the left ventricle is mainly supplied during diastole. The fluctuations in right ventricular blood flow are much less distinct because right ventricular pressure (PRV) is lower.

### 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.

– exhibits ***autoregulation***.
– exhibits active and reactive hyperemia.
– The most important local metabolic factors are **hypoxia** and **adenosine**.
– For example, **increases in myocardial contractility** are accompanied by an increased demand for $O_2$. To meet this demand, compensatory vasodilation of coronary vessels occurs and, accordingly, both blood flow and $O_2$ delivery to the contracting heart increase (active hyperemia).
– During **systole**, mechanical compression of the coronary vessels reduces blood flow. After the period of occlusion, blood flow increases to repay the $O_2$ debt (reactive hyperemia).
– Sympathetic nerves play a minor role.

# 33. Coronary reserve. Ischaemic heart disease.

## Coronary reserve

### Myocardial $O_2$ consumption ($\dot{V}_{O_2}$)

Is defined as $Q_{cor}$ times the arteriovenous $O_2$ concentration difference, $(C_a–C_v)_{O_2}$.
The myocardial $(C_a–C_v)_{O_2}$ is relatively high (0.12 L/L blood), and *oxygen extraction* at rest ($[C_a–C_v]_{O_2}/C_aO_2$ = 0.12/0.21) is almost 60% and, thus, not able to rise much further. Therefore, an increase in $Q_{cor}$ is practically the only way to increase myocardial $V_{O_2}$ when the $O_2$ 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 $Q_{cor}$ (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 $O_2$ 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.

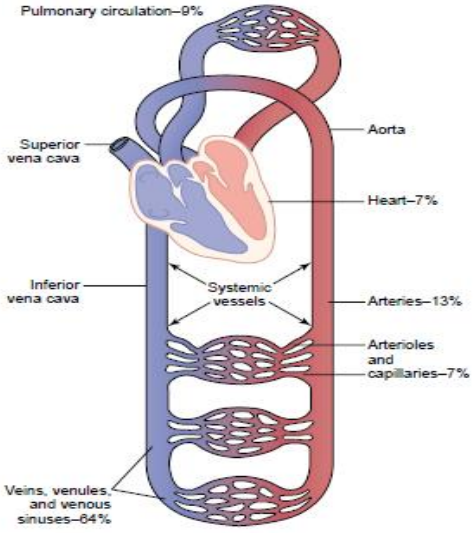
# 34. Cardiovascular system – general principles

## 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.

## 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.



Distribution of blood (in percentage of total blood) in the different parts of the circulatory system.

## 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.**

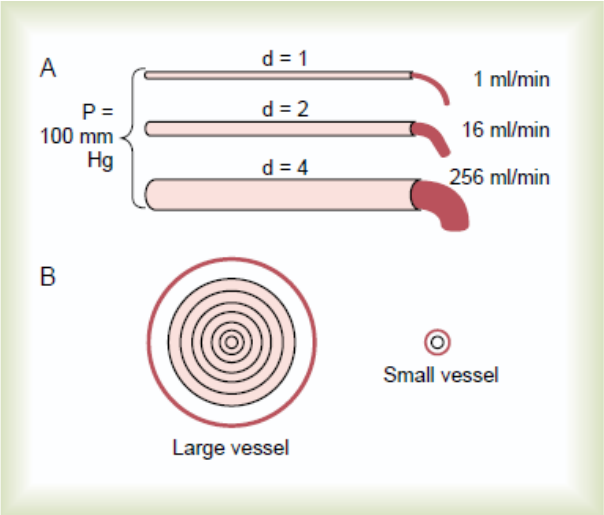
**3. In general the arterial pressure is controlled independently of either local blood flow control or cardiac output control**

## 35. Significance of Poiseuille-Hagen formula for blood flow

In the **Hagen–Poiseuille equation** the flow resistance (R) in a tube of known length (l) is dependent on the viscosity (η) of the fluid in the tube and the fourth power of the inner radius of the tube ($r^4$). Decreasing the radius by only about 16% will therefore suffice to double the resistance.

**Very Slight Changes in Diameter of a Vessel Can Change Its Conductance Tremendously!**

The cause of this great increase in conductance when the diameter increases can be explained by referring to Figure to the right, 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.
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 **h** 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.

# 36. Vascular resistance

**Resistance**

– Poiseuille's equation gives factors that change the resistance of blood vessels.

$$R = \frac{8\,\eta\,l}{\pi\,r^4}$$

*where:*
$R$ = resistance
$\eta$ = viscosity of blood
$l$ = length of blood vessel
$r^4$ = radius of blood vessel to the fourth power

– Resistance is directly proportional to the viscosity of the blood. **For example,** increasing viscosity by increasing hematocrit will increase resistance and decrease blood flow.
– Resistance is directly proportional to the length of the vessel.
– Resistance is inversely proportional to the **fourth power of the vessel** radius. This relationship is powerful. **For example,** if blood vessel radius decreases by a factor of 2, then resistance increases by a factor of 16 ($2^4$), and blood flow accordingly decreases by a factor of 16.

## 1. Resistances in parallel or series

**a. Parallel resistance** is illustrated by the systemic circulation. Each organ is supplied by an artery that branches off the aorta. The total resistance of this parallel arrangement is expressed by the following equation:

$$\frac{1}{R_{total}} = \frac{1}{R_a} + \frac{1}{R_b} + \dots \frac{1}{R_n}$$

$R_a$, $R_b$, and $R_n$ are the resistances of the renal, hepatic, and other arteries, respectively. The total resistance is less than the resistance of any of the individual arteries.

**b. Series resistance** is illustrated by the arrangement of blood vessels within a given organ. Each organ is supplied by a large artery, smaller arteries, arterioles, capillaries, and veins arranged in series. The total resistance is the sum of the individual resistances, as expressed by the following equation:

$$R_{total} = R_{artery} + R_{arterioles} + R_{capillaries}$$

– The largest proportion of resistance in this series is contributed by the **arterioles.**

## 2. Laminar flow versus turbulent flow

– Laminar flow is streamlined (in a straight line); turbulent flow is not.
– **Reynold's number** predicts whether blood flow will be laminar or turbulent.
– When Reynold's number is increased, there is a greater tendency for **turbulence,** which causes audible vibrations called **bruits.** Reynold's number (and therefore turbulence) is increased by the following factors:

**a.** ↓ blood viscosity (e.g., ↓ hematocrit, **anemia**)

**b.** ↑ blood velocity (e.g., **narrowing of a vessel**)

# 37. Blood pressure. Hypertension.

## Blood pressure (BP)

It is a force exerted by circulating blood on the walls of blood vessels, and is one of the principal vital signs. During each heartbeat, BP varies between a maximum (**systolic**) and a minimum (**diastolic**) pressure. The mean BP, due to pumping by the heart and resistance in blood vessels, decreases as the circulating blood moves away from the heart through arteries.

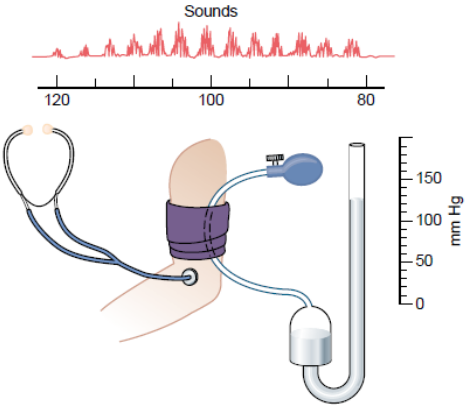
The term *blood pressure* usually refers to the pressure measured at a person's upper arm. It is measured on the inside of an elbow at the brachial artery, which is the upper arm's major blood vessel that carries blood away from the heart.

### *Measurement*

Arterial pressure is most commonly measured via a ***sphygmomanometer***, which historically used the height of a column of mercury to reflect the circulating pressure. BP values are reported in millimetres of mercury (mmHg), though aneroid and electronic devices do not use mercury.

For each heartbeat, BP varies between systolic and diastolic pressures. Systolic pressure is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting. Diastolic pressure is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood. An example of normal measured values for a resting, healthy adult human is 120 mmHg systolic and 80 mmHg diastolic (written as 120/80 mmHg).

***! [Also see Q. 43 and 44 in part A]***




Auscultatory method for measuring systolic and diastolic arterial pressures.

## Hypertension

Refers to arterial pressure being **abnormally high**, as opposed to *hypotension*, when it is abnormally low. Hypertension has several sub-classifications including, hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly.

| Classification | Systolic pressure | | Diastolic pressure | |
|---|---|---|---|---|
| | mmHg | kPa | mmHg | kPa |
| Normal | 90–119 | 12–15.9 | 60–79 | 8.0–10.5 |
| Prehypertension | 120–139 | 16.0–18.5 | 80–89 | 10.7–11.9 |
| Stage 1 | 140–159 | 18.7–21.2 | 90–99 | 12.0–13.2 |
| Stage 2 | ≥160 | ≥21.3 | ≥100 | ≥13.3 |
| Isolated systolic hypertension | ≥140 | ≥18.7 | <90 | <12.0 |

**Tests typically performed are classified as follows:**

| System | Tests |
|---|---|
| Renal | Microscopic urinalysis, proteinuria, serum BUN (blood urea nitrogen) and/or creatinine |
| Endocrine | Serum sodium, potassium, calcium, TSH (thyroid-stimulating hormone). |
| Metabolic | Fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides |
| Other | Hematocrit, electrocardiogram, and Chest X-ray |

# 38. Arterial elasticity – significance

## Vascular Distensibility

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.

☆ 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:

$$\text{Vascular distensibility} = \frac{\text{Increase in volume}}{\text{Increase in pressure} \times \text{Original volume}}$$

That is, if 1 mm Hg causes a vessel that originally contained 10 millimeters of blood to increase its volume by 1 milliliter, the distensibility would be 0.1 per mm Hg, or 10 per cent per mm Hg.

### 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.

### Capacitance (compliance)

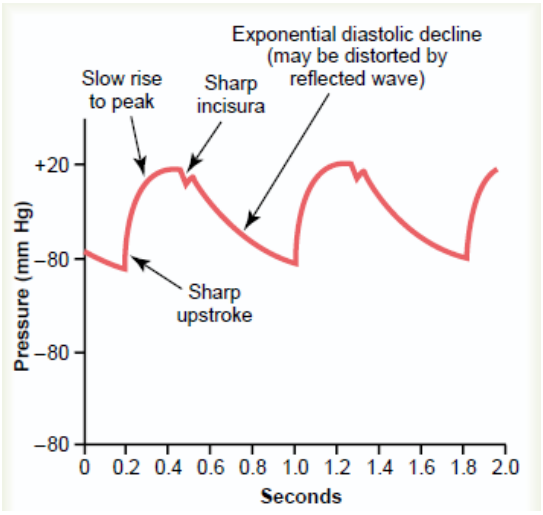
– describes the **distensibility** of blood vessels.
– is **inversely related to elastance.** The greater the amount of elastic tissue in a blood vessel, the higher the elastance, but the lower the compliance.
– can be expressed by the following equation:

$$C = \frac{V}{P}$$

*wnere:*
$C$ = capacitance or compliance (ml/mm Hg)
$V$ = volume (ml)
$P$ = pressure (mm Hg)

– is directly proportional to volume and inversely proportional to pressure.
– describes how volume changes in response to a change in pressure.
– is much **greater for veins than for arteries.** As a result, more blood volume is contained in the veins **(unstressed volume)** than in the arteries **(stressed volume).**
– Changes in the capacitance of the veins produce changes in unstressed volume. For example, a decrease in venous capacitance decreases unstressed volume and increases stressed volume by shifting blood from the veins to the arteries.
– Capacitance of the arteries **decreases with age;** as a person ages, the arteries become stiffer and less distensible.

# 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***.

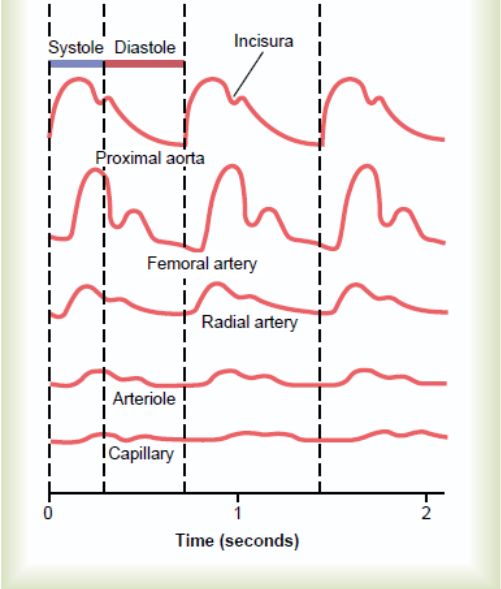
Two major factors affect the pulse pressure: (1) the *stroke volume output* of the heart and (2) the *compliance (total distensibility)* of the arterial tree.

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.




Changes in the pulse pressure contour as the pulse wave travels toward the smaller vessels.

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:

- Vasoconstriction and vasodilation, and hence the control of blood pressure
- Blood clotting (thrombosis & fibrinolysis)
- Atherosclerosis
- Formation of new blood vessels (angiogenesis)
- Inflammation
- **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.

## Endothelial exchange processes

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** $\mathbf{K_f}$ (=water permeability k · exchange area A) and the **effective filtration pressure** $\mathbf{P_{eff}}$ ($Q_f = K_f \cdot P_{eff}$). $P_{eff}$ 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 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 ($ET_B$ receptors), or histamine ($H_1$ 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 $ET_B$ receptors, or can cause *vasoconstriction* via $ET_A$ receptors in the vascular musculature. When substances such as angiotensin II or ADH (= vasopressin; $V_1$ receptor) bind to an endothelial cell, they release endothelin-1, which diffuses to and constricts the adjacent vascular muscles with the aid of $ET_A$ receptors.

- **Epinephrine** (**E**): High concentrations of E from the adrenal medulla have a *vasoconstrictive* effect ($\alpha_1$ adrenoceptors), whereas low concentrations exert *vasodilatory* effects by way of $\beta_2$ adrenoceptors in the *myocardium, skeletal muscle* and *live*. The effect of E mainly depends on which type of adrenoceptor is predominant in the organ. $\alpha_1$- adrenoceptors are predominant in the blood vessels of the *kidney* and *skin*.

- **Eicosanoids**: Prostaglandin (PG) $F_{2\alpha}$ and the thromboxanes $A_2$ (released from platelets) and $B_2$ have *vasoconstrictive* effects, while $PGI_2$ (= prostacyclin, e.g. released from endothelium) and $PGE_2$ 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 $Ca^{2+}$ 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

## Structure of the Microcirculation and Capillary System

The microcirculation of each organ is organized specifically to serve that organ's needs. In general, each nutrient artery entering an organ branches six to eight times before the arteries become small enough to be called *arterioles,* which generally have internal diameters of only 10 to 15 micrometers. Then the arterioles themselves branch two to five times, reaching diameters of 5 to 9 micrometers at their ends where they supply blood to the capillaries.

### *Structure of the Capillary beds*

- Metarterioles branch into the capillary beds. At the junction of the arterioles and capillaries is a smooth muscle band called the **precapillary sphincter.**
- True capillaries do not have smooth muscle; they consist of a single layer of **endothelial cells** surrounded by a basement membrane.
- Clefts (pores) between the endothelial cells allow passage of water-soluble substances. The clefts represent a very small fraction of the surface area (< 0.1%).
- **Blood flow through the capillaries is regulated by contraction and relaxation of the arterioles and the precapillary sphincters.**

### *Passage of substances across the capillary wall*

1. **Lipid-soluble substances**
   - cross the membranes of the capillary endothelial cells by **simple diffusion.**
   - include **$O_2$ and $CO_2$.**
2. **Small water-soluble substances**
   - cross via the water-filled clefts between the endothelial cells.
   - include **water, glucose,** and **amino acids.**
   - Generally, protein molecules are too large to pass freely through the clefts.
   - In the brain, the clefts between endothelial cells are exceptionally tight **(blood–brain barrier).**
   - In the liver and intestine, the clefts are exceptionally wide and allow passage of protein. These capillaries are called **sinusoids.**
3. **Large water-soluble substances**
   - can cross by **pinocytosis.**

### *Fluid exchange across capillaries*

1. **The Starling equation**

$$J_v = K_f [(P_c - P_i) - (\pi_c - \pi_i)]$$

*where:*
$J_v$ = fluid movement (ml/min)
$K_f$ = hydraulic conductance (ml/min · mm Hg)
$P_c$ = capillary hydrostatic pressure (mm Hg)
$P_i$ = interstitial hydrostatic pressure (mm Hg)
$\pi_c$ = capillary oncotic pressure (mm Hg)
$\pi_i$ = interstitial oncotic pressure (mm Hg)

2. **Factors that increase filtration**
   - **a.** ↑ $P_c$—caused by increased arterial or venous pressure
   - **b.** ↓ $P_i$
   - **c.** ↓ $\pi_c$—caused by decreased protein concentration in the blood
   - **d.** ↑ $\pi_i$—caused by inadequate lymphatic function

### *Regulation of Vasomotion*

The most important factor found thus far to affect the degree of opening and closing of the metarterioles and precapillary sphincters is the concentration of ***oxygen*** in the tissues. When the rate of oxygen usage by the tissue is great so that tissue oxygen concentration decreases below normal, the intermittent periods of capillary blood flow occur more often, and the duration of each period of flow lasts longer, thereby allowing the capillary blood to carry increased quantities of oxygen (as well as other nutrients) to the tissues.

# 43. Venous pressure

### Venous Pressure & Flow

The pressure in the venules is 12-18 mm Hg. It falls steadily in the larger veins to about 5.5 mm Hg in the great veins outside the thorax. The pressure in the great veins at their entrance into the right atrium **(central venous pressure)** averages 4.6 mm Hg but fluctuates with respiration and heart action.

Peripheral venous pressure, like arterial pressure, is affected by gravity. It is increased by 0.77 mm Hg for each cm below the right atrium and decreased by a like amount for each 1 cm above the right atrium the pressure is measured

When blood flows from the venules to the large veins, its average velocity increases as the total cross- sectional area of the vessels decreases. In the great veins, the velocity of blood is about one-fourth that in the aorta, averaging about 10 cm/s.

### Thoracic Pump

During inspiration, the intrapleural pressure falls from -2.5 to -6 mm Hg. This negative pressure is transmitted to the great veins and, to a lesser extent, the atria, so that central venous pressure fluctuates from about 6 mm Hg during expiration to approximately 2 mm Hg during quiet inspiration. The drop in venous pressure during inspiration aids venous return. When the diaphragm descends during inspiration, intra-abdominal pressure rises, and this also squeezes blood toward the heart because backflow into the leg veins is prevented by the venous valves.

### Effects of Heartbeat

The variations in atrial pressure are transmitted to the great veins, producing the **a, c,** and **v waves** of the venous pressure-pulse curve . Atrial pressure drops sharply during the ejection phase of ventricular systole because the atrioventricular valves are pulled downward, increasing the capacity of the atria. This action sucks blood into the atria from the great veins. The sucking of the blood into the atria during systole contributes appreciably to the venous return, especially at rapid heart rates.

Close to the heart, venous flow becomes pulsatile. When the heart rate is slow, two periods of peak flow are detectable, one during ventricular systole, due to pulling down of the atrioventricular valves, and one in early diastole, during the period of rapid ventricular filling

### Muscle Pump

In the limbs, the veins are surrounded by skeletal muscles, and contraction of these muscles during activity compresses the veins. Pulsations of nearby arteries may also compress veins. Since the venous valves prevent reverse flow, the blood moves toward the heart. During quiet standing, when the full effect of gravity is manifest, venous pressure at the ankle is 85-90 mm Hg.
Pooling of blood in the leg veins reduces venous return, with the result that cardiac output is reduced, sometimes to the point where fainting occurs. Rhythmic contractions of the leg muscles while the person is standing serve to lower the venous pressure in the legs to less than 30 mm Hg by propelling blood toward the heart.

### Measuring Venous Pressure

**Central venous pressure** can be measured directly by inserting a catheter into the thoracic great veins. **Peripheral venous pressure** correlates well with central venous pressure in most conditions. To measure peripheral venous pressure, a needle attached to a manometer containing sterile saline is inserted into an arm vein. The peripheral vein should be at the level of the right atrium (a point 10 cm or half the chest diameter from the back in the supine position). The values obtained in mm of saline can be converted into mm Hg by dividing by 13.6 (the density of mercury). The amount by which peripheral venous pressure exceeds central venous pressure increases with the distance from the heart along the veins. The mean pressure in the antecubital vein is normally 7.1 mm Hg, compared with a mean pressure of 4.6 mm Hg in the central veins.

A fairly accurate estimate of central venous pressure can be made without any equipment by simply noting the height to which the external jugular veins are distended when the subject lies with the head slightly above the heart. The vertical distance between the right atrium and the place the vein collapses (the place where the pressure in it is zero) is the venous pressure in mm of blood.

Central venous pressure is decreased during negative pressure breathing and shock. It is increased by positive pressure breathing, straining, expansion of the blood volume, and heart failure. In advanced congestive heart failure or obstruction of the superior vena cava, the pressure in the antecubital vein may reach values of 20 mm Hg or more.

# 44. Venous return. Venous stasis and embolism.

## Venous Return

Blood from the capillaries is collected in the veins and returned to the heart. The **driving forces** for this venous return are:
**(a)** *vis a tergo*, i.e., the postcapillary blood pressure (BP) (ca. 15 mmHg);
**(b)** the suction that arises due to lowering of the cardiac valve plane in systole;
**(c)** the pressure exerted on the veins during skeletal muscle contraction (*muscle pump*); the valves of veins prevent the blood from flowing in the wrong direction,
**(d)** the increased abdominal pressure together with the lowered intrathoracic pressure during inspiration, which leads to thoracic venous dilatation and suction.

## 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 represents an accessory route through which fluid can flow from the interstitial spaces into the blood. Most important, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function without which we would die within about 24 hours.

***Lymphatic organs include:*** **thymus**, **lymph nodes**, **spleen**, **tonsils**, **lymph nodules** (in the wall of intestine (lymphonoduli solitarii and Peyer's patches) and in the wall of respiratory and urinary passages).

### *Lymph channels of the body*

Essentially all the lymph vessels from the lower part of the body eventually empty into the ***thoracic duct,*** which in turn empties into the blood venous system at the juncture of the *left* internal jugular vein and left subclavian vein (the ***venous angle***).

Lymph from the left side of the head, the left arm, and parts of the chest region also enters the thoracic duct before it empties into the veins.

Lymph from the right side of the neck and head, the right arm, and parts of the right thorax enters the *right lymph duct* (much smaller than the thoracic duct), which empties into the blood venous system at the juncture of the *right* subclavian vein and internal jugular vein.

Note: Normal drainage from breast is to *anterior* and *posterior axillary*, *infraclavicular* and *internal thoracic* groups. With pathological blockage from disease the spread can be to opposite side, *cervical*, *peritoneal cavity* and *liver*, and *inguinal glands*.

### *Function of the lymphatic system*

The lymphatic system has four interrelated functions: it is responsible for the removal of interstitial fluid from tissues; it absorbs and transports *fatty acids* and *fats* as chyle to the circulatory system; and to Nicklas cells and it transports immune cells to and from the lymph nodes in to the sheppardian part of the bone. The lymph transports antigen-presenting cells (APCs), such as dendritic cells, to the lymph nodes where an immune response is stimulated. The lymph also carries lymphocytes from the efferent lymphatics exiting the lymph nodes.

The lymphatic system also plays a central role in controlling **(1)** the concentration of proteins in the interstitial fluids, **(2)** the volume of interstitial fluid, and **(3)** the interstitial fluid pressure. Once the interstitial fluid protein concentration reaches a certain level and causes a comparable increase in interstitial fluid volume and interstitial fluid pressure, the return of protein and fluid by way of the lymphatic system becomes great enough to balance exactly the rate of leakage of these into the interstitium from the blood capillaries.

### The three major types of lymphocyte

**NK cells** are a part of *innate immune system* and play a major role in defending the host from both *tumors* and virally infected cells. NK cells distinguish infected cells and tumors from normal and uninfected cells by recognizing level changes of a surface molecule called ***MHC (major histocompatibility complex) class I***. NK cells are activated in response to a family of *cytokines* called *interferons*. Activated NK cells release ***cytotoxic (cell-killing) granules*** which then destroy the altered cells. They were named "natural killer cells" because of the initial notion that they do not require prior activation in order to kill cells which are missing MHC class I.

**T cells (Thymus cells)** and **B cells (bone cells)** are the major cellular components of the *adaptive immune response*. T cells are involved in *cell-mediated immunity* whereas B cells are primarily responsible for *humoral immunity* (relating to antibodies). The function of T cells and B cells is to recognize specific “non-self” antigens, during a process known as antigen presentation. Once they have identified an invader, the cells generate specific responses that are tailored to maximally eliminate specific pathogens or pathogen infected cells. B cells respond to pathogens by producing large quantities of antibodies which then neutralize foreign objects like bacteria and viruses. In response to pathogens some T cells, called *T helper cells*, produce cytokines that direct the immune response while other T cells, called *cytotoxic T cells*, produce toxic granules that induce the death of pathogen infected cells. Following activation, B cells and T cells leave a lasting legacy of the antigens they have encountered, in the form of *memory cells*. Throughout the lifetime of an animal these memory cells will “remember” each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again.

# 46. Pulmonary circulation

## Physiologic Anatomy of the Pulmonary Circulatory System

### *Pulmonary Vessels*

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.

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.

### *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*

There are two main pairs of arteries that supply the cerebral arteries and the cerebellum:

- **Internal carotid arteries**: These large arteries are the left and right branches of the ***common carotid arteries*** in the neck which enter the skull, as opposed to the ***external carotid*** branches which supply the facial tissues. The internal carotid artery branches into the anterior cerebral artery and continues to form the ***middle cerebral artery***
- **Vertebral arteries**. These smaller arteries branch from the ***subclavian arteries*** which primarily supply the shoulders, lateral chest and arms. Within the cranium the two vertebral arteries fuse into the ***basilar artery***, which supplies the midbrain, cerebellum, and usually branches into the ***posterior cerebral artery***.

Both internal carotid arteries, within and along the floor of the cerebral vault, are interconnected via the anterior communicating artery. Additionally, both internal carotid arteries are interconnected with the basilar artery via bilateral ***posterior communicating arteries***.

The **circle of Willis**, long considered to be an important anatomic vascular formation, provides backup circulation to the brain. In case one of the supply arteries is occluded, the circle of Willis provides interconnections between the internal carotid arteries and basilar artery along the floor of the cerebral vault, providing blood to tissues that would otherwise become *ischemic*.

### *Cerebral venous drainage*

The venous drainage of the cerebrum can be separated into two subdivisions: superficial and deep. The superficial system is composed of ***dural venous sinuses***, which have wall composed of dura mater as opposed to a traditional vein. The dural sinuses are, therefore located on the surface of the cerebrum. 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*. 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 circulation**

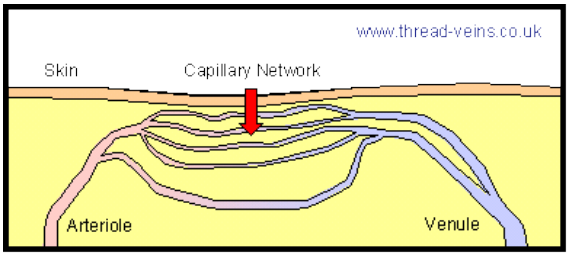
- is controlled almost entirely by **local metabolic factors.**
- exhibits autoregulation.
- exhibits active and reactive hyperemia.
- The **most important local vasodilator for the cerebral circulation is $CO_2$** (or pH). If the partial pressure of carbon dioxide ($Pco_2$) is increased (pH is decreased), there is vasodilation of the cerebral arterioles to increase blood flow to the brain.
- Sympathetic nerves play a minor role.
- Vasoactive substances in the systemic circulation have little or no effect on cerebral circulation because such substances are excluded by the blood–brain barrier.

# 48. Skin circulation

### 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 innervation.** Cutaneous blood flow is under extrinsic control.
- **Temperature regulation** is the principal function of the cutaneous sympathetic nerves. Increased ambient temperature leads to cutaneous vasodilation, allowing dissipation of excess body heat.
- **Trauma** produces the "triple response" in skin—a red line, a red flare, and 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 $O_2$/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 reduces 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 $\alpha_1$-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 $\beta_2$-adrenogenic receptors causing vasodilation)
- vasodilation → increases blood flow → more efficient rate of $O_2$/$CO_2$ 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

### *Intestinal circulation*

- Intestine is supplied via branches of the ***superior*** and ***inferior mesenteric*** aa (colic, illeal, jejunal aa/vv)
- Intestinal circulation is capable of extensive auto-regulation. Thus the blood flow to the small intestine can double after a meal to allow for sufficient exchange of nutrients - this can last up to 3 hours

### *Hepatic circulation*

- The liver and viscera receive up to 30% of CO via celiac, superior & inferior mesenteric aa
- It receives 1L from the portal vein (blood from intestines, pancreas and spleen) and 0.5L from the hepatic artery (branch of celiac a)
- Hepatic portal system:
  - carries the blood from the GI tract and spleen to the liver before it enters the inferior vena cava.
  - This is needed because this blood has digestive end-products and absorbed toxins from the GI tract and bilirubin from hemoglobin destruction in the spleen. The liver is in charge of processing these substances.
  - Blood in the **splenic vein** from the spleen receives blood from the **inferior mesenteric vein** draining the large intestine, and then combines with the **superior mesenteric vein** coming from the small intestine to form the portal vein (hepatic portal vein) which enters the liver.
  - The liver also receives oxygenated blood through the **hepatic artery** and blood from these two sources mixes in liver sinusoids which are lined with the hepatocytes (liver cells). Once processed by these hepatocytes the blood returns to the circulation through the **hepatic vein** → IVC
- The liver is known to have sympathetic fibers from T3-T12 spinal roots and splanchnic nerves, which provides vasoconstriction of the intrahepatic portal veins. The hepatic artery receives symp. inv. from the hepatic sympathetic plexus. A drop in systemic BP → diffuse noradrenergenic discharge → intrahepatic portal vein constricts → increases portal pressure →blood flow through liver decreases and is usually bypassed/diverted (note – mesenteric vessels would also be constricted thus reducing portal blood flow)

### *Reservoir function of splanchnic circulation*

The whole visceral circulation is a reservoir of blood. For example, the liver consists of 25-30% blood, contraction of capacitance vessels of the viscera can pump a litre of blood into the arterial circulation in less than 1 minute. During exercise, vasoconstriction decreases the blood "storage" in the liver and splanchnic bed to allow for sufficient blood supply to the exercising muscles.

Other organs which act as reservoirs are: skin (subdermal capillary system), lungs, and spleen

# 50. Placental and fetal circulation

## Placenta

The maternal placenta acts as the "gut" (absorption of nutrients), "kidneys" (removal of waste products) and "lungs" of the fetus (uptake of $O_2$ and elimination of $CO_2$). Although the *fetal $O_2$-hemoglobin dissociation curve* is shifted to the left compared to that of adults, only 60% (0.6) of placental hemoglobin is saturated with $O_2$.

In the fetus, not yet active or hardly active organs such as the lungs receive little blood.

The **fetal cardiac output** (from both ventricles) is about 0.2 L/min per kg body weight. The **fetal heart rate** rises from an initial 65 $min^{-1}$ (week 5) to 130–160 $min^{-1}$ in later weeks. Approx. 50% of the blood ejected from the heart flows through the placenta, the other half supplies the body (35%) and lungs (15%) of the fetus. This is supplied by the left and right heart, which function essentially *in parallel* until after the birth (see below).

## 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 $O_2$ concentration ($O_2$ 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

## Circulation during birth

The exchange of $O_2$, $CO_2$, nutrients, and waste materials through the placenta stops abruptly during birth. This leads to a rise in blood $P_{CO_2}$, triggering chemosensors that induce a strong breathing reflex. The resultant *inspiratory movement* causes negative pressure (suction) in the thoracic cavity, which removes the blood from the placenta and umbilical vein (*placental transfusion*) and expands the lungs. The unfolding of the lungs and the rise in alveolar $P_{O_2}$ reduce the resistance in the pulmonary circulation, and the blood flow increases while the pressure decreases. Meanwhile, the resistance in the systemic circulation increases due to occlusion or clamping of the umbilical cord. This changes the direction of blood flow in the **ductus arteriosus**, resulting in a *left-to-right shunt*. The pulmonary circulation therefore receives aortic blood for a few days after birth. The right atrial filling volume decreases due to the lack of placental blood, while that of the left atrium increases due to the increased pulmonary blood flow. Due to the resultant pressure gradient from the left to right atrium and to a decrease in vasodilatory prostaglandins, the **foramen ovale** closes after birth. The ductus arteriosus and ductus venosus also close, and the systemic and pulmonary circulation now form serial circuits. The closure of the ductus arteriosus is promoted by the rise in blood $P_{O_2}$ (*a mitochondrial $O_2$ sensor forms $H_2O_2$→ $K^+$ channels blocked → depolarization → L-type $Ca^{2+}$ channels open→ vasoconstriction*).

# 52. Intrapulmonary and pleural pressure. Pneumothorax.

**Transpulmonary pressure** is a term used to describe the difference between the *alveolar pressure* and the *pleural pressure* in the lungs. During human ventilation, air flows because of pressure gradients. Pressure in the respiratory system can be measured either in the air spaces of the lungs (alveolar pressure) or in the pleural fluid (intrapleural pressure). Since atmospheric pressure is relatively constant, pressure in the lungs must be higher or lower than atmospheric pressure for air to flow between the atmosphere and the alveoli.

$$P_{tp} = P_{alv} - P_{pl}$$

Where $P_{tp}$ is *transpulmonary pressure*, $P_{alv}$ is *alveolar pressure*, and $P_{pl}$ is *pleural pressure*.

At rest (before inspiration begins)

- **Alveolar pressure equals atmospheric pressure.**
- **Intrapleural pressure is negative.**
- Intrapleural pressure can be measured by a **balloon catheter in the esophagus**

During inspiration

- **The inspiratory muscles contract and cause the volume of the thorax to increase**.
  → decrease in alveolar pressure
  → the **pressure gradient** between the atmosphere and the alveoli now causes air to flow into the lungs.
- **Intrapleural pressure becomes more negative** (because lung volume increases during inspiration, the elastic recoil strength of the lungs also increases)
- Changes in intrapleural pressure during inspiration are used to measure the **dynamic compliance** of the lungs.

During expiration

- **Alveolar pressure becomes greater than atmospheric pressure** (this occurs because alveolar gas is compressed by the elastic forces of the lung) , with the result that air flows out of the lungs.
- **Intrapleural pressure returns to its resting value during a normal (passive) expiration**.

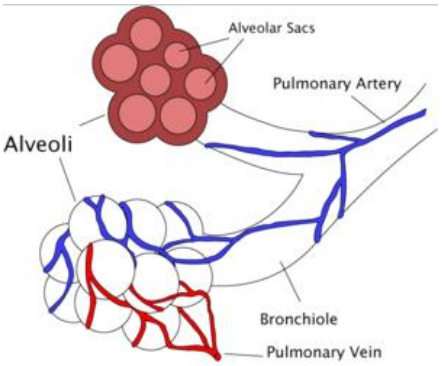
## Pneumothorax

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. Side the intrapleural pressure on the affected side is now atmospheric, the mediastinum shifts toward the normal side. If the communication between the pleural space and the exterior remains open **(open** or **sucking pneumothorax)**, more air moves in and out of the pleural space each time the patient breathes.

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.

# 53. Alveolar surface tension. Surfactant.




## Alveolar Surface Tension

An important factor affecting the compliance of the lungs is the surface tension of the film of fluid that lines the alveoli. The magnitude of this component at various lung volumes can be measured by removing the lungs from the body of an experimental animal and distending them alternately with saline and with air while measuring the intrapulmonary pressure. Because saline reduces the surface tension to nearly zero, the pressure-volume curve obtained with saline measures only the tissue elasticity, whereas the curve obtained with air measure both tissue elasticity and surface tension.

## Surfactant

The low surface when the alveoli are small is due to the presence in the fluid lining the alveoli of *surfactant*. If the surface tension is not kept low when the alveoli become smaller during expiration, they collapse in accordance with the law of Laplace. In spherical structures like the alveoli, the distending pressure equals 2 times the tension divided by the radius (P= 2T/r); if T is not reduced as r is reduced, the tension overcomes the distending pressure.

**Pulmonary surfactant** is a surface-active lipoprotein complex (phospholipoprotein) formed by *type II alveolar cells*. The proteins and lipids that surfactant comprises have both a hydrophilic region and a hydrophobic region. By adsorbing to the air-water interface of alveoli with the hydrophilic headgroups in the water and the hydrophobic tails facing towards the air, the main lipid component of surfactant, *dipalmitoylphosphatidylcholine*, reduces surface tension.

Surfactant is important at birth. The fetus makes respiratory movements in utero, but the lungs remain collapsed until birth. After birth, the infant makes several strong inspiratory movements and the lungs expand. Surfactant keeps them from collapsing again. Surfactant also help to prevent pulmonary edema.

Maturation of surfactant in the lungs is accelerated by glucocorticoid hormones.

# 54. Compliance of lungs. Respiratory work.

## Compliance

**Pulmonary compliance** (or **lung compliance**) is the ability of the lungs to stretch during a change in volume relative to an applied change in pressure. Lung compliance is defined as the volume change per unit of pressure change across the lung.

Pulmonary surfactant increases compliance by decreasing the surface tension of water.

## Functional significance of abnormally high or low compliance

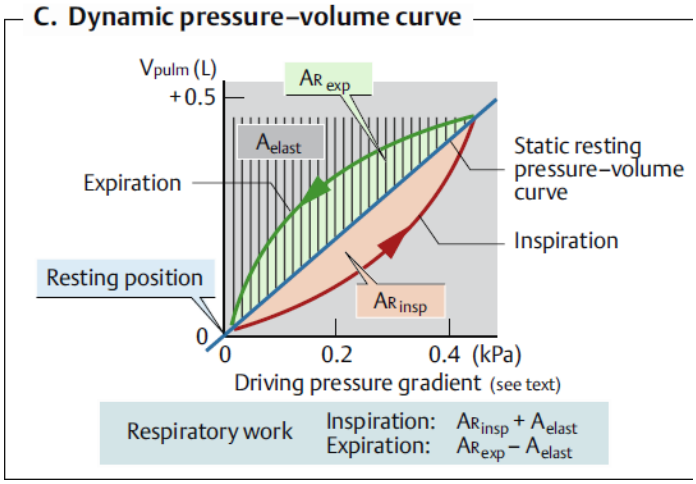
- Low compliance indicates a stiff lung and means extra work is required to bring in a normal volume of air. This occurs as the lungs in this case become fibrotic, lose their distensibility and become stiffer.
- In a highly compliant lung, as in emphysema, the elastic tissue has been damaged, usually due to their being overstretched by chronic coughing. Patients with emphysema have a very high lung compliance due to the poor elastic recoil, they have no problem inflating the lungs but have extreme difficulty exhaling air. In this condition extra work is required to get air out of the lungs.

## Calculation

Compliance is calculated using the following equation, where ΔV is the change in volume, and ΔP is the change in pleural pressure:

$$C = \frac{\Delta V}{\Delta P}$$

## Respiratory Work




The colored areas within the loop ($A_{Rinsp}$ and $A_{Rexp}$; →**C**) represent the inspiratory and expiratory PV work exerted to overcome flow resistance. The cross-hatched area (→**C**) is the work required to overcome the intrinsic elastic force of the lungs and chest ($A_{elast}$). *Inspiratory work* is defined as $A_{Rinsp} + A_{elast}$. The inspiratory muscles must overcome the elastic force, whereas the same elastic force provides the (passive) driving force for expiration at rest (sign reverses for $A_{elast}$). Thus, *expiratory work* is $A_{Rexp} - A_{elast}$. Expiration can also require muscle energy if $A_{Rexp}$ becomes larger than $A_{elast}$—e.g., during forced respiration or if RL is elevated.

# 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 [$SO_2$].

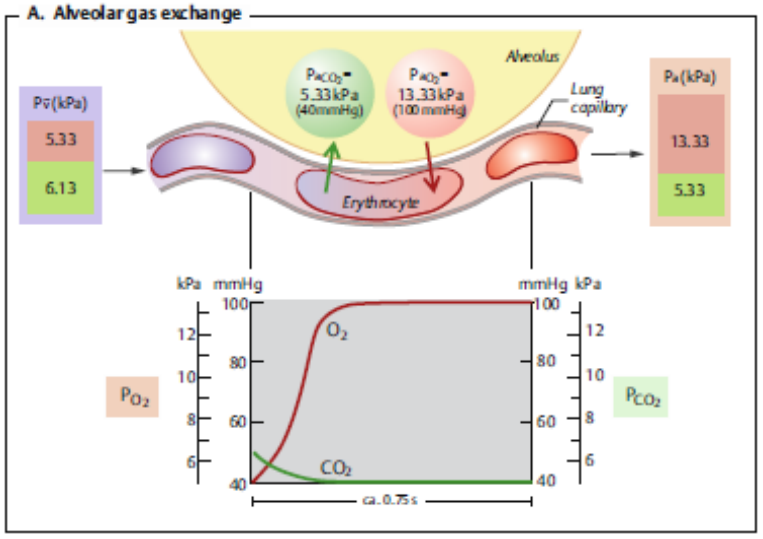
**Composition of dry atmosphere, by volume**

| Gas | Volume |
|---|---|
| Nitrogen ($N_2$) | (78.084%) |
| Oxygen ($O_2$) | (20.946%) |
| Argon (Ar) | (0.9340%) |
| Carbon dioxide ($CO_2$) | (0.0380%) |
| Neon (Ne) | (0.001818%) |
| Helium (He) | (0.000524%) |
| Methane ($CH_4$) | (0.000179%) |
| Krypton (Kr) | (0.000114%) |
| Hydrogen ($H_2$) | (0.000055%) |
| Nitrous oxide ($N_2O$) | (0.00003%) |
| Xenon (Xe) | ($9 \times 10^{-6}$%) |
| Ozone ($O_3$) | (0% to $7 \times 10^{-6}$%) |
| Nitrogen dioxide ($NO_2$) | ($2 \times 10^{-6}$%) |
| Iodine (I) | ($1 \times 10^{-6}$%) |
| Carbon monoxide (CO) | (0.00001%) |

## Composition of alveolar air

Oxygen continuously diffuses out of the gas in the alveoli into the bloodstream, and $CO_2$ continuously diffuses into the alveoli from the blood. In the steady state, inspired air mixes with the alveolar gas, replacing the $O_2$ that has entered the blood and diluting the $CO_2$ that has entered the alveoli. Part of this mixture is expired. The $O_2$ content of the alveolar gas then falls and its $CO_2$ content rises until next inspiration. Since the volume of gas in the alveoli is about 2L at the end of expiration, each 350mL increment of inspired and expired air has relativley little effect on $PO_2$ and $PCO_2$. Indeed, the composition of alveolar gas remains remarkably constant, not only at rest but also under a variety of other conditions.

## 56. Gas exchange in lungs and tissues




**Alveolar ventilation.** Only the alveolar part of the tidal volume reaches the alveoli. The rest stays in the dead space.

The **exchange of gases** between the alveoli and the blood occurs by **diffusion**, as described by Fick's law of diffusion. The driving "force" for this diffusion is provided by the *partial pressure differences* between alveolar space and erythrocytes in pulmonary capillary blood (→**A**). The mean alveolar partial pressure of $O_2$ ($PAO_2$) is about 13.3 kPa (100mmHg) and that of $CO_2$ ($PACO_2$) is about 5.3 kPa (40 mmHg).
The mean partial pressures in the "venous" blood of the pulmonary artery are approx. 5.3 kPa (40mmHg) for $O_2$ ($PVO_2$) and approx. 6.1 kPa (46mmHg) for $CO_2$ (PVCO2).
Hence, the mean **partial pressure difference** between alveolus and capillary is about 8 kPa (60mmHg) for $O_2$ and about 0.8 kPa (6mmHg) for $CO_2$.

Under normal resting conditions, the blood in the pulmonary capillary is in contact with the alveolus for about 0.75 s. This **contact time** (↑**A**) is long enough for the blood to equilibrate with the partial pressure of alveolar gases.
$CO_2$ diffuses much more rapidly than $O_2$.

During physical work (high cardiac output), the contact time falls to a third of the resting value.

### Gas exchange in tissues

$O_2$ diffuses from the peripheral blood to adjacent tissues and $CO_2$ in the opposite direction. Sufficient $O_2$ delivery is ensured by a dense capillary network with a gas exchange area of about $1000m^2$. Diffusion distance is only about 10-25 µm. The driving force for diffusion is the difference in partial pressures of oxygen ($\Delta P_{O_2}$) in the capillary blood and mitochondria where $P_{O_2}$ must not fall below 0, 1 kPa. Using Fick's principle oxygen consumption of a given organ is given by the following formula: $V_{O_2} = Q([O_2]_a - [O_2]_v)$

→ consumption of $O_2$ of an organ is calculated as the difference between the arterial supply ( where Q is the rate of blood flow in the organ L/min) and non-utilized venous $O_2$.
Oxygen supply varies according to the type and function of the organ.

$E_{O_2} = ([O_2]_a - [O_2]_v)/[O_2]_a$ $E_{O_2}$ describes the $O_2$

Under resting conditions: $E_{O_2}$ *(brain) = 0, 04 (4%)* $E_{O_2}$ *(kidney) =0, 07 (7%)*

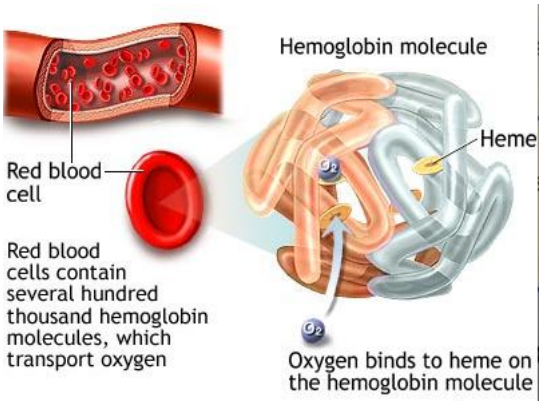
# 57. Transport of $O_2$. Oxygen-haemoglobin dissociation curve.

**>** $O_2$ is carried to in the blood in two forms: dissolved or bound to hemoglobin (most important).

**>** Hemoglobin, at its normal conc., increases the $O_2$-carrying capacity of blood seventyfold.

## Hemoglobin

- is a globular protein of four subunits
- each subunit contains a heme portion, which is a complex of **protoporphyrin IX** and **ferrous iron ($Fe^{2+}$)**.
- each subunit is a polypeptide chain. The hemoglobin tetramer can be envisioned as being composed of two identical dimers, **$(\alpha\beta)_1$** and **$(\alpha\beta)_2$**.



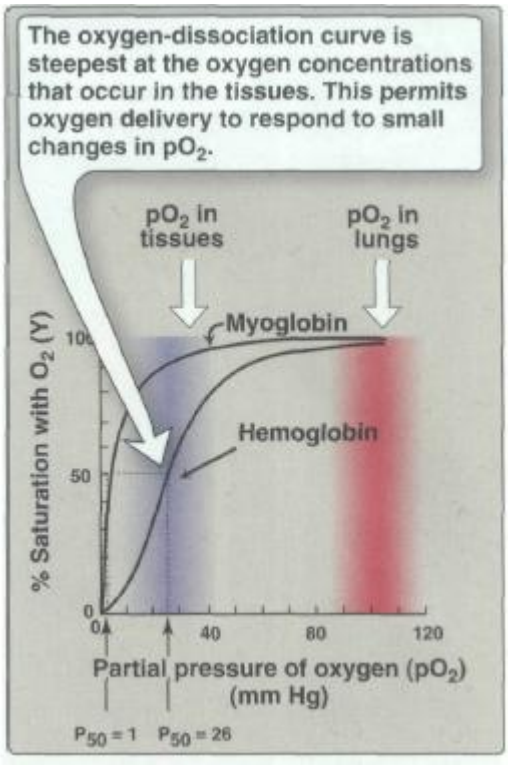

## Fetal hemoglobin [hemoglobin F (HbF)]

- in **fetal hemoglobin**, the **B chains are replaced by ɣ chains.**
- the $O_2$ affinity of fetal hemoglobin is higher than the $O_2$ affinity of adult hemoglobin (left-shift) because 2,3-diphosphoglycerate (DPG) binds less avidly.
- because the $O_2$ affinity fo fetal hemoglobin is higher than the $O_2$ affinity of adult hemoglobin, $O_2$ movement from mother to fetus is facilitated.

## Oxygen dissociation curve

- A plot of Y measured at different partial pressures of oxygen is called the oxygen dissociation curve.

**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 group increases the oxygen affinity of the remaining 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, as shown by the steep upward curve in the region near 20 to 30 mm Hg.




**Shift of the oxygen-dissociation curve:**
Hemoglobin from which 2,3-BPG has been removed has a high affinity for oxygen. However, as seen in the red blood cell, the presence of 2,3-BPG significantly reduces the affinity of hemoglobin for oxygen, shifting the oxygen-dissociation curve to the right (Figure This reduced affinity enables hemoglobin to release oxygen efficiently at the partial pressures found in the tissues.

# 58. Transport of $CO_2$

## Forms of $CO_2$ in blood

> $CO_2$ is produced in the tissues and carried to the lungs in the venous blood in three forms:

**1.** Disolved $CO_2$ (small amount), which is free in solution

**2.** Carbaminohemoglocin (small amount), which is $CO_2$ bound to hemoglobin

**3. $HCO_3^-$** [from hydration of $CO_2$ in red blood cells], which is the major form (90%)

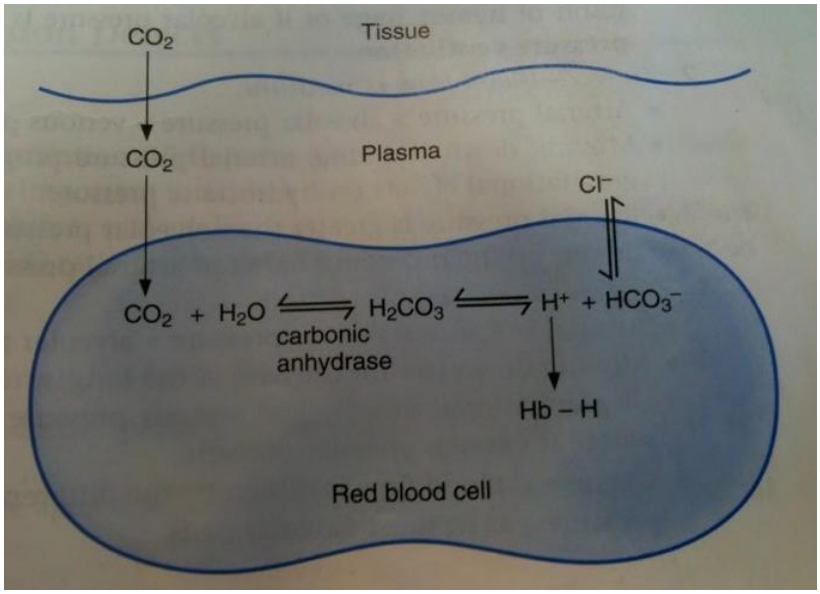
## Transport of $CO_2$ as $HCO_3^-$ (figure below)

**1. $CO_2$ is generated in the tissues** and diffues freely into the venous plasma and then into the RBCs.

**2.** In the RBCs, $CO_2$ combines with $H_2O$ to form $H_2CO_3$, a reaction that is catalyzed by **carbonic anhydrase**. $H_2CO_3$ dissociates into $H^+$ and $HCO_3^-$.

**3. $HCO_3^-$** leaves the TBCs in exchnage for $Cl^-$ **(chloride shift)** and is transported to the lungs in the plasma. $HCO_3^-$ is the major form in which $CO_2$ is transported to the lungs.

**4.** $H^+$ is buffered inside the RBCs by **deoxyhemoglobin**.




**5. In the lungs,** all of the above reactions occur in reverse. $HCO_3^-$ enters the RBCs in exchange for $Cl^-$. $HCO_3^-$ recombines with $H^+$ to form $H_2CO_3$, which decomposes into $CO_2$ and $H_2O$. Thus, $CO_2$, originally generated in the tissues, is expired.

## 59. Herring-Breuer reflexes

In addition to the central nervous system respiratory control mechanisms operating entirely within the brain stem, sensory nerve signals from the lungs alsohelp 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.* The Hering-Breuer inflation reflex is an increase in the duration of expiration produced by steady lung inflation, and the Hering-Breuer deflation reflex is a decrease in the duration of expiration produced by marked deflation of the lung.

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.

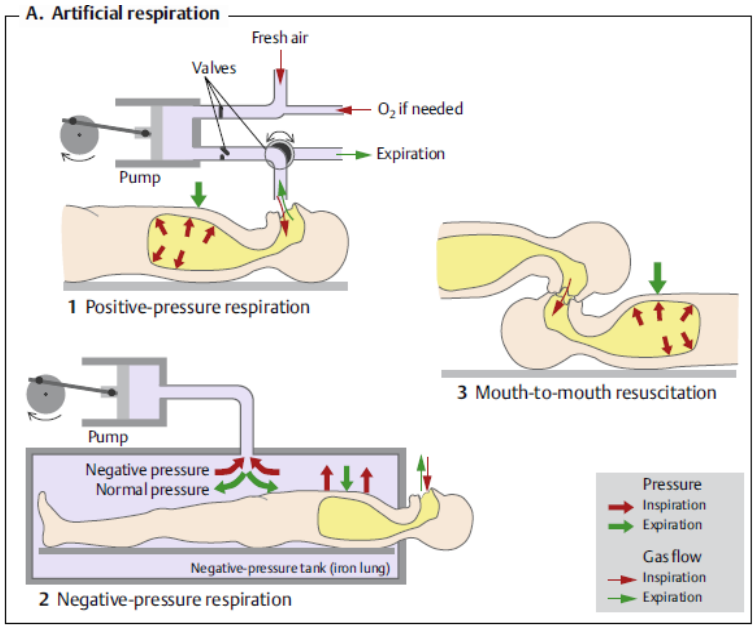
### Responses mediated by receptors in the Airways & Lungs

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. Artefecial 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–1. The expiratory $O_2$ 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, Composition and Functions of Saliva

Saliva is produced in and secreted from the salivary glands. In the salivary glands, the secretory (**zymogen**) granules containing the salivary enzymes are discharged from the acinar cells into the ducts.

About 1500 mL of saliva is secreted per day. The pH of saliva from resting glands is slightly less than 7.0, but during active secretion, it approaches 8.0. Saliva contains two digestive enzymes: **lingual lipase**, secreted by glands on the tongue, and **salivary α-amylase**, secreted by the salivary glands. Saliva also contains **mucins**, glycoproteins that lubricate the food, bind bacteria, and protect the oral mucosa. It also contains the *secretory immune globulin IgA*; *lysozyme*, which attacks the walls of bacteria; *lactoferin*; which binds iron and is bacteriostatic; and *prolinerich proteins* that protect tooth enamel and bind toxic tannins.

Saliva performs a number of important functions. It facilitates swallowing, keeps the mouth moist, serves as a solvent for the molecules that stimulate the taste buds, aids speech by facilitating movements of the lips and tongue, and keeps the mouth and teeth clean. The saliva also has some antibacterial action, and patients with deficient salivation **(xerostomia)** have a higher than normal incidence of dental caries. The buffers in the saliva help maintain the oral pH at about 7.0. they also help neutralize gastric acid and relieve heartburn when gastric juice is regurgitated into the esophagus.

The ionic composition of saliva varies considerably from species to species and from gland to gland. In general, however, saliva secreted in the acini is probably isotonic, with concentrations of $Na^+$, $K^+$, Cl-, and $HCO_3^-$ that are close to those in plasma.

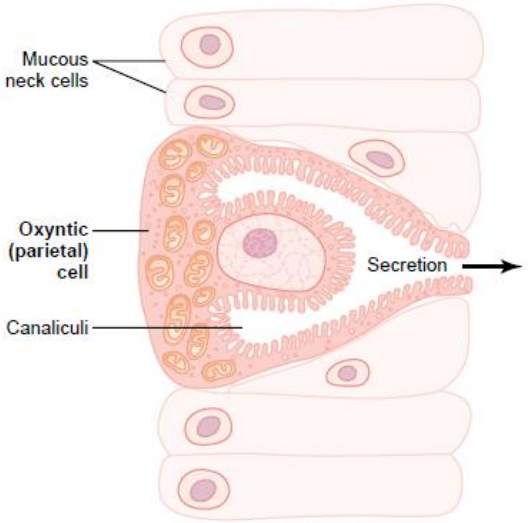
## Control of Salivary Secretion

Salivary secretion is under neural control. Stimulation of the parasympathetic nerve supply causes profuse secretion of watery saliva with a relatively low content of organic material. Associated with this is a pronounced vasodilation in the gland, which appears to be due to the local release of VIP. This polypeptide is a cotransmitter with acetylcholine in some of the postganglionic parasympathetic neurons. Atropine and other cholinergic blocking agents reduce salivary secretion.

Stimulation of the sympathetic nerve supply causes vasoconstriction and, in humans, secretion of small amounts of saliva rich in organic constituents from the submandibular glands.

Food in the mouth causes reflex secretion of saliva, and so does stimulation of the vagal afferent fibers at the gastric end of the esophagus.

## 63. Gastric production of HCL

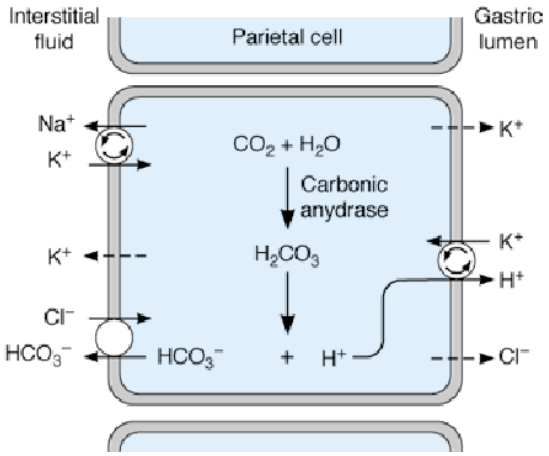



### Basic Mechanism of Hydrochloric Acid Secretion

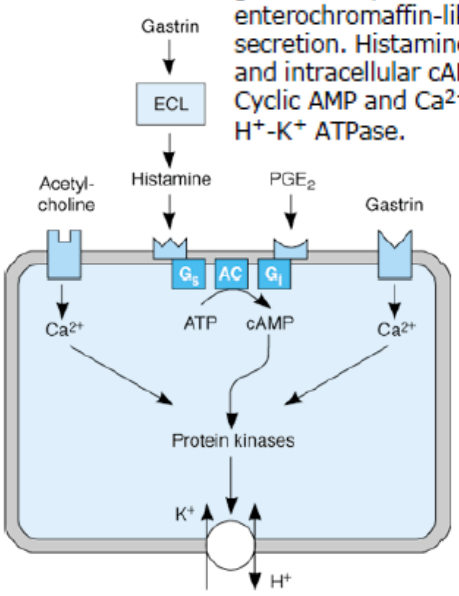
When stimulated, the parietal cells secrete an acid solution that contains about 160 millimoles of hydrochloric acid per liter, which is almost exactly isotonic with the body fluids. The pH of this acid is about 0.8, demonstrating its extreme acidity. At this pH, the hydrogen ion concentration is about 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.

### Secretion by parietal cells

HCL secretion by parietal cells in the stomach is demonstrated in the figure on the right.
Active transport by ATPase is indicated by arrows in circles. $H^+$ is secreted into the gastric lumen in exchange for $K^+$ by $H^+$-$K^+$ ATPase. $HCO_3$- is exchanged for $CL^-$ in the interstitial fluid by an antiport, and $Na^+$-$K^+$ ATPase keeps intracellular $Na^+$ low. Dashed arrows indicate diffusion.

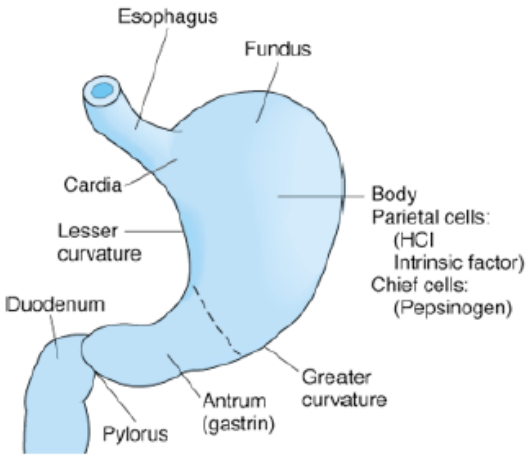



### Regulation of Gastric Acid Secretion by the Parietal Cell.




Regulation of gastric acid secretion by the parietal cell. Acid secretion is increased by acetylcholine acting on $M_3$ muscarinic receptors to increase intracellular $Ca^{2+}$ and by gastrin acting on gastrin receptors to increase intracellular $Ca^{2+}$. In addition, gastrin stimulates histamine secretion by enterochromaffin-like (ECL) cells, and this is the principal way in which gastrin stimulates $H^+$ secretion. Histamine binds to $H_2$ receptors, and via $G_s$, this increases adenylyl cyclase (AC) activity and intracellular cAMP. $PGE_2$ acts via $G_i$ to decrease adenylyl cyclase activity and intracellular cAMP. Cyclic AMP and $Ca^{2+}$ act via protein kinases to increase the transport of $H^+$ into the gastric lumen by $H^+$-$K^+$ ATPase.

## 64. Functions of the stomach




Bolus (masticated food) enters the stomach through the esophagus via the esophageal sphincter. The stomach releases proteases (protein-digesting enzymes such as pepsin) and hydrochloric acid, which kills or inhibits bacteria and provides the acidic pH for the proteases to work. Food is churned by the stomach through muscular contractions of the wall - reducing the volume of the fundus, before looping around the fundus and the body of stomach as the boluses are converted into chyme (partially-digested food). Chyme slowly passes through the pyloric sphincter and into the duodenum, where the extraction of nutrients begins.

In humans, the stomach has a relaxed, near empty volume of about 45 ml. It is a distensible organ. It normally expands to hold about 1 liter of food, but will hold as much as 2-3 liters (whereas a newborn baby will only be able to retain 30ml).

### Control of Secretion and Motility

The movement and the flow of chemicals into the stomach are controlled by both the autonomic nervous system and by the various digestive system hormones:

| | |
|---|---|
| Gastrin | The hormone *gastrin* causes an increase in the secretion of HCl from the parietal cells, and pepsinogen from chief cells in the stomach. It also causes increased motility in the stomach. Gastrin is released by G-cells in the stomach in response to distenstion of the antrum, and digestive products(especially large quantities of incompletely digested proteins). It is inhibited by a pH normally less than 4 (high acid), as well as the hormone somatostatin. |
| Cholecystokinin | *Cholecystokinin* (CCK) has most effect on the gall bladder, causing gall bladder contractions, but it also decreases gastric emptying and increases release of pancreatic juice which is alkaline and neutralizes the chyme. |
| Secretin | In a different and rare manner, *secretin*, produced in the small intestine, has most effects on the pancreas, but will also diminish acid secretion in the stomach. |
| Gastric inhibitory peptide | *Gastric inhibitory peptide* (GIP) decreases both gastric acid release and motility. |
| Enteroglucagon | *enteroglucagon* decreases both gastric acid and motility. |

Other than gastrin, these hormones all act to turn off the stomach action.

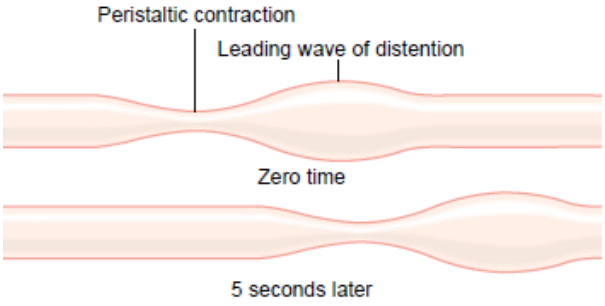
# 65. Motility of the gastrointestinal tract

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* (illustrated in figure).

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.

*Effectual* peristalsis requires an active **myenteric plexus**.

**Mixing Movements**

Mixing movements differ in different parts of the alimentary tract. In some areas, the peristaltic contractions themselves cause most of the mixing.

## 66. Composition and function of pancreatic juice

The pancreatic juice contains enzymes that are of major importance in digestion (table below).
Its secretion is controlled in part by a reflex mechanism and in part by the gastrointestinal hormone secretin and cholecystokinin (CCK).

| Source | Enzyme | Activator | Substrate | Catalytic Function or Products |
|---|---|---|---|---|
| Exocrine pancreas | Trypsin (trypsinogen) | Entero-peptidase | Proteins and polypeptides | Cleave peptide bonds on carboxyl side of basic amino acids (arginine or lysine) |
| | Chymotrypsins (chymotrypsinogens) | Trypsin | Proteins and polypeptides | Cleave peptide bonds on carboxyl side of aromatic amino acids |
| | Elastase (proelastase) | Trypsin | Elastin, some other proteins | Cleaves bonds on carboxyl side of aliphatic amino acids |
| | Carboxypeptidase A (procarboxypeptidase A) | Trypsin | Proteins and polypeptides | Cleave carboxyl terminal amino acids that have aromatic or branched aliphatic side chains |
| | Carboxypeptidase B (procarboxypeptidase B) | Trypsin | Proteins and polypeptides | Cleave carboxyl terminal amino acids that have basic side chains |
| | Collpase (procolipase) | Trypsin | Fat droplets | Facilitates exposure of active site of pancreatic lipase |
| | Pancreatic lipase | ... | Triglycerides | Monoglycerides and fatty acids |
| | Bile salt-acid lipase | | Cholesteryl esters | Cholesterol |
| | Cholesteryl ester hydrolase | ... | Cholesteryl esters | Cholesterol |
| | Pancreatic α-amylase | $Cl^-$ | Starch | Same as salivary α-amylase |
| | Ribonuclease | ... | RNA | Nucleotides |
| | Deoxyribonuclease | ... | DNA | Nucleotides |
| | Phospholipase $A_2$ (prophospholipase $A_2$) | Trypsin | Phospho-lipids | Fatty acids, lysophospholipids |

### Regulation of the Secretion of Pancreatic Juice

Secretion of pancreatic juice is primarily under hormonal control. **Secretin** acts on the pancreatic ducts to cause secretion of a very alkaline pancreatic juice that is rich in HCO3- and poor in enzymes. **Cholecystokinin** acts on the acinar cells to cause the release of zymogen granules and production of pancreatic juice rich in enzymes but low in volume. Its effect is mediated by phospholipase C.

Like CCK, *acetylcholine* acts on acinar cells via phospholipase C to cause discharge of zymogen granules, and stimulation of the vagi causes secretion of a small amount of pancreatic juice rich in enzymes.

# 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

- A large part of amino acid synthesis
- The liver performs several roles in carbohydrate metabolism:
    - *Gluconeogenesis* (the synthesis of glucose from certain amino acids, lactate or glycerol). Note that humans and some other mammals cannot synthesize glucose from glycerol.
    - *Glycogenolysis* (the breakdown of glycogen into glucose)
    - *Glycogenesis* (the formation of glycogen from glucose)(muscle tissues can also do this)
- The liver is responsible for the mainstay of protein metabolism, synthesis as well as degradation
- The liver also performs several roles in lipid metabolism:
    - *Cholesterol synthesis*
    - *Lipogenesis*, the production of triglycerides (fats).
- The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X and XI, as well as protein C, protein S and antithrombin.
- 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.
- 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.
- 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.
- 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

- The breakdown of insulin and other hormones
- The liver breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin).
- 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.
- The liver converts ammonia to urea. Review

## Other functions

- 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.

- 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.
- The liver produces albumin, the major osmolar component of blood serum.
- 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

### Production

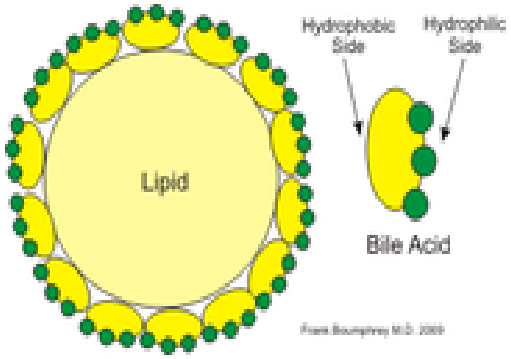
Bile is produced by **hepatocytes** in the liver, draining through the many bile ducts that penetrate the liver. During this process, the epithelial cells add a watery solution that is rich in bicarbonates that dilutes and increases alkalinity of the solution. Bile then flows into the common hepatic duct, which joins with the cystic duct from the **gallbladder** to form the common bile duct. The common bile duct in turn joins with the pancreatic duct to empty into the duodenum. If the *sphincter of Oddi* is closed, bile is prevented from draining into the intestine and instead flows into the gallbladder, where it is stored and concentrated to up to five times its original potency between meals. This concentration occurs through the absorption of water and small electrolytes, while retaining all the original organic molecules. Cholesterol is also released with the bile, dissolved in the acids and fats found in the concentrated solution. When food is released by the stomach into the duodenum in the form of chyme, the duodenum releases cholecystokinin, which causes the gallbladder to release the concentrated bile to complete digestion.

The human liver can produce close to one litre of bile per day (depending on body size). About 95% of the salts secreted in bile are reabsorbed in the terminal ileum and re-used. Blood from the ileum flows directly to the hepatic portal vein and returns to the liver where the hepatocytes reabsorb the salts and return them to the bile ducts to be re-used, sometimes two to three times with each meal.

### 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 |

## Physiological functions




Bile acts to some extent as a surfactant, helping to emulsify the fats in the food. Bile salt anions have a hydrophilic side and a hydrophobic side, and therefore tend to aggregate around droplets of fat (triglycerides and phospholipids) to form micelles, with the hydrophobic sides towards the fat and hydrophilic towards the outside. The hydrophilic sides are positively charged due to the lecithin and other phospholipids that compose bile, and this charge prevents fat droplets coated with bile from re-aggregating into larger fat particles. Ordinarily, the micelles in the duodenum have a diameter of around 14-33 µm.

The dispersion of food fat into micelles thus provides a largely increased surface area for the action of the enzyme pancreatic lipase, which actually digests the triglycerides, and is able to reach the fatty core through gaps between the bile salts. A triglyceride is broken down into two fatty acids and a monoglyceride, which are absorbed by the villi on the intestine walls. After being transferred across the intestinal membrane, fatty acids are reformed into triglycerides, and then absorbed into the lymphatic system through lacteals. Without bile salts, most of the lipids in the food would be passed out in feces, undigested.

Since bile increases the absorption of fats, it is an important part of the absorption of the fat-soluble substances, such as the vitamins D, E, K and A.

Besides its digestive function, bile serves also as the route of excretion for bilirubin, a byproduct of red blood cells recycled by the liver. Bilirubin derives from hemoglobin by glucuronidation.

The alkaline bile also has the function of neutralizing any excess stomach acid before it enters the ileum, the final section of the small intestine. Bile salts also act as bactericides, destroying many of the microbes that may be present in the food.

## 69. Digestion in the small intestine

The small intestine is where most chemical digestion takes place. Most of the digestive enzymes that act in the small intestine are secreted by the pancreas and enter the small intestine via the pancreatic duct. The enzymes enter the small intestine in response to the hormone cholecystokinin, which is produced in the small intestine in response to the presence of nutrients. The hormone secretin also causes bicarbonate to be released into the small intestine from the pancreas in order to neutralize the potentially harmful acid coming from the stomach.

The three major classes of nutrients that undergo digestion are proteins, lipids (fats) and carbohydrates:

- **Proteins** and **peptides** are degraded into amino acids. Chemical breakdown begins in the stomach and continues in the small intestine. Proteolytic enzymes, including trypsin and chymotrypsin, are secreted by the pancreas and cleave proteins into smaller peptides. Carboxypeptidase, which is a pancreatic brush border enzyme, splits one amino acid at a time. Aminopeptidase and dipeptidase free the end amino acid products.
- **Lipids** (fats) are degraded into fatty acids and glycerol. **Pancreatic lipase** breaks down triglycerides into free fatty acids and monoglycerides. Pancreatic lipase works with the help of the salts from the bile secreted by the liver and the gall bladder. Bile salts attach to triglycerides to help emulsify them, which aids access by pancreatic lipase. This occurs because the lipase is water-soluble but the fatty triglycerides are hydrophobic and tend to orient towards each other and away from the watery intestinal surroundings. The bile salts are the "middle man" that holds the triglycerides in the watery surroundings until the lipase can break them into the smaller components that are able to enter the villi for absorption.
- Some **carbohydrates** are degraded into simple sugars, or monosaccharides (e.g., glucose). **Pancreatic amylase** breaks down some carbohydrates (notably starch) into oligosaccharides. Other carbohydrates pass undigested into the large intestine and further handling by intestinal bacteria. Brush border enzymes take over from there. The most important brush border enzymes are ***dextrinase*** and ***glucoamylase*** which further break down oligosaccharides. Other brush border enzymes are *maltase*, *sucrase* and *lactase*. Lactase is absent in most adult humans and for them lactose, like most poly-saccharides are not digested in the small intestine. Some carbohydrates, such as cellulose, are not digested at all, despite being made of multiple glucose units.

## 70. Functions of colon

The large intestine comes after the small intestine in the digestive tract and measures approximately 1.5 meters in length. Although there are differences in the large intestine between different organisms, the large intestine is mainly responsible for storing waste, reclaiming water, maintaining the water balance, absorbing some vitamins, such as vitamin K, and providing a location for flora-aided fermentation.

By the time the chyme has reached this tube, most nutrients and 90% of the water have been absorbed by the body. At this point some electrolytes like sodium, magnesium, and chloride are left as well as indigestible parts of ingested food (e.g., a large part of ingested amylose, protein which has been shielded from digestion heretofore, and dietary fiber, which is largely indigestible carbohydrate in either soluble or insoluble form). As the chyme moves through the large intestine, most of the remaining water is removed, while the chyme is mixed with mucus and bacteria (known as gut flora), and becomes feces. The ascending colon receives fecal material as a liquid. The muscles of colon then move the watery waste material forward and slowly absorb all the excess water. The stools get to become semi solid as they move along into the descending colon. The bacteria break down some of the fiber for their own nourishment and create acetate, propionate, and butyrate as waste products, which in turn are used by the cell lining of the colon for nourishment. The large intestine produces no digestive enzymes -— chemical digestion is completed in the small intestine before the chyme reaches the large intestine. The pH in the colon varies between 5.5 and 7 (slightly acidic to neutral).

Most people can avoid problems in their colon simply by eating a diet which is high in fiber and fruits and low in lean meat.

## 71. Resorption of lipids in the small intestine

### Digestion of Lipids in Small Intestine

(1) **Bile acids** emulsify lipids in the small intestine, increasing the surface area for digestion
(2) **Pancreatic lipases** hydrolyze lipids to fatty acids, monoglycerides, cholesterol, and lysolecithin. The enzymes are *pancreatic lipase*, *cholesterol ester hydrolase*, and *phospholipase* $A_2$.
(3) The hydrophobic products of lipid digestion are solubilized in **micelles** by **bile acids.**

### Absorption of lipids

a. Micelles bring the products of lipid digestion into contact with the absorptive surface of intestinal cells. Then, **fatty acids, monoglycerides, and cholesterol diffuse across the luminal membranes into the cells**. Glycerol is hydrophilic and is not contained in the micelles.
b. In the intestinal cells, the products of lipid digestion are **re-esterified** to triglycerides, cholesterol ester, and phospholipids and, with *apoproteins*, form **chylomicrons**.
c. Chylomicrons are transported out of the intestinal cells by **exocytosis**. Because chylomicrons are too large to enter the capillaries, they are transferred to **lymph vessels** and are added to the bloodstream via the thoracic duct.

## 72. Resorption of minerals and water in small intestine

The average intake of water (in beverages and foodstuffs) is roughly 1.5 L per day.
An additional 7 L of fluid are secreted into the gastrointestinal (GI) tract (saliva, gastric juices, bile, pancreatic juice and intestinal secretions), whereas only about 0.1 L/day is eliminated in the feces.
The digestive tract must therefore absorb a net volume of at least 8.4 L of water per day.
GI **absorption of water** occurs mainly in the jejunum and ileum, with smaller quantities being absorbed by the colon. Water is driven through the intestinal epithelium by osmosis.
When solutes ($Na^+$, $Cl^-$, etc.) are absorbed in the intestine, water follows.
(The stool contains only small quantities of $Na^+$, $Cl^-$ and water.) Conversely, the secretion of substances into the lumen or the ingestion of non-absorbable substances leads to water fluxes into the lumen. Poorly absorbable substances therefore act as *laxatives* (e.g. sulfate, sorbitol, polyethylene glycol).

Water absorption is mainly driven by the **absorption of Na+, Cl–** and **organic compounds**.
The luminal concentration of $Na^+$ and $Cl^-$ steadily decreases from the duodenum to the colon. That of $Na^+$, for example, is approximately 145 mmol/L in the duodenum, 125 mmol/L in the ileum and only 40 mmol/L in the colon. $Na^+$ is absorbed by various **mechanisms**, and the *$Na^+$-$K^+$-ATPase* on the basolateral cell membrane is the primary driving mechanism for all of them.

- **Symport of $Na^+$ and organic substances**: $Na^+$ passively influxes into cells of the duodenum and jejunum via symporter carriers, which actively cotransport glucose, amino acids, phosphates and other compounds (secondary active transport). Since this is an electrogenic transport mechanism, a *lumen-negative transepithelial potential* (L**N**TP) forms that drives Cl– out of the lumen.
- **Parallel transport of $Na^+$ and $Cl^-$**: Na+ ions in the lumen of the ileum are exchanged for $H^+$ ions while $Cl^-$ is exchanged for $HCO_3^-$ at the same time. The $H^+$ ions combine with $HCO_3^-$ to yield $H_2O + CO_2$, which diffuse out of the lumen. Most $Na^+$, $Cl^-$ and, by subsequent osmosis, $H_2O$ is absorbed by this electroneutral transport mechanism.
- **$Na^+$ diffusion**: $Na^+$ in the colon is mainly absorbed through luminal *$Na^+$ channels*.
  This type of $Na^+$ transport is electrogenic and aldosterone-dependent. The related lumen-negative transepithelial potential (L**N**TP) either leads to $K^+$ secretion or drives $Cl^-$ out of the lumen.

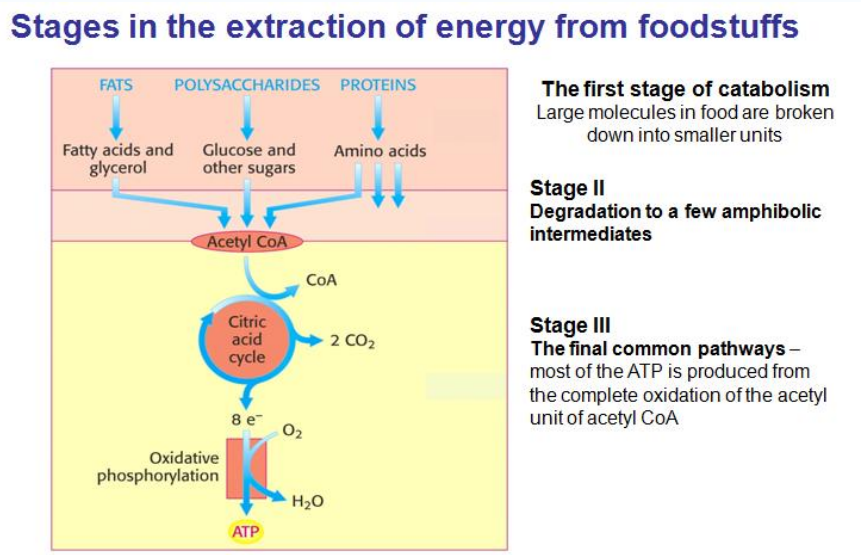
- The **$Cl^-$ secretion** mechanism of epithelial cells (mainly *Lieberkühn's crypts*) is similar to that of the acini of salivary glands. The efflux of $Cl^-$ into the lumen and the associated efflux of $Na^+$ and water are stimulated by cAMP and regulated by neurons and hormones such as *VIP (vasoactive intestinal peptide)* and prostaglandins. The physiological function of this form of $H_2O$ secretion could be to dilute viscous chyme or to ensure the recirculation of water (from the crypts → lumen → villi → crypts) to promote the absorption of poorly soluble substances.

- In addition to **$HCO_3^-$** from pancreatic juice, $HCO_3^-$ is also secreted into the intestinal lumen by the small and large intestine. **$K^+$** is secreted (*aldosterone-dependent*) by crypt cells of the colon (luminal $K^+$ concentration 90 mmol/l**!**) and reabsorbed via the *$H^+$-$K^+$ pump* of the surface epithelium. The aldosterone-dependent $K^+$ secretion/absorption ratio determines the net amount of $K^+$ excreted. *Diarrhea* results in losses of $K^+$ and $HCO_3^-$ (hypokalemia and metabolic acidosis).

- **$Ca^{2+}$.** The stool contains one-third of the dietary $Ca^{2+}$ intake. $Ca^{2+}$ is absorbed in the upper part of the small intestine with the aid of intracellular *calcium-binding protein* (**CaBP**). Calcitriol increases CaBP synthesis, thereby increasing $Ca^{2+}$ absorption. Deficiencies of vitamin D or substances that form water-insoluble compounds with $Ca^{2+}$ (phytin, oxalate, fatty acids) decrease Ca2+ absorption.

- **Iron absorption** occurs mainly in the duodenum. Fe supplied by the diet (hemoglobin, myoglobin found chiefly in meat and fish) is absorbed relatively efficiently as a **heme-Fe** by *HCP1* (heme carrier protein 1). Within mucosal cells, $Fe^{3+}$ is released by *heme oxygenase* and reduced to $Fe^{2+}$ which is transported across the cell by ***mobilferrin***. It either enters the bloodstream or remains in the mucosa as a ferritin-Fe(III) complex and returns to the gut lumen during cell turnover.

## 73. Intermediary metabolism




## 74. Nitrogen balance

Nitrogen balance is the measure of nitrogen output subtracted from nitrogen input.

Blood urea nitrogen can be used in estimating nitrogen balance, as can the urea concentration in urine.

- A **positive value** is often found during periods of growth, tissue repair or pregnancy. This means that the intake of nitrogen into the body is greater than the loss of nitrogen from the body, so there is an increase in the total body pool of protein.
- A **negative value** can be associated with burns, fevers, wasting diseases and other serious injuries and during periods of fasting. This means that the amount of nitrogen excreted from the body is greater than the amount of nitrogen ingested.

During growth and tissue repair (convalescence) the body is in positive N balance, i.e. intake is greater than loss and there is an increase in the total body pool of protein. In fevers, fasting, and wasting diseases the loss is greater than the intake and the individual is in negative balance; there is a net loss of protein from the body

- ✓ It can be used in the evaluation of malnutrition.

# 75. Metabolism of cholesterol. Atherosclerosis.

## 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

## *Iron Metabolism*

The total quantity of iron in the body averages 4 to 5 grams, about 65 per cent of which is in the form of hemoglobin. About 4 per cent is in the form of myoglobin, 1 per cent is in the form of the various heme compounds that promote intracellular oxidation, 0.1 per cent is combined with the protein transferrin in the blood plasma, and 15 to 30 per cent 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*

When iron is absorbed from the small intestine, it immediately combines in the blood plasma with a beta globulin, ***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 mainly with a protein, *apoferritin,* to form *ferritin.* This iron stored as ferritin is called *storage iron.*

Smaller quantities of the iron in the storage pool are in an extremely insoluble form called ***hemosiderin.*** 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.

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.

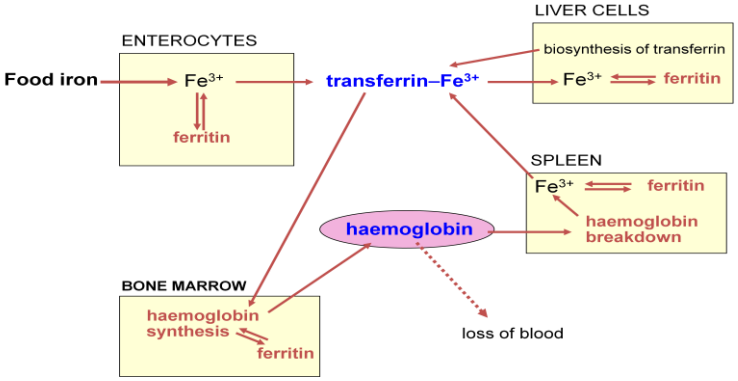
### *Absorption of Iron from the Intestinal Tract*

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, two of the most important sources of iron in the diet. 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, at a maximum rate of only a few milligrams per day. 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



## 77. Bone formation and resorption

The cells responsible for bone formation are **osteoblasts** and the cells responsible for bone resorption are **osteoclasts**.

Later, **ossification-specific factors** begin to appear. One of the most interesting is the *transcription factor Cbfa1*. Mice in which the gene for Cbfa1 is knocked out develop to term with their skeletons made exclusively of cartilage; no ossification occurs.

Stromal cells in the bone marrow, osteoblasts, and T lymphocytes all express a molecule called RANKL (**RANK** ligand) on their surface, and when they come in contact with appropriate monocytes they bind to RANKL receptors (RANK) on the surfaces of the monocytes. They also secrete M-CSF, and it binds to a receptor, c-fins, on the monocytes. This combination converts monocytes into osteoclasts.

Osteoclasts erode and absorb previously formed bone. Throughout life, bone is being constantly resorbed and new bone is being formed. First, osteoclasts resorb bone, and then osteoblasts lay down new bone in the same general area.

**Ossification** (or **osteogenesis**) is the process of laying down new bone material by cells called osteoblasts. It is synonymous with bone tissue formation. There are two processes resulting in the formation of normal, healthy bone tissue. Intramembranous ossification is the direct laying down of bone into the primitive connective tissue (mesenchyme), while endochondral ossification involves cartilage as a precursor.

In fracture healing, endochondral osteogenesis is the most commonly occurring process, for example in fractures of long bones treated by plaster of Paris, whereas fractures treated by open reduction and stabilization by metal plate and screws may heal by intramembranous osteogenesis.

# 78. Hyperthermia and hypothermia

## Hyperthermia

Is an elevated body temperature due to failed thermoregulation. Hyperthermia occurs when the body produces or absorbs more heat than it can dissipate. When the elevated body temperatures are sufficiently high, hyperthermia is a medical emergency and requires immediate treatment to prevent disability and death.

The most common causes are heat stroke and adverse reactions to drugs. Heat stroke is an acute condition of hyperthermia that is caused by prolonged exposure to excessive heat and/or humidity. The heat-regulating mechanisms of the body eventually become overwhelmed and unable to effectively deal with the heat, causing the body temperature to climb uncontrollably. Hyperthermia is a relatively rare side effect of many drugs, particularly those that affect the central nervous system.

In **malignant hyperthermia**, various mutations of the *gene coding for the ryanodine receptor* lead to excess $Ca^{2+}$ release during muscle contraction triggered by stress. This in turn leads to contractures of the muscles, increased muscle metabolism, and a great increase in heat production in muscle. The increased heat production causes a marked rise in body temperature that is fatal if not treated.

Hyperthermia can be created artificially by drugs or medical devices. Hyperthermia therapy may be used to treat some kinds of cancer and other conditions, most commonly in conjunction with radiotherapy.

Hyperthermia differs from fever in the mechanism that causes the elevated body temperatures: a fever is caused by a change in the body's temperature set-point.

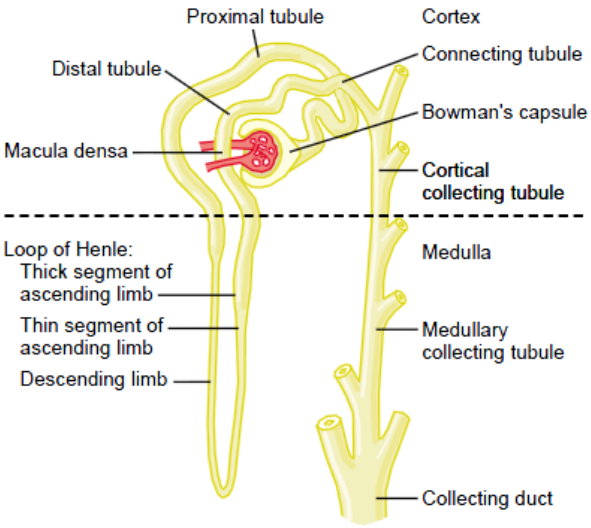
The opposite of hyperthermia is hypothermia, which occurs when an organism's temperature drops below that required for normal metabolism.

## Hyperthermia

In hibernating mammals, body temperature drops to low levels without causing any demonstrable ill effects on subsequent arousal. When the skin or the blood is cooled enough to lower the body temperature in nonhibernating animals and in humans, metabolic and physiological processes slow down. Respiration and heart rate are very low, blood pressure is low, and consciousness is lost.

Humans tolerate body temperatures of 21-24 *C (70-75 *F) without permanent ill effects, and induced hypothermia has been used in surgery. On the other hand, accidental hypothermia due to prolonged exposure to cold air or cold water is a serious condition and requires careful monitoring and immediate rewarming.

# 79. Functional morphology of nephron




## The Nephron Is the Functional Unit of the Kidney

Each kidney in the human contains about 1 million *nephrons,* each capable of forming urine.

Each nephron contains **(1)** a tuft of glomerular capillaries 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 ascending 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***. 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.

# 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

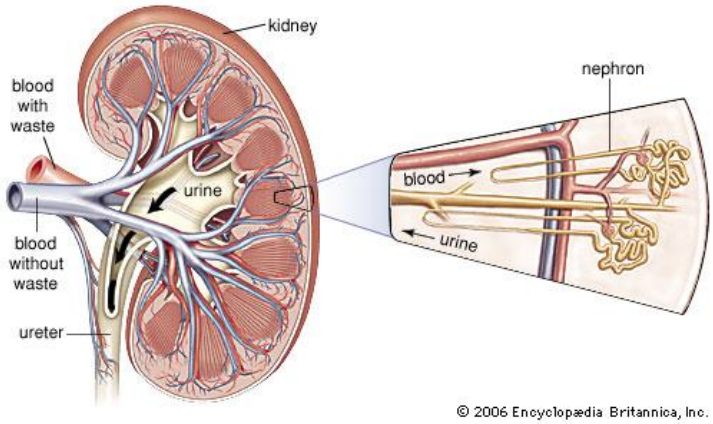
In general, tubular reabsorption is quantitatively more important than tubular secretion in the formation of urine, but secretion plays an important role in determining the amounts of potassium and hydrogen ions and a few other substances that are excreted in the urine. Most substances that must be cleared 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

## Renal blood flow




In a resting adult, the kidneys receive 1.2-1.3 L of blood per minute, or just under 25% of the cardiac output. Renal blood flow can be measured with electromagnetic or other types of flow meters, or it could be determined by applying the Fick principle to the kidney – ie, by measuring the amount of a given substance taken up per unit of time and dividing this value by the arteriovenous difference for the substance across the kidney. Since the kidney filters plasma, the **renal plasma flow** equals the amount of a substance excreted per unit of time divided by the renal arteriovenous difference as long as the amount of red cells is unaltered during the passage through the kidney.

Renal blood flow can be measured by infusing *p*-aminohippuric acid (PAH) and determine its urine and plasma concentrations. PAH is filtered by the glomeruli and secreted by the tubular cells, so that its **extraction ratio** (arterial conc. minus the renal venous conc. divided by arterial conc.) is higher. For example, when PAH is infused at low doses, 90 % of the PAH in arterial blood is removed in a single circulation through the kidney. It has therefore become common to calculate the "renal plasma flow" by dividing the amount of PAH in the urine by the plasma PAH level, ignoring the level in renal venous blood. The value obtained should be called the **effective renal plasma flow (ERPF)** to indicate that the level of renal venous plasma was not measured. In humans, ERPF averages about 625 mL/min.

$$\text{Effective renal plasma flow (ERPF)} = \frac{U_{PAH}\,\dot{V}}{P_{PAH}} = \text{Clearance of PAH } (C_{PAH})$$

## Regulation of the Renal Blood flow

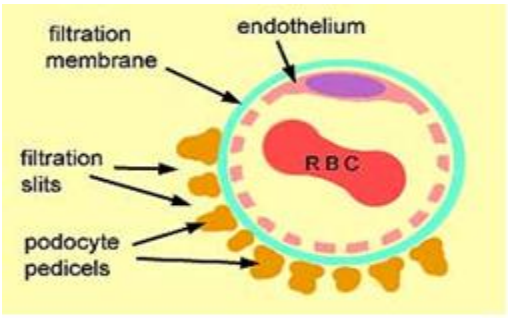
- ✓ Norepinephrine constricts the renal vessels.
- ✓ Dopamine causes renal vasodilatation and natriuresis.
- ✓ Angiotensin exerts a great effect on the efferent arterioles.
- ✓ Prostaglandins increase blood flow in the renal cortex and decrease flow in renal medulla
- ✓ Acetylcholine also produces renal vasodilatation.
- ✓ A high protein diet raises glomerular capillary pressure and increase renal blood flow

## Autoregulation of Renal Blood Flow

When the kidney is perfused at moderate pressures, the renal vascular resistance varies with the pressure so that renal blood flow is relatively constant. Renal autoregulation is present in denervated and in isolated, perfused kidneys but is prevented by administration of drugs that paralyze vascular smooth muscle. It is probably produced in part by a direct contractile response of the smooth muscle of the afferent arteriole to stretch. NO may also be involved. Angiotensin II also appears to play a role by constricting the efferent arterioles, thus maintaining the glomerular filtration rate.

# 82. Glomerular filtration

## Measuring GFR




The **glomerular filtration rate (GFR)** can be measured in intact experimental animals and humans by measuring the excretion and plasma level of a substance that is freely filtered through the glomeruli and neither secreted nor reabsorbed by the tubules. The amount of such a substance in the urine per unit of time must have been provided by filtering exactly the number of milliliters of plasma that contained this amount. Therefore, if a substance is designed by the letter X, the GFR is equal to the conc. of X in urine ($U_x$) times the **urine flow** per unit of time (V) divided by the **arterial plasma level** of X ($P_x$), or $U_xV/P_x$. This value is called the clearance of X ($C_x$).

## Substances Used to Measure GFR

A suitable substance for measuring the GFR should be nontoxic and not metabolized by the body. **Inulin**, a polymer of fructose, meets the criteria in humans and most animals and is extensively used to measure GFR. In practice, a loading dose of inulin is administrated intravenously, followed by a sustaining infusion to keep the arterial plasma level constant. After the inulin has equilibrated with body fluids, an accurately timed urine specimen is collected and a plasma sample is obtained halfway through the collection. Plasma and urinary inulin conc. are determined and the clearance calculated.

In dogs, cats, rabbits, and a number of other mammalian species, **clearance of creatinine ($C_{Cr}$)** can also be used to determine the GFR, but in primates, including humans, some creatinine is secreted by the tubules and some may be reabsorbed. Plasma creatinine determinations are inaccurate at low creatinine levels because the method for determining creatinine measures small amounts of other plasma constitutes. In spite of this, the clearance of endogenous creatinine is frequently measured in patients.

## Normal GFR

The GFR in an average-sized man is approx. 125 mL/min. Values in women are 10% lower than those in men. A rate of 125 mL/min is 7.5 L/h, or 180 L/d, whereas the normal urine volume is about 1 L/d. Thus, 99% or more of the filtrate is normally reabsorbed.

## Control of GFR

Factors include the size of the capillary bed, the permeability of the capillaries, and the hydrostatic and osmotic pressure gradients across the capillary wall. For each nephron:

$$GFR = K_f[(P_{GC} - P_T) - (\pi_{GC} - \pi_T)]$$

**$K_f$**, the glomerular ultrafiltraton coefficient, is the product of the glomerular capillary wall hydraulic conductivity (i.e., its permeability) and the effective filtration surface area. **$P_{GC}$** is the mean hydrostatic pressure in the glomerular capillaries, **$P_T$** the mean hydrostatic pressure in the tubule, **$\pi_{GC}$** the osmotic pressure of the plasma in the glomerular capillaries, and **$\pi_T$** the osmotic pressure pf the filtrate in the tubule.

>> The ratio of the GFR to the renal plasma flow (RPF), the **filtration fraction**, is normally 0.16-0.20.

## 83. Function of renal tubules

### Mechanism of Tubular Reabsorption & Secretion

Small proteins and some peptide hormones are reabsorbed in the proximal tubules by endocytosis. Other substances are secreted or reabsorbed in the tubules by passive diffusion between cells and through cells by facilitated diffusion down chemical or electrical gradients or active transport against such gradients. Movement is by way of ion channels, exchangers, cotransporters, and pumps.

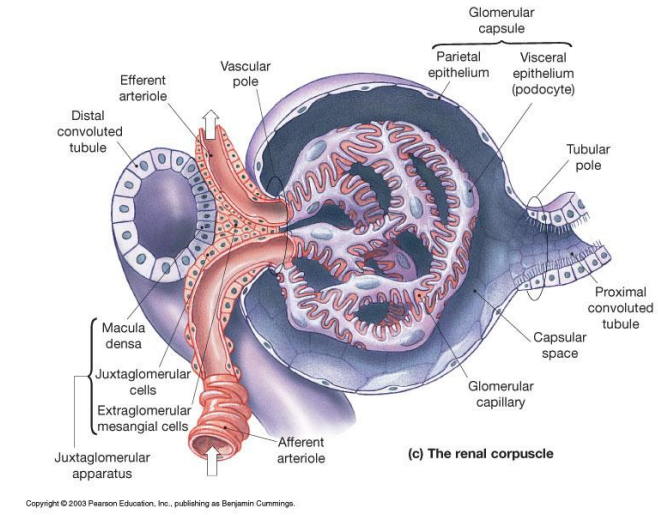
It is important to know that the pumps and other units in the luminal membrane are different from those in the basolateral membrane. It is this different distribution that makes possible net movement of solutes across epithelia.

Like transport systems, elsewhere, renal active transport systems have a maximal rate, or **transport maximum ($T_m$)**, at which they can transport a particular solute. Thus, the amount of a particular solute transport is proportionate to the amount present up to the $T_m$, for the solute, but at higher conc., the transport mechanism is **saturated** and there is no appreciable increment in the amount transported. However, the $T_m$ for some systems are high, and it is difficult to saturate them.

It should be noted that the tubular epithelium, like that of the small intestine and gallbladder, is a **leaky epithelium** in that the tight junctions between the cells permit the passage of some water and electrolytes. The degree to which the leakage by this **paracellular pathway** contributes to the net flux of fluid and solute into and out of the tubules is controversial since it is difficult to measure, but current evidence seems to suggest that it is a significant factor. One indication of this is that paracellin-1, a protein localized to tight junctions, is related to $Mg^{2+}$ reabsorption, and loss-of-function mutation of its gene causes severe $Mg^{2+}$ and $Ca^{2+}$ loss in the urine.

## 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 and Macula Densa 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**

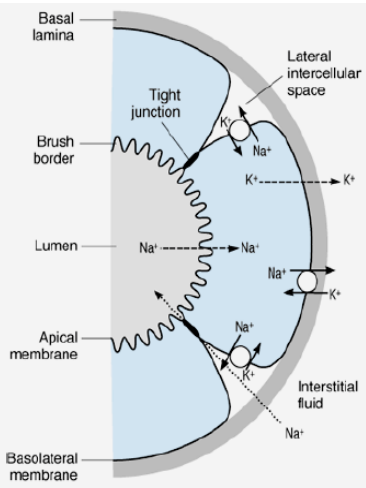
Macula densa cells are columnar epithelium thickening of the distal tubule. The macula densa senses sodium chloride concentration in the distal tubule of the kidney and secretes a locally active (paracrine) *vasopressor* which acts on the adjacent afferent arteriole to decrease glomerular filtration 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

## Na+ Reabsorption

The reabsorption of *$Na^+$ and $Cl^-$* plays a major role 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.




Mechanism for $Na^+$ reabsorption in the proximal tubule. Solid lines indicate active transport; dashed lines indicate cotransport; and the dotted line indicates passive diffusion. Note that $Na^+$ moves from the lumen into the cells by cotransport and that $Na^+$ and $H_2O$ diffuse into the tubular lumen at the intercellular tight junctions.

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 $Na^+$–2$Cl^-$–$K^+$ 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 channels in the collecting ducts**, and this is *the portion that is regulated by aldosterone in the production of homeostatic adjustments in $Na^+$ balance*.

## 87. Transport of glucose in kidneys

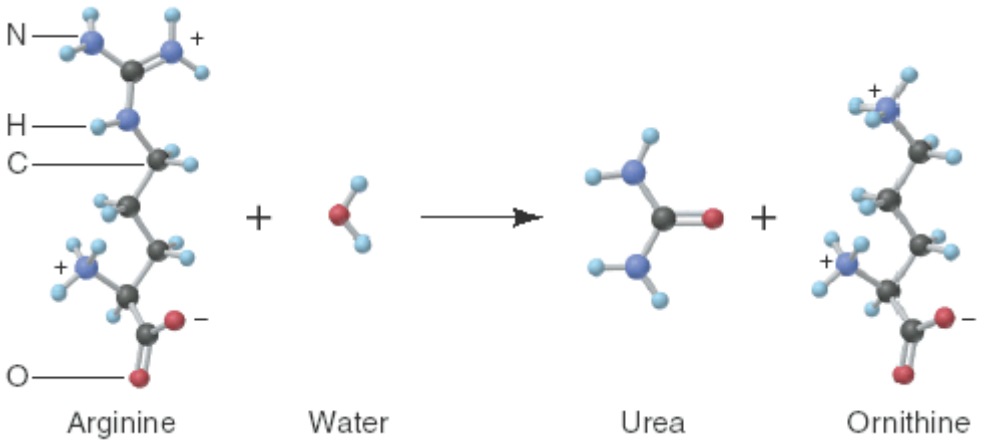
Glucose reabsorption in the kidneys is similar to glucose reabsorption in the intestine. Glucose and $Na^+$ bind to common carrier SGLT 2 in the luminal membrane, and glucose is carried into the cell as $Na^+$ moves down its electrical and chemical gradient. The $Na^+$ is then pumped out of the cell into the interstitium, and the glucose is transported by GLUT 2 into the interstitial fluid.

The common carrier specifically binds the d isomer of glucose, and the rate of transport of D-glucose is many times greater than that of L-glucose. Glucose transport in the kidneys is inhibited, as it is in the intestine, by the plant glucoside **phlorhizin**, which competes with D-glucose for binding to the carrier.

## 88. Urea formation

Most of the $NH^{4+}$ formed by deamination of amino acids in the liver is converted to urea, and the urea is excreted in the urine. The $NH^{4+}$ forms carbamoyl phosphate, and in the mitochondria it is transferred ornithine, forming citrulline. The enzyme involved is *ornithine carbamoyltransferase*. Citrulline is converted to arginine, after which urea is split off and ornithine is regenerated.

Most of the urea is formed in the liver, and in severe liver disease the blood urea nitrogen (BUN) falls and blood $NH_3$ rises. Congenital deficiency of ornithine carbamoyltransferase can also lead to NH3 intoxication, even in individuals who are heterozygous for this deficiency.



# 89. Hyper- and hypotonic urine. Counter-current system.

## Hyper- and hypotonic urine

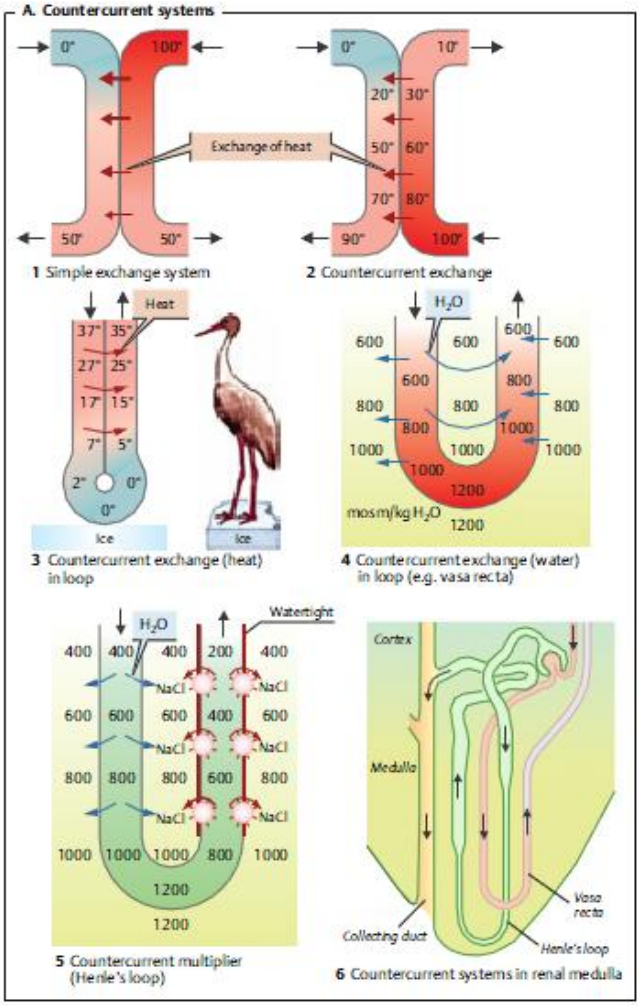
The **osmolality** of plasma and glomerular filtrate is about 290 mOsm/kgH2O (=$P_{osm}$); that of the final urine ($U_{osm}$) ranges from50 (hypotonic urine in extreme water diuresis) to about 1200mOsm/kg H2O (hypertonic urine in maximally concentrated urine).

## 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 *C) 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 *C 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.

# 90. Osmotic and water diuresis

## Water diuresis

Is the excretion of urine after drinking water; results from reduced secretion of the antidiuretic hormone of the neurohypophysis in response to the lowered osmotic pressure of the blood.

## Osmotic diuresis

Osmotic diuresis is increased urination caused by the presence of certain substances in the small tubes of the kidneys. The excretion occurs when substances such as glucose enter the kidney tubules. The substances cause an increase in the osmotic pressure within the tubule, causing retention of water within the lumen, and thus reduces the reabsorption of water, increasing urine output (ie. diuresis). The same effect can be seen in therapeutics such as Mannitol.

Substances in the circulation can also increase the amount of circulating fluid by increasing the osmolarity of the blood. This has the effect of pulling water from the interstitial space, making more water available in the blood and causing the kidney to compensate by removing it as urine. In hypotension, often colloids are used intravenously to increase circulating volume in themselves, but as they exert a certain amount of osmotic pressure, water is therefore also moved, further increasing circulating volume. As blood pressure increases, the kidney removes the excess fluid as urine.

Sodium, chloride, potassium are excreted in Osmotic diuresis, originating from Diabetes Mellitus (DM). Osmotic diuresis results in dehydration from polyuria and the classic polydipsia (excessive thirst) associated with DM.

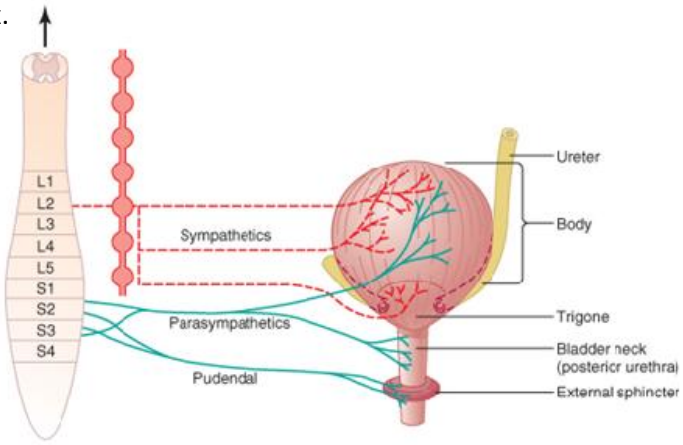
**Differences**

It is important to recognize the difference between osmotic diuresis and water diuresis. In water diuresis, the amount of water reabsorbed in the proximal portions of the nephron is normal, and the maximal urine flow that can be produced is about 16mL/min. In osmotic diuresis, increased urine flow is due to decreased water reabsorption in the proximal tubules and loops and very large urine flows can be produced.

## 91. Micturition

**Urination**, also known as micturition, is the process of disposing of urine from the urinary bladder through the urethra to the outside of the body. In healthy humans the process of urination is under voluntary control. In infants, elderly individuals and those with neurological injury, urination may occur as an involuntary reflex. In other animals, in addition to urination serving the purpose of expulsion of waste material, the act can serve to mark territory or express submissiveness.

Physiologically, micturition involves coordination between the central, autonomic and somatic nervous systems. Brain centers that regulate urination include the pontine micturition center, periaqueductal gray, and the cerebral cortex.




In healthy individuals, the lower urinary tract has two discrete phases of activity: the storage (or guarding) phase, when urine is stored in the bladder; and the voiding phase, when urine is released through the urethra. The state of the reflex system is dependent on both a conscious signal from the brain and the firing rate of sensory fibers from the bladder and urethra. At low bladder volumes, afferent firing is low, resulting in excitation of the outlet (the sphincter and urethra), and relaxation of the bladder. At high bladder volumes, afferent firing increases, causing a conscious sensation of urinary urge. When the individual is ready to urinate, he or she consciously initiates voiding, causing the bladder to contract and the outlet to relax. Voiding continues until the bladder empties completely, at which point the bladder relaxes and the outlet contracts to re-initiate storage.
The muscles controlling micturition are controlled by the autonomic and somatic nervous systems. During the storage phase the internal urethral sphincter remains tense and the detrusor muscle relaxed by sympathetic stimulation. During micturition, parasympathetic stimulation causes the detrusor muscle to contract and the internal urethral sphincter to relax. The external urethral sphincter (sphincter urethrae) is under somatic control and is consciously relaxed during micturition.

# 92. Effects of thyroid hormones

## Physiologic functions of thyroid hormones

### Calorigenic effect

- the body's metabolic rate in increased along with oxygen consumption and heat production
- ↑ metabolic rate and ↑ oxygen consumption are a criterion of thyroid gland activity → +/- 20% deviation indicates abnormal function of thyroid gland
- Thyroid gland is also stimulated when exposed to the cold to increase heat production

### Metabolic effects

- rapid uptake of glucose by the cell
- enhanced glycolysis
- enhanced gluconeogenesis
- increased glucose absorption from GIT
- mobilization of fatty acids from adipose tissue is enhanced
- oxidation of fatty acids is enhanced
- it decreases cholesterol , phospholipids and TAG concentration in the plasma
- enhanced secretion of cholesterol into bile
- increases number of LDL receptors on the liver and therefore decreases LDL concentration in the blood

### Effects on growth and development

- is especially important for growth in childhood
- essential for normal bone growth
- it potentiates the effects of growth hormone
- hyperthyroidism causes rapid and enhanced growth of children
- hypothyroidism causes prolonged and reduced growth of children

### Effects on CVS

- increased blood flow and CO
    I. ***increased metabolism ⇨ grater quantities of metabolic end products ⇨ vasodilation ⇨ increased blood flow ⇨ increased cardiac output***
- increased heart rate
    I. direct effect on excitability
    ***II.*** indirect effect - ***TH increase the number and affinity of β-adrenergic receptors in the heart ⇨ consequently increase its sensitivity to inotropic and chronotropic effects of catecholamines (tachycardia, increase of cardiac output)***
- increased heart strength

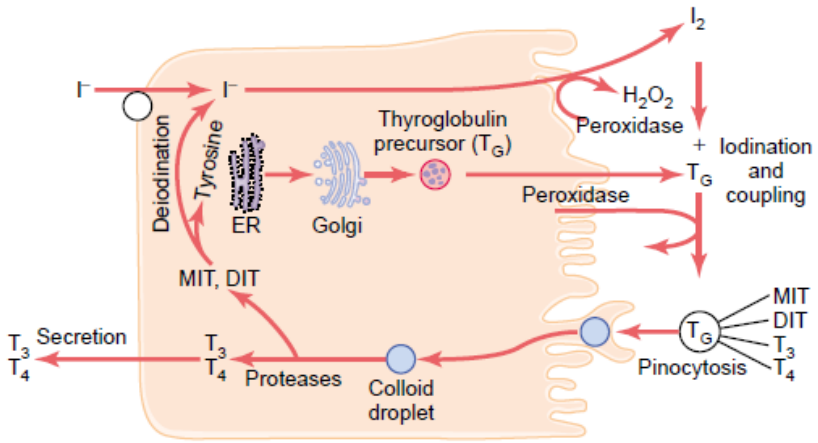
### Effects on CNS

- in hypothyroidism – brain development is retarded, mental retardation develops, myleinisation of nerve fibers is defective (prolonged reflex time which is also of use in diagnosis in clinical practice → Achilles tendon reflex)
- leading to cretinism with symptoms described above + failure of bone growth
- soft tissue growth is normal therefore giving the child an obese appearance
- in hyperthyroidism – extreme nervousness and psycho-neurotic tendencies

### Effects on catecholamines

- Thyroid hormones potentiate effects of catecholamines on metabolic rate, nervous system and cardiovascular system
- ***⇧ level of TH = ⇧ efficiency of catecholamines***
- ***⇩ level of TH = ⇩ efficiency of catecholamines***

# 93. Metabolism of iodine; Thyroid hormones synthesis




Biosynthesis of thyroid hormones

- all chemical reactions occur within the Thyroglobulin molecule
- **iodide** ($I^-$) is taken up from the blood by iodide pumps and transferred into the colloid
- *Perchlorate decreases iodide uptake by competitive inhibition*
- *TSH stimulates the active transport of iodide*
- **Oxidation** of iodide to iodine by peroxidases and H2O2
- **Iodination** of thyrosines within the thyroglobulin molecule
    I. 1 iodine + thyrosine = MIT, 2 iodines + thyrosine = DIT
- **Coupling of iodothyrosines**:
- DIT + DIT = tetraiodothyronine (T4 - thyroxine)
- MIT + DIT = triiodothyronine (T3)
- every step of the biosynthesis is stimulated by TSH
- T3 and T4 are than taken up from the colloid by pinocytosis
- The vesicles fuse with lysosomes
    I. T3 and T4 are converted into active form by proteases
- They are then released into the blood where they bind carrier proteins

**1. TBG –** thyroxine binding globulin — highest affinity

**2. TBPA –** thyroxine binding prealbumin

**3. albumin** — highest binding capacity

- thyroxine is largely a prohormone and only 25% as active as T3
- it is therefore converted to T3 via **deiodination** by deiodinase
- this involves the removal of an iodine from the **outer ring**
- if it occurs on the inner ring – **inactive reverse T3** is formed
    I. which can still bind the receptor and acts as a competitive inhibitor
    II. the condition is called **Reverse T3 Dominance**
    III. it may also be a physiological condition if T3 action needs to be low
    IV. e.g. during stress situations adrenal gland releases excessive cortisol which inhibits the conversion of T4 to T3

# 94. Hyper- and hypothyroidism

## Hyperthyroidism

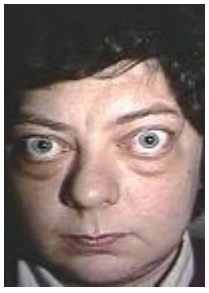
**Causes of Hyperthyroidism (Toxic Goiter, Thyrotoxicosis, Graves' Disease)**
In most patients with hyperthyroidism, the thyroid gland is increased two to three times normal size. The number of cells is increased greatly and each cell increases its rate of secretion severalfold. Plasma TSH concentrations are less than normal in almost all patients and often are essentially zero. Other substances that have actions similar to those of TSH are found in the blood in 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 designed **TSI**. They have a prolonged stimulating effect on the thyroid gkand, 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 the 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 is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.

**Symptoms of Hyperthyroidism**

- a high state of excitability, intolerance to heat, increased sweating, mild to extreme weight loss, varying degrees of diarrhea, muscle weakness, nervousness or other psychic disorders, extreme fatigue but inability to sleep, and tremor of the hands.

**Exophthalmos.** Most people with hyperthyroidism develop some degree of protrusion of the eyeballs. This condition is called *exophthalmos*. The cause of the protruding of eyes is edematous swelling of the retro-orbital tissues and degenerative changes in the extraocular muscles. In most patients, immunoglobulins can be found in the blood that reacts with the eye muscles.



**Treatment of Hyperthyroidism**. The most direct treatment for hyperthyroidism is surgical removal of the thyroid gland.

- ✓ Propylthiouracil (inhibits thyroid hormone synthesis by blocking peroxidase)
- ✓ Thyroidectomy
- ✓ β-blockers (adjunct therapy)

Other way is to inject radioactive iodine, which can destroy most of the secretory cells of the thyroid gland. Usually 5 millicuries of radioactive iodine is given to the patient.

## 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 cause progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone.

**Endemic Colloid Goiter Caused by Dietary Iodide Deficiency**. The term "goiter" means greatly enlarged thyroid gland. 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 normal suppression of TSH production by the anterior pituitary. The follicles become tremendous in size, and the thyroid gland may increase 10 to 20 times normal size.

**Idiopathic Nontoxic 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 portions of the gland growing while other portions are being destroyed by the thyroiditis.

Among the abnormalities often encountered are the following:

1. *Deficient iodide-trapping mechanism*, in which iodine is not pumped adequately into the thyroid cells
2. *Deficient peroxidase system*, in which the iodides are not oxidized to the iodine state
3. *Deficient coupling of iodinated tyrosine 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

Finally, some foods contain *goitrogenic substances* that have a propylthiouracil-type of antithyroid activity, thus also leading to TSH-stimulated enlargement of the thyroid gland. Such goitrogenic substances are found especially in some varieties of turnips and cabbages.

**Physiological Characteristics of Hypothyroidism**. The physiological effects 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.

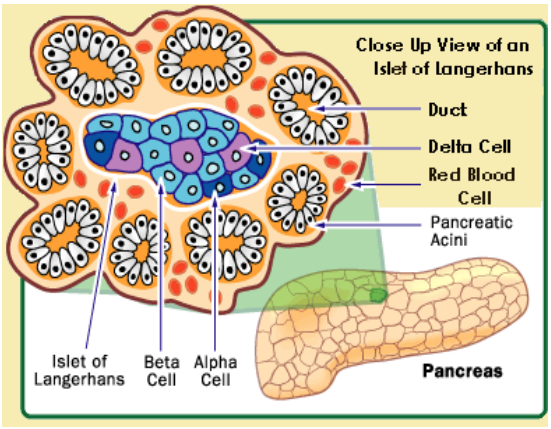
**Myxedema**. *Myxedema*, develops in the patient with almost total lack of thyroid hormone function. In this condition, for reasons not explained, greatly increased quantities of *hyaluronic acid* and *chondroitin sulfate* bound with protein form excessive tissue gel in the interstitial spaces, and this causes total quantity of interstitial fluid to increase. Because of the gel nature of the excess fluid, it is mainly immobile, and the edema is nonpitting type.

**Atherosclerosis in Hypothyroidism**. Lack of thyroid hormone increase 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 free thyroxine in the blood is low. The basal metabolic rate in myxedema ranges between -30 and -50. And the secretion of TSH by the anterior pituitary when a test dose of TRH (*thyrotropin-releasing hormone*) is administered is usually greatly increased.

**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.

## 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.

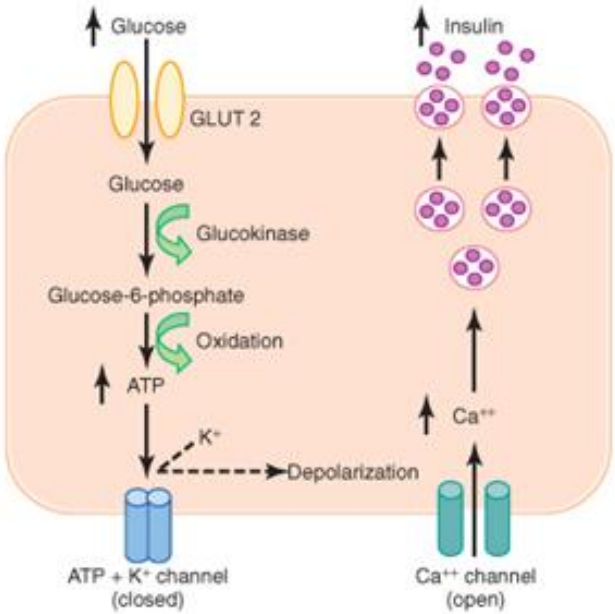
# 96. Insulin – mechanism of action

## Insulin synthesis

- insulin is secreted by **beta cells** from islands of Langerhans
- it is synthesized as preproinsulin containing a leader sequence of aa. which is removed once it enters the ER → GA → stored in vesicles
- proinsulin has 1/10 the activity of insulin, after removal of the **C-peptide** insulin is formed (shortly before secretion)
- it consists of an A and B chain connected via disulfide bridges
- insulin circulates **unbound** in the blood and has a half time of **5 minutes**
- 80% is degraded in the liver and kidneys by ***insulin protease***

## Insulin secretion

- as mentioned before insulin is stored in vesicles
- these are released in response to ***high glucose levels in the blood***
- beta cells contain **GLUT-2** transporter which facilitate the transport of glucose inside the cells *(at a rate that is proportional to the blood concentration in the physiologic range)* ***GLUT-2 does not depend on insulin***
- inside the cell it is converted to glucose 6-P by glucokinase
- ATP which closes ATP-sensitive K+ channels
- that causes the cell membrane to depolarize and opens voltage-gated Ca2+ channels
- Ca2+ influx leads to fusion of insulin vesicles with the membrane
- Insulin is released via exocytosis
- Additional voltage-gated K+ channels open and K+ diffuses outside the cell which restores the resting membrane potential




## Non-metabolic effects

- mild antidiuretic effects → water retention (less glucose in urine)
- hypoglycemic dose of insulin can induce lung edema

## Metabolic effects of insulin

- increased permeability of glucose, amino acids, K+ within **seconds**
    I. glucose via GLUT transporters
- **glycogen synthesis** in skeletal muscle and liver (via glycogen synthase)
- **TAG synthesis** in adipocytes and liver (in the liver formed VLDL transports TAGs to adipocytes)
- Inhibition of liver phosphorylase – glycogen is not split to glucose
- Activation of glucokinase – phosphorylation of glucose – cannot diffuse back
- **Stimulates Glycolysis** – activates phosphofructokinase and pyruvate kinase
- **Inhibition of gluconeogenesis and its enzymes**
    I. Pyruvate carboxylase
    II. Fructose 1,6-bisphosphatase
    III. Glucose 6-phosphatase
- **Inhibition of HSL** (hormone sensitive lipase – TAG of adipocytes to FFAs)
- Transport of glucose into adipocytes – converted to glycerol 3-P
- Stimulation of protein synthesis
- Inhibition of protein degradation (signals that aa. are not needed for gluconeogenesis)

## *Effects of insulin on fat metabolism*

- insulin promotes fat synthesis and storage
    I. first it increases the transport of glucose into the liver cell
    II. where it is converted to glycogen
    III. after a certain concentration of glycogen is reached (5 – 6 %)
    IV. the glycogen inhibits its further synthesis
    V. the excess glucose is glycolytically cleave to pyruvate
    VI. enters the TCA cycle and is converted to Acetyl-CoA
    VII. Acetyl-CoA is formed in excess and causes increase of citrate
    VIII. Citrate is a major stimulant of fat synthesis and acetyl-CoA is a major component for fatty acid synthesis
    IX. Citrate stimulates acetyl-CoA carboxylase, which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA
    X. Fatty acid synthesis proceeds and eventually TAGs will be formed
    XI. These are released from the liver via lipoproteins
    XII. Insulin further stimulates lipoprotein lipase which is present in the endothelium of capillaries in adipose tissue
    XIII. Lipoprotein lipase splits TAGs into FFAs and glycerol which diffuse into the adipocytes and are converted back to TAGs
    XIV. Insulin also inhibits hormone-sensitive lipase
    XV. And promotes glucose transport through the membrane from which glycerol is formed that accepts FFAs transported in the lipoproteins

## *Effect of insulin on protein metabolism and growth*

- insulin has a direct effect on permeability of cells to amino acids
- increases uptake of amino acids by the cells and incorporation into proteins
- increases translation of mRNA → activates ribosomal maschinery
- stimulates especially formation of enzymes needed for storage of carbohydrates and fats
- inhibits the rate of protein breakdown and therefore release of amino acids
- in the liver it depresses gluconeogenesis since abundant glucose is present therefore conserving the body's proteins
- growth hormone and insulin act synergistically on body growth
    I. in the absence of one of them the body fails to grow probably because of their differences in specificity for amino acid uptake

# 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*.

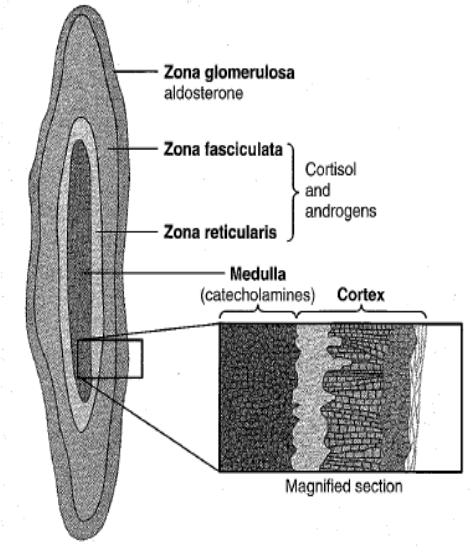
## Diabetes mellitus (DM)

One type of DM is *insulin-dependent diabetes mellitus* **(IDDM),** or type 1 DM, which is caused by an insulin deficiency. Another type is *non-insulin-dependent DM* **(NIDDM)**, or type 2 DM, which is caused by the decreased efficacy of insulin and sometimes occurs even in conjunction with increased insulin concentrations.

DM is characterized by an abnormally high plasma glucose concentration (*hyperglycemia*), which leads to *glucosuria*.

Large quantities of *fatty acids* are liberated since lipolysis is no longer inhibited. The fatty acids can be used to produce energy via acetylcoenzyme A (acetyl-CoA); however, this leads to the formation of acetoacetic acid, acetone (*ketosis*), and β-oxybutyric acid (*metabolic acidosis*). Because hepatic fat synthesis is insulin-independent and since so many fatty acids are available, the liver begins to store triacylglycerols, resulting in the development of *fatty liver*.

## 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 Cortes Has Three Distinct Layers

1. The **zona glomerulosa**, a thin layer of cells that lie just underneath the capsule, constitutes about 15 per cent of the adrenal cortex. These cells are the only ones in the adrenal gland capable of secreting significant amounts of **aldosterone** because they contain the enzyme *aldosterone synthase*, which is necessary for the synthesis of aldosterone. The secretion of these cells is controlled mainly by the extracellular fluid concentration of *angiotensin II* and *potassium*, both of which stimulate aldosterone secretion.
2. The **zona fasciculata**, the middle and widest layer, constitutes about 75 per cent of the adrenal cortex 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**, as well as small amounts of estrogens and some glucocorticoids. *ACTH* also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone*, released from the pituitary, may also be involved.

Adrenocortical Hormones Are Steroids Derived from Cholesterol

All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol. Approximately 80 per cent of the cholesterol used for steroid synthesis is provided by low-density lipoproteins (LDL) in the circulating plasma. The LDLs, which have high concentrations of cholesterol, diffuse from the plasma into the interstitial fluid and attach to specific receptors contained in structures called coated pits on the adrenocortical cell membranes. The coated pits are then internalized by *endocytosis*, forming vesicles that eventually fuse with cell lysosomes and release cholesterol that can be used to synthesize adrenal steroid hormones.
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**; this is the rate-limiting step in the eventual formation of adrenal steroids. Essentially all these steps occur in the *mitochondria* and the *endoplasmic reticulum*.

Adrenocortical Hormones Are Bound to Plasma Proteins

Approximately 90 to 95 per cent 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; therefore, cortisol have a relatively long half-life of 60 to 90 minutes. Only about 60 per cent of the circulating aldosterone combines with the plasma proteins, so that about 40 per cent is in the free form; as a result, aldosterone has a relatively short half-life of about 20 minutes.

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 per cent 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 therefore filtered readily by the kidneys and excreted in the urine.

The normal conc. of aldosterone in blood is about 6 nanograms per 100ml, and the average secretory rate is approx. 150 µg/day (0.15mg/day).
The conc. of cortisol in the blood averages 12 µg/100ml, and the secretory rate averages 15 to 20 mg/day.

## Functions of the Mineralocorticoids – Aldosterone

- Mineralocorticoid deficiency causes severe renal sodium chloride wasting and hyperkalemia
- Aldosterone increases renal tubular reabsorption of sodium and secretion of potassium
- Excess aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium conc.
- Excess aldosterone causes hypokalemia and muscle weakness; Too little aldosterone causes hyperkalemia and cardiac toxicity
- Excess Aldosterone increases tubular hydrogen ion secretion, and causes mild alkalosis

- Aldosterone stimulates sodium and potassium transport in sweat glands, salivary glands, and intestinal epithelial cells; the effect on the sweat glands is important to conserve body salt in hot environments, and the effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva are lost. Aldosterone also greatly increases sodium absorption by the intestines, especially in the colon, which prevents loss of sodium in the stools.

### Cellular Mechanism of Aldosterone Action

1st, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.

2nd, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic **receptor protein**, a protein that has a stereomolecular configuration that allows only aldosterone or very similar compounds to combine with it.

3rd, the aldosterone-receptor complex or a product of this complex diffuses into the nucleus, where it may undergo further alternations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.

4th, the messenger RNA diffuses back into the cytoplasm, where, operating in conjugation with the ribosomes, it causes protein formation. The proteins formed are a mixture of (1) one or more enzymes and (2) membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membranes. One of the enzymes especially increased is **sodium-potassium adenosine triphosphatase**, which serve as the principal part of the pump for sodium and potassium exchange at the *basolateral membrane* of the renal tubular cells.

Thus, aldosterone does not have an immediate effect on sodium transport; rather, this effect await the sequence of events that leads to the formation of the specific intracellular substances required for sodium transport.

### Regulation of Aldosterone Secretion

1. Increased potassium ion conc. in the extracellular fluid greatly *increases* aldosterone secretion.
2. Increased activity of the rennin-angiotensin system (increased levels of angiotensin II) also greatly *increases* aldosterone secretion.
3. Increased sodium ion conc. in the extracellular fluid *very slightly decreases* aldosterone secretion.
4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion.

## Malfunctions

**Hypoadrenalism-Addison's Disease**, results from failure of the adrenal cortices to produce adrenocortical hormones, and this in turn is most frequently caused by primary atrophy of the adrenal cortices.(includes mineralocorticoid and glucocorticoid deficiency, and *melanin pigmentation*).

**Hyperadrenalism-Crushing's syndrome**, mostly ascribable to abnormal amounts of cortisol, but excess secretion of androgens may also cause important effects.

**Primary Aldosteronism (Conn's syndrome)**, occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldosterone; *hypokalemia*, slight increase in extracellular fluid and blood volume, very slight increase in plasma sodium conc., and, almost always, hypertension. Especially interesting are occasional periods of muscle paralysis caused by hypokalemia.

# 99. Metabolic and anti-inflammatory affects of glucocorticoids

- Adrenocortical hormones are synthesized from the same precursor – cholesterol (most steps are catalyzed by cytochrome P450 enzymes)
- 95% of secreted glucocorticoids are cortisol only a small amount constitutes corticosterone and cortisone
- Secretory rates of glucocorticoids are high in the morning and low in the late evening (circadian rhythm)
- More than 90% of glucocorticoids are bound to plasma proteins
    I. ***α2 globulin (transcortin, CBG – corticosteroid-binding protein)***
    II. ***albumins***
- bound steroids are physiologically inactive, but they have longer half-life (60 – 90 min) → protection against degradation
- they are degraded in the liver
    I. reduction
    II. conjugation with glucoronic acid
    III. excretion mainly via urine (15% in the stool)

Effects on carbohydrate metabolism

- stimulation of gluconeogenesis in the liver mainly by using the aminoacids from protein degradation
    I. enhances transcription of enzymatic machinery in the liver
    II. increases the release of amino acids from extrahepatic tissue such as muscle into the plasma
- increase in glucose which is used to produce glycogen in the liver
    I. glycogen can be converted to glucose in times of need stimulated by epinephrine
- moderate decrease in glucose utilization → inhibiting oxidation of NADH/H+
    I. NAD+ is needed in glycolysis as oxidizing agent
- Excess glucocorticoids decrease sensitivity of tissues such as skeletal muscle and adipose tissue to insulin which causes a rise in blood glucose levels
- the hyperglycemia may be high enough to cause ***adrenal diabetes***

Effects on protein metabolism

- protein synthesis mainly of enzymes needed for gluconeogenesis in the liver but also plasma proteins
    I. switch on mRNA transcription for enzymes
    II. but also increase of plasma proteins
    III. enhances transport of aa into hepatocytes
- protein degradation in extrahepatic tissues
    I. but in skeletal muscle and myocardium
    II. decreased formation of enzymes and proteins in general in extrahepatic tissues
    III. reduces transport of aa into extrahepatic cells

→ ***cortisol mobilizes amino acids from extrahepatic tissues***

Effects on fat metabolism

- ***mobilization of fatty acids and cholesterol*** → stimulates HSL → increase in FFAs
- enhances oxidation of FFAs (energy metabolism is shifted to the lipids)
    I. reduces the uptake of glucose to form **α-glycerophosphate** (glycerol 3-P) therefore oxidation may prevail
- ***Cushing syndrome***: centripetal obesity due to excess cortisol
    I. Fat deposition in the head and chest region (moon face)
    II. Fat is probably more rapidly generated in these regions as compared to the periphery which results in centripetal obesity

*NOTE: the shift in energy metabolism takes several hours and is not as rapid as that caused by low insulin*

*BONE* - decrease of bone formation (major effect)

- increase of bone absorption

*MUSCLE* - protein catabolic effect → muscle atrophy and weakness

- positive inotropic effect

*CT* - inhibition of synthesis of collagen, GAGs and hyaluronic acid

- thinning of the skin → easily ruptured

*CVS* - enables response of vessels to vasoconstrictive stimuli (Epinephrine, Norepinephrine)

*KIDNEY* - increases perfusion of kidney → increase in glomerular filtration

- hypocorticalism → decreased GF → water retention → toxic amounts of water

*CNS* - can elevate the mood, interferes with sleep

- receptors in brain stem, reticular activating system, hippocampus

## Anti-inflammatory effects

- administration of large amounts of cortisol *blocks the inflammatory response*
    - either by prevention:
        I. stabilizes lysosomal membranes → low conc. of proteolytic enzymes
        II. decrease of capillary permeability
        III. decrease of phagocytosis and migration of WBCs
        IV. suppresses the immune system (production of lymphocytes)
        V. attenuates fever via inhibition of IL-1 from WBCs
            1. 2 – 5 due to decrease in prostaglandins and leukotrienes
    - or by rapid resolution:
        I. blocks factors promoting inflammation (histamine, bradykinin ,leukotrienes, prostaglandins)
        II. accelerates healing

## Regulation of cortisol secretion

Mental & physical stress → hypothalamus → CRF → ACTH → G protein → adenylyl cyclase → cAMP → protein kinase A → CEH (cholesterol hydrolase)

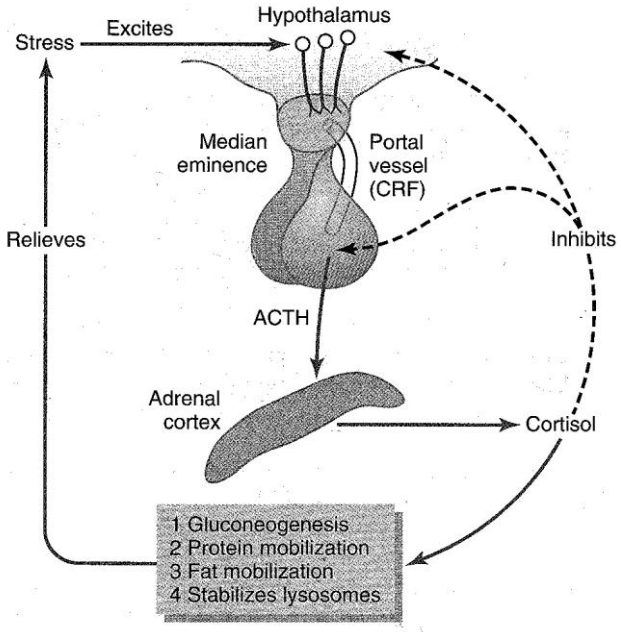
*CEH – catalyzes formation of pregnenolone from cholesterol*

*NOTE: corticotropin (ACTH) stimulates the formation of **20 α-hydroxycholesterol** the zona glomerulosa is also stimulated by angiotensin II*

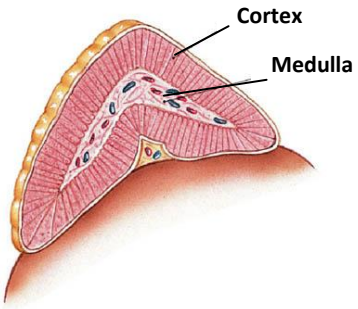
Negative feedback is exerted by cortisol itself on the hypothalamus and the ACTH secreting cells in the anterior pituitary gland

Stimuli of glucocorticoids secretion comprise

- ***infection***
- ***trauma***
- ***hypoglycaemia***
- ***depression***
- ***anxiety***



# 100. Adrenal medulla. Synthesis of cathecholamines

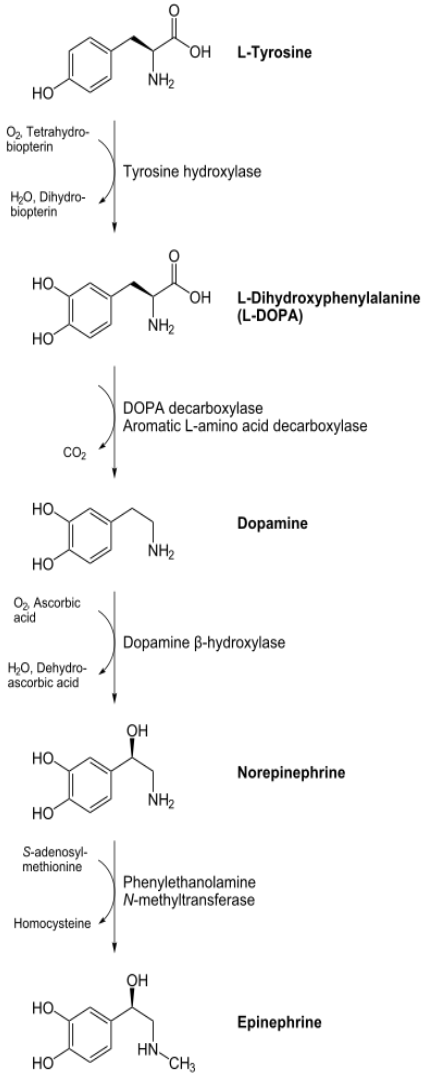



The **adrenal medulla** is part of the adrenal gland. It is located at the center of the gland, being surrounded by the adrenal cortex. It is the inner most part of the adrenal gland, consisting of cells that secrete epinephrine, norepinephrine, and a small amount of dopamine in response to stimulation by sympathetic preganglionic neurons.

The adrenal medulla consists of irregularly shaped cells grouped around blood vessels. These cells are intimately connected with the sympathetic division of the autonomic nervous system. In fact, these adrenal medullary cells are modified postganglionic neurons, and preganglionic autonomic nerve fibers lead to them directly from the central nervous system.

## Synthesis of cathecholamines

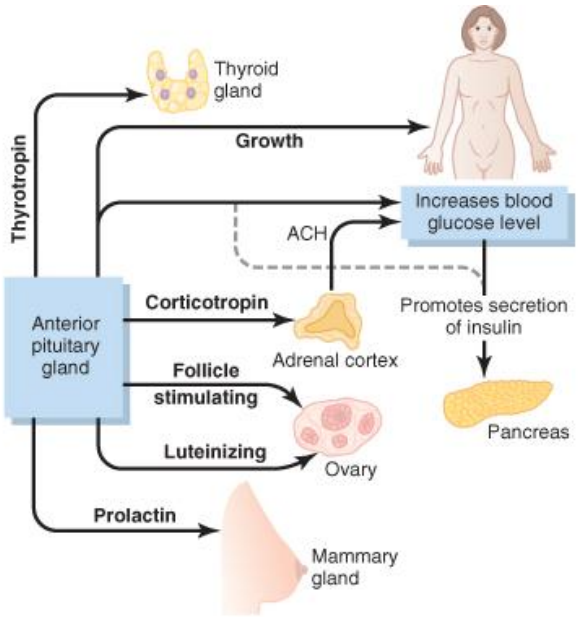
**Dopamine** is the first catecholamine to be synthesized from steps shown. **Norepinephrine** and **epinephrine**, in turn, are derived from further modifications of dopamine. Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed 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

- The hypophysis or pituitary gland is a small gland (1cm diameter) and it lies on the sella turcica
- Physiologically it is divided into the anterior part (adenohypophysis) and the posterior part (neurohypophysis)
- The hypophysis and hypothalamus are joined by the infundibulum or the hypophyseal stalk
- Six important peptide hormones plus several less important ones are secreted by the *anterior* pituitary, and two important peptide hormones are secreted by the *posterior* pituitary

<u>Anterior hypophysis</u>




- Growth hormone (**GH**) promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation. (from somatotropes)
- Adrenocorticotropin (**corticotropin**) controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats. (from corticotropes)
- Thyroid-stimulating hormone (**TSH**) controls the rate of secretion of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body. (from thyrotropes)
- **Prolactin** promotes mammary gland development and milk production. (from lactotropes/mamotropes)
- Two separate gonadotropic hormones, follicle-stimulating hormone and luteinizing hormone **(FSH/LH)**, control growth of the ovaries and testes, as well as their hormonal and reproductive activities. (from gonadotropes)

<u>Posterior hypophysis</u>

- **Antidiuretic hormone** (also called vasopressin) controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids.
- **Oxytocin** helps express milk from the glands of the breast to the nipples during suckling and possibly helps in the delivery of the baby at the end of gestation

The connection

- secretion by the anterior pituitary is controlled by hormones called *hypothalamic releasing* and *hypothalamic inhibitory hormones* secreted within the hypothalamus itself at the median eminence by unconventional nerve endings into minute blood vessels called *hypothalamic-hypophyseal portal vessels*→ adenohypophysis

- In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion

| Hormone | Structure | Anterior Pituitary |
|---|---|---|
| Thyrotropin-releasing hormone (TRH) | Peptide of 3 amino acids | Stimulates secretion of TSH by thyrotropes |
| Gonadotropin-releasing hormone (GnRH) | Single chain of 10 amino acids | Stimulates secretion of FSH and LH by gonadotropes |
| Corticotropin-releasing hormone (CRH) | Single chain of 41 amino acids | Stimulates secretion of ACTH by corticotropes |
| Growth hormone-releasing hormone (GHRH) | Single chain of 44 amino acids | Stimulates secretion of growth hormone by somatotropes |
| Growth hormone inhibitory hormone (somatostatin) | Single chain of 14 amino acids | Inhibits secretion of growth hormone by somatotropes |
| Prolactin-inhibiting hormone (PIH) | Dopamine (a catecholamine) | Inhibits secretion of prolactin by lactotropes |

- The posterior pituitary consists of many supporting structures called pituicytes. They support nerve endings coming from the supra-optic and paraventricular nuclei of the thalamus.

- These nerves carry ADH and Oxytocin with protein carrier molecules called *neurophysins*.

- *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.

# 102. Glandotropic hormones of anterior pituitary gland

Pituitary Gonadotropins & Prolactin

**FSH** and **LH** are each made up of an α and an β subunit. They are glycoproteins that contain the hexoses mannose and galactose, the hexosamines *N*-acetylgalactosamine and *N*-acetylglycosamine, and the methylpentose fucose. They also contain sialic acid. The carbohydrate in the gonadotropin molecules increases their potency by markedly slowing their metabolism. The half-life of human FSH is about 170 min; and the half-life of LH is about 60min. Loss-of-function mutations in the FSH receptors cause hypogonadism. Gain-of-function mutations cause a spontaneous form of *ovarian hyperstimulation syndrome*, a condition in which many follicles are stimulated and cytokines are released from the ovary, causing increased vascular permeability and shock.
The half-life of prolactin is about 20min.

## Receptors

The receptors of FSH and LH are serpentine receptors coupled to adenyl cyclase through Gs. In addition, each has an extended, glycosylated extracellular domain. The human prolactin receptor resembles the growth hormone receptor and is one of the superfamily of receptors that includes the growth hormone receptor and receptor for many cytokines and hematopoietic growth factors. It dimerizes and activates the JAK-STAT and other intracellular enzyme cascades.

## Actions

The testes and ovaries become atrophic when the pituitary is removed or destroyed. FSH helps maintain the spermatogenic epithelium by stimulating Sertoli cells in the male and is responsible for the early growth of ovarian follicles in the female. LH is tropic to the Leydig cells and, in females, is responsible for the final maturation of the ovarian follicles and estrogen secretion from them. It is also responsible for ovulation, the initial formation of the corpus luteum, and secretion of progesterone. Prolactin causes milk secretion from the breast after estrogen and progesterone priming. Its effect on the breast involves increased action of mRNA and increased production casein and lactalbumin. Prolactin also inhibits the effects of gonadotropins, possibly by an action at the level of the ovary.

# 103. Growth hormone and growth factor (IGF)

Growth hormone, also called *somatotropic hormone* or ***somatotropin***. It causes growth of almost all tissues of the body which are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater number of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

## 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.

Growth hormone promotes protein deposition in tissues by:

- Enhancement of amino acid transport through the cell membranes
- Enhancement of RNA translation to cause protein synthesis by the ribosomes
- *Increased nuclear transcription of DNA to form RNA*
- Decreased catabolism of proteins and amino acids

Growth hormone enhances fat utilization for energy

In tissues throughout the body, growth hormone enhances the conversion of fatty acids to acetyl coenzyme A 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.

**"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 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 to stimulate the uptake and utilization of glucose in skeletal muscle and fat and to inhibit gluconeogenesis (glucose production) by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion.

**Necessity of insulin and carbohydrate for the growth-promoting action of growth hormone**. Growth hormone fails to cause growth in animals that lacks a pancreas; it also fails to cause growth if carbohydrates are excluded from the diet. 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

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.

*Growth hormone strongly stimulates osteoblasts*. Therefore, the bones can continue to become thicker under the influence of growth hormone.

## 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 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 for somatomedins have been isolated, but so far the most important of these is *somatomedin C* (also called IGF-I).

**Short duration of action of growth hormone but prolonged action of somatomedin C**.
Somatomedin C attaches strongly to a protein carrier 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, with half-life of about 20 hours (20 min. for growth hormone). This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion.

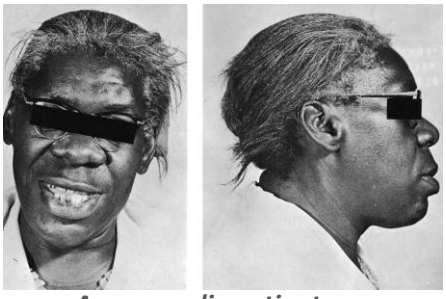
## Regulation of Growth Hormone Secretion

Several factors 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 conc. of fatty acids in the blood
3. *exercise*
4. *excitement*
5. *trauma*

**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.
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 adenylyl cyclase system inside the cell membrane, increasing the intracellular level of cyclic adenosine monophosphate (cAMP). This has both a short-term and a long-term effect. The short-term effect is to increase calcium ion transport into the cell; within minutes, this causes fusion of the growth hormone secretory vesicles with the cell membrane and release of the hormone into the blood. The long-term effect is to increase transcription in the nucleus by the genes to stimulate the synthesis of new growth hormone.

## Abnormalities of Growth Hormone Secretion

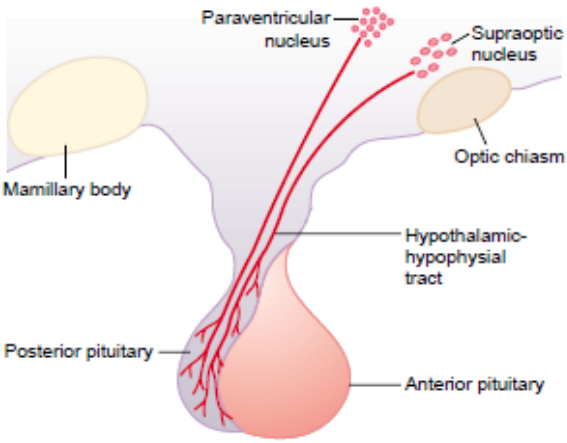


*Acromegalic patient.*

- **Panhypopituitarism** – decrease in secretion may be congenital, mostly result of a tumor.
- **Dwarism** –result from generalized deficiency of anterior pituitary secretion during childhood.
- **Gigantism** – excessive production of growth hormone. Body tissues grow rapidly, incl. bones.
- **Acromegaly** – if an acidophilic tumor occurs after adolescence – that is, after the epiphyses of the long bones have fused with the shafts – the person cannot grow taller, but the bones become thicker and the soft tissue can continue. Enlargement is especially marked in the bones of the hands and feet and in the membranous bones (e.g. skull, vertebrae), because their growth does not cease at adolescence.

# 104. Formation and secretion of posterior pituitary hormones

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 surface 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.
*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 *exocytosis* and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they only are loosely bound to each other, the hormone separates almost immediately.

Both oxytocin and ADH (vasopressin) are polypeptides, each containing nine amino acids.

## Physiological Functions of ADH

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. In the luminal membranes of the tubular epithelial cells of the collecting ducts, immediately inside the cell membranes are large number of special vesicles that have highly water-permeable pores called *aquaporins*. When ADH acts on the cell, its first combines with the 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.

### Regulation of ADH

**Osmotic regulation**. There are modified neuron receptors called, *osmoreceptors*. The exact location of the receptors is not known. When the extracellular fluid becomes to concentrated, fluid is pulled by osmosis out of the osmoreceptors cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion.
Concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them.

**Vasoconstrictor and Pressure Effects of ADH, and Increased ADH Secretion Caused by Low Blood Volume**. Higher conc. of ADH have a potent effect on 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. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion.

## Oxytocin Hormone

**Oxytocin Causes Contraction of Pregnant Uterus**. The hormone *oxytocin*, in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation.

**Oxytocin Aids in Milk Ejection by the Breasts**. Oxytocin plays an especially important role in lactation. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breasts 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.

# 105. Hypothalamic releasing hormones (see q. 101)

# 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 [$Ca^{2+}$].
- Is synthesized and secreted by the **chief cells** of the parathyroid glands.

**1.** ***Secretion of PTH***

- is controlled by serum [$Ca^{2+}$] through negative feedback. **Decreased serum [$Ca^{2+}$] increases PTH secretion**.
- Mild decreases in serum [$Mg^{2+}$] stimulate PTH secretion.
- Severe secretion in serum [$Mg^{2+}$] 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 [$Ca^{2+}$]** 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 $Ca^{2+}$ and phosphate from the bone mineral into the ECF. Alone, this effect on bone would not increase the serum ionized [$Ca^{2+}$] because phosphate complexes $Ca^{2+}$.
   - 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 [$Ca^{2+}$] 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 $Ca^{2+}$ reabsorption*** in the distal tubule. Which also increases the serum [$Ca^{2+}$].

d. ***PTH increases intestinal $Ca^{2+}$ absorption*** indirectly by stimulating the production of 1.25-dihydrocholecalciferol in the kidney.

## Vitamin D

- Provides $Ca^{2+}$ 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.** ↓ serum [$Ca^{2+}$]
  **b.** ↑ PTH levels
  **c.** ↓ serum [phosphate]

**2.** ***Actions of 1,25-dihydroxycholecalciferol***

- are coordinated to **increase both [$Ca^{2+}$] and [phosphate]** in ECF to **mineralize new bone**.

**a.** ***Increases intestinal $Ca^{2+}$ absorption***. Vitamin D-dependent $Ca^{2+}$-binding protein (**calbindin D-28K**) is induced by 1,25-dihydroxycholecalciferol.
> PTH increases intestinal $Ca^{2+}$ 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 $Ca^{2+}$ and phosphate***

**d.** ***Increase bone resorption***, which provides $Ca^{2+}$ and phosphate from "old" bone to mineralize "new" bone.

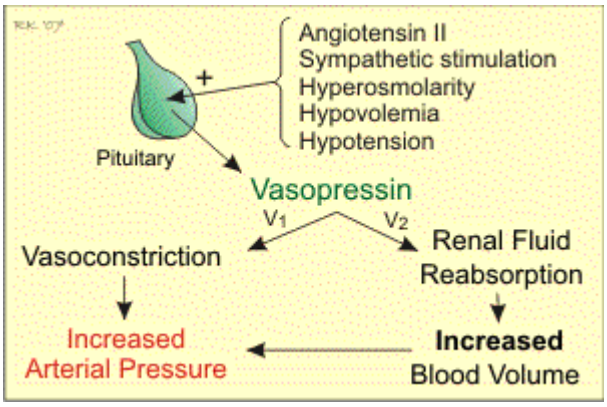
## Calcitonin

- is synthesized and secreted by the **parafollicular cells** of the thyroid.
- secretion is stimulated by an increase in serum [$Ca^{2+}$]
- acts primarily to **inhibit bone resorption**.
- can be used to **treat hypercalcemia**.

# 107. Vasopressin and natriuretic hormone

## Physiological Functions of ADH (=antidiuretic hormone = ***vasopressin***)

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. In the luminal membranes of the tubular epithelial cells of the collecting ducts, immediately inside the cell membranes are large number of special vesicles that have highly water-permeable pores called *aquaporins*. When ADH acts on the cell, its first combines with the 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.




### Regulation of ADH

**Osmotic regulation**. There are modified neuron receptors called, *osmoreceptors*. The exact location of the receptors is not known. When the extracellular fluid becomes to concentrated, fluid is pulled by osmosis out of the osmoreceptors cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion.
Concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them.

**Vasoconstrictor and Pressure Effects of ADH, and Increased ADH Secretion Caused by Low Blood Volume**. Higher conc. of ADH have a potent effect on 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. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion.

## Natriuretic hormone

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.

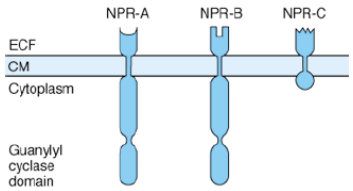



**Figure 24-8.** Diagrammatic representation of natriuretic peptide receptors. The NPR-A and NPR-B receptor molecules have intracellular guanylyl cyclase domains, whereas the clearance receptor, NPR-C, has only a small cytoplasmic domain. CM, cell membrane.

## Secretion & Metabolism

The conc. of ANP in plasma is about 5 fmol/mL in humans. 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.

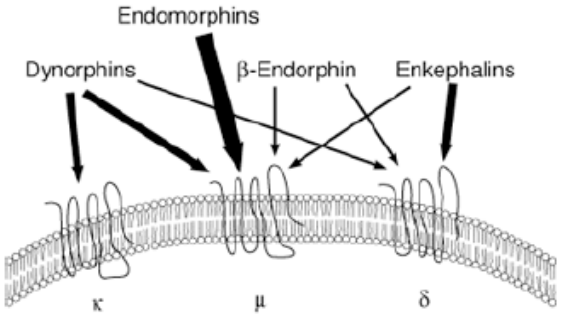
# 108. Endorphins and enkephalins

## Opioid Peptides

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.




## Endorphins

**Endorphins** are endogenous opioid polypeptide compounds. They are produced by the pituitary gland and the hypothalamus in vertebrates during exercise, excitement, pain, consumption of spicy food and orgasm, and they resemble the opiates in their abilities to produce analgesia and a feeling of well-being. Endorphins work as "natural pain relievers".

When a nerve impulse reaches the spinal cord, endorphins are released which prevent nerve cells from releasing more pain signals.

## Mechanism of action

**β-endorphin** is released into blood from the pituitary gland and into the spinal cord and brain from hypothalamic neurons. β-endorphin is a cleavage product of pro-opiomelanocortin (POMC) which is also the precursor hormone for adrenocorticotropic hormone (ACTH). The behavioral effects of β-endorphin are exerted by its actions in the brain and spinal cord, and probably the hypothalamic neurons are the major source of β-endorphin at these sites. In situations where the level of ACTH is increased (e.g. Cushing's syndrome), the level of endorphins also increases slightly.

β-endorphin has the highest affinity for the **$\mu_1$ opioid receptor**, slightly lower affinity for the $\mu_2$ and δ opioid receptors and low affinity for the $\kappa_1$ opioid receptors. μ opioid receptors are the main receptor through which morphine acts. Classically, μ opioid receptors are presynaptic, and inhibit neurotransmitter release; through this mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and disinhibit the dopamine pathways, causing more dopamine to be released. By hijacking this process, exogenous opioids cause inappropriate dopamine release, and lead to aberrant synaptic plasticity, which causes addiction. Opioid receptors have many other and more important roles in the brain and periphery however, modulating pain, cardiac, gastric and vascular functions as well as possibly panic and satiation, and receptors are often found at postsynaptic locations as well as presynaptically.

# 109. Pineal gland. Circadian rhythm.

## Anatomy of Pineal Gland

The pineal gland arises from the roof of the third ventricle and is connected by a stalk to the *posterior commissure* and *habenular commissure*. The pineal stroma contains neuroglia and parenchymal cells. Like other endocrine glands, the pineal has highly permeable fenestrated capillaries. In young animals and infants, the pineal is large, and the cells tend to be arranged in alveoli. It begins to involute before puberty, and, in humans, small concretions of calcium phosphate and carbonate **(pineal sand)** appear in the tissue.

It produces **melatonin**, a hormone that affects the modulation of wake/sleep patterns and photoperiodic (seasonal) functions.

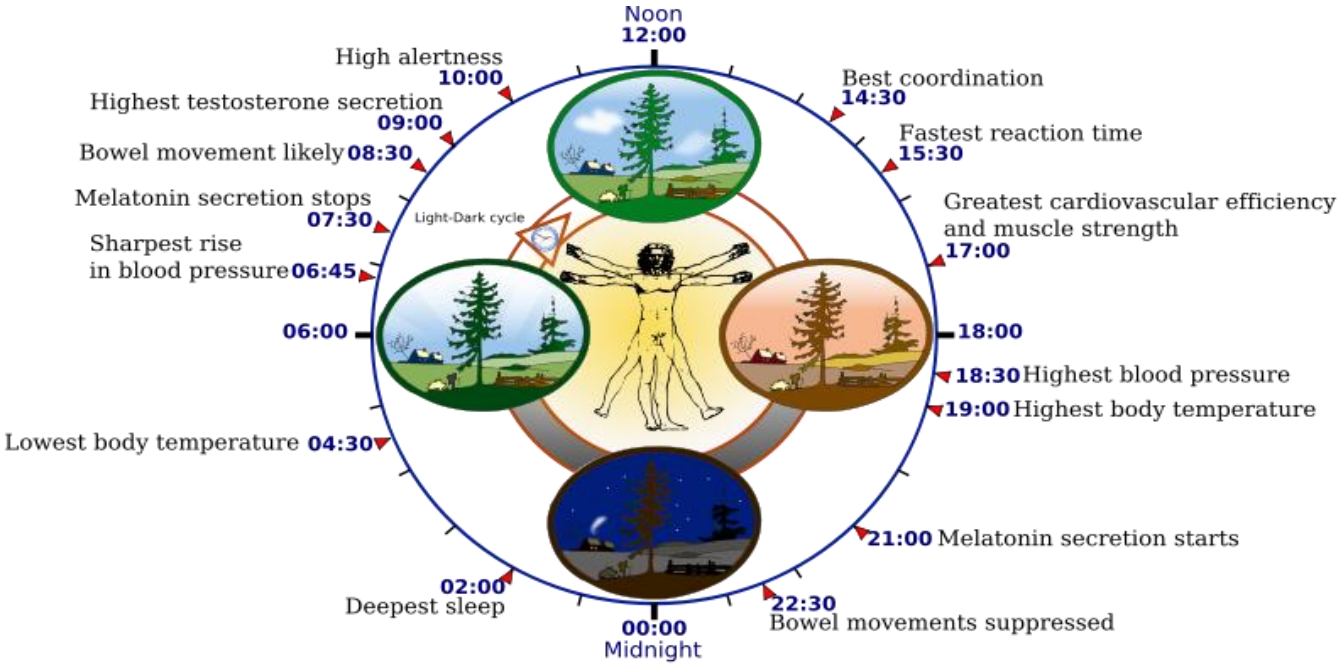
## Regulation of Secretion

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 Gland

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

It is defined as cyclic changes in the ovaries of sexual mature females. The cycle includes 3 phases:

1. ***preovulatory*** (estrogenic) – follicles gradually grow and produce estrogen, the phase is controlled by **FSH** produced by adenohypophysis.
2. ***Ovulatory*** or ***ovulation*** – a time of follicle rupture and expelling of the ***secondary oocyte***.
3. **postovulatory (progesteronic)** – a phase of formation of the corpus luteum and production of progesterone. It is controlled by **LH** produced by the adenohypophysis.

Ovarian follicle growth (Ovarian cycle)

- **follicular phase**
  - primordial follicles with a single layer of ***granulosa cells*** are present
  - develop into primary oocytes which have several layers of granulosa cells after the secretion of FSH and LH
  - esp. FSH secretion promotes follicle maturation into secondary oocytes which obtain ***theca cells*** (derived from the spindle-shaped fibroblasts)
    - theca cells → secrete androgen precursor
    - granulosa cells → convert the precursor into estradiol (an estrogen)
  - which further mature into Graafian follicles developing an antrum due to the accumulation of the follicular fluid (which contains the estrogens)
    - the estrogens stimulate formation of FSH receptors
    - increasing the sensitivity of granulosa cells to FSH
    - FSH and estrogens also promotes formation of LH receptors
  - One Graafian follicle outgrows the others which undergo ***atresia*** allowing only one follicle to leave the ovaries
  - ***Ovulation – occurs 14 days after onset of menstruation***
  - LH is necessary for final maturation of follicle and ovulation (LH surge)
  - LH also stimulates conversion of granulosa and theca cells into ***progesterone-secreting cells***
  - Ovulation occurs due to swelling of follicle and rupture of the stigma

- **luteal phase**
  - after ovulation the remaining granulosa and theca cells become lutein cell forming the corpus luteum
  - this step is stimulated by LH
  - secreting mainly progesterone but also estrogen
  - LH stimulates secretion of female sex hormones by the corpus luteus
    - If fertilization occurs and therefore development of fertilized ovum into blastocyst it will secrete **hCG** (human chorionic gonadotropin)
    - Corpus luteum is called – **corpus luteum graviditatis**
    - If fertilization does not occur the corpus luteum involutes into the **corpus albicans** (scar tissue) 12 days after ovulation

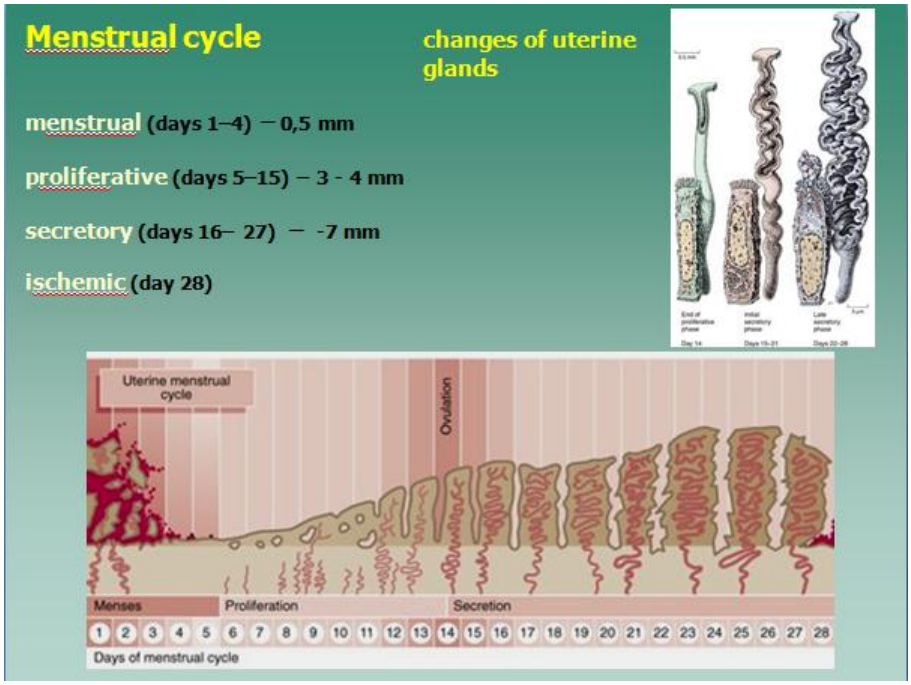
## 111. Uterine cycle

- the **menstrual phase** - from the 1rst to 4th days of the cycle, is characterized by menstrual bleeding. The phase is induced by rapidly decrease of the levels of progesterone and estrogens. The endometrium is reduced to only the basalis containing the basal portions of the uterine glands.

- the **proliferative phase** - (follicular phase - because it coincides with the development of ovarian follicles and the production of estrogen)- from 5th to 14th days. Is characterized by proliferation of uterine gland cells as well as connective tissues cells and deposition of the ground substance. The endometrium is 2-3 mm thick and contains straight and unbranched uterine glands, coiled arteries grow into the regenerating stroma. The phase is controlled with **estrogens**.

- the **secretory phase (luteal phase )**- starts after ovulation and ends at day 26, controlled with progesterone secreted by the corpus luteum. The functionalis becomes thicker (5-6 mm at the end of the s. p.) and edematous. Gland are coiled and branched and their cells begin to accumulate glycogen below the nuclei. Functionalis can be divided into the ***pars compacta*** (superficially) and ***pars spongiosa*** (contains dilated lumens of uterine glands).

- the **ischemic phase** - days 27 to 28. Is characterized by a spasm of coiled blood vessels following with subsequent ischemia and necrosis of blood vessel walls and of the functionalis. Immediately after blood constriction follows ruptures of vessels and menstrual bleeding.



# 112. Physiology of pregnancy

- is characterized by steadily increasing levels of estrogen and progesterone, which maintain the endometrium for the fetus, suppress ovarian follicular function (by inhibiting FSH and LH secretion), and stimulate development of the breasts.
- The rate at which the **corticotropin-releasing hormone (CRH)** concentration rises seems to determine the duration of the pregnancy.

## 1. *Fertilization*

– If fertilization occurs, the corpus luteum is rescued from regression by **human chorionic gonadotropin (hCG)**, which is produced by the placenta.

## 2. *First trimester*

– The corpus luteum (stimulated by **hCG**) is responsible for the production of estradiol and progesterone.
– Peak levels of hCG occur at gestational week 9 and then decline.

## 3. *Second and third trimester*

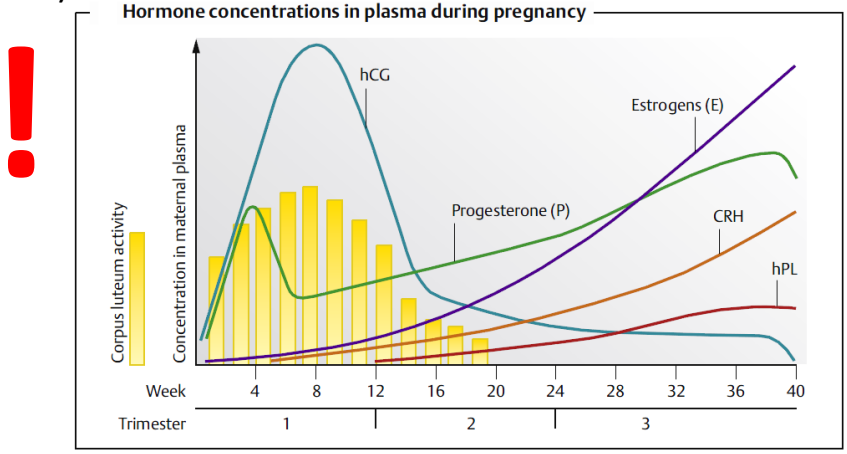
– **Progesterone** is produced by the placenta.
– **Estrogens** are produced by interplay of the **fetal adrenal gland** and the placenta. The fetal adrenal gland synthesized *dehydroepiandrosterone-sulfate (DHEA-S)*, which is then hydroxylated in the fetal liver. These intermediates are transferred to the placenta, where enzymes remove sulfate and aromatize to estrogens. **The major placental estrogen is *estriol***.
– **Human placental lactogen (hPL 0= human chorionic somatomammotropin, hCS)** is produced throughout pregnancy. It stimulates mammary enlargement and lactogenesis.

## 4. *Parturition*

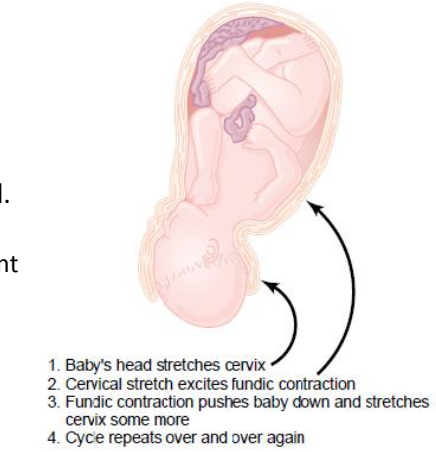
– Throughout pregnancy, progesterone increases the threshold of uterine contraction.
– Near term, the estrogen/progesterone ratio increases, which makes the uterus more sensitive to contractile stimuli.
– ***Estrogens*** increases uterine contractility, partly by increasing the number of gap junctions between adjacent uterine smooth muscle cells.
– From 7$^{th}$ month onward, estrogen secretin continues to increase while progesterone secretion remains constant or perhaps even decreases slightly.

## 5. *Lactation*

– Estrogens and progesterone stimulate the growth and development of the breasts throughout pregnancy.
– **Prolactin levels increase steadily during pregnancy** because estrogen stimulates prolactin secretion from the anterior pituitary.
– **Lactation does not occur during pregnancy because estrogen and progesterone block the action of prolactin on the breast.**
– After parturition, estrogen and progesterone levels decrease abruptly and lactation occurs.
– Lactation is maintained by suckling, which stimulates both oxytocin and prolactin secretion.
– **Ovulation is suppressed** as long as lactation continues because prolactin has the following effects:
**a.** Inhibits hypothalamic GnRH secretion.
**b.** Inhibits the action of GnRH on the anterior pituitary, and consequently inhibits LH and FSH secretion.
**c.** Antagonizes the actions of LH and FSH on the ovaries.
–> **Oxytocin** is released in the last 2-3 weeks approx. Increased levels of oxytocin results in increased contraction and opposite **(positive feedback)**.



# 113. Physiology of parturition and lactation



Theory for the onset of intensely strong contractions during labor.

## Parturition

- *Parturition* means birth of the baby. Toward end of pregnancy, uterine develops such strong contractions that the baby is expelled.
- Hormonal factors that increase uterine contractility:
  - ***Estrogens*** increase the number of gap junctions between adjacent uterine smooth muscle cells.
  - ***Oxytocin*** secreted by the neurohypophysis specifically causes uterine contraction
  - ***Fetal oxytocin, cortisol, prostaglandins***
- Mechanical factors that increase uterine contractility:
  - Fetal movements can also elicit smooth muscle contraction.
  - Stretch or irritation of the cervix
- Onset of Labor – A positive feedback mechanism for its initiation:
  - ***Labor*** - the weaker uterine contractions becomes stronger and causes the stretching of cervix and later force the baby through the birth canal, thereby causing parturition.
  - ***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.

## Lactation

- development of the breasts is stimulated by the monthly increase in estrogen and is even more stimulated by the large amount secreted during pregnancy
  - only during pregnancy the mammary glands fully develop
- 4 other hormones play important roles in the development of the glands
  - Growth hormone
  - Prolactin
  - Parathyroid hormone
  - Glucocorticoids
  - insulin
- these hormones are necessary to provide $Ca^{2+,}$ glucose, amino acids and fats for the breast milk
- progesterone causes synergistically with all aforementioned hormones growth of the breast lobules and their secretory characteristics *(like that of endometrium)*
- estrogen and progesterone inhibit lactation
- **prolactin** (from the hypophysis) and ***human chorionic somatomammotropin*** stimulate the secretion of milk
- However the net effect is only a small amount of milk secretion per day
- After parturition progesterone and estrogen levels decline and prolactin prevails
- Ejection process of milk
  - Milk is continuously secreted into the duct system but not ejected
  - Baby suckles on the nipples – spinal cord – hypothalamus – oxytocin is released by neurohypophysis and prolactin secretion by adenohypophysis
  - ***Oxytocin*** causes contraction of myoepithelial cells which surround the alveoli which causes milk ejection
  - ***Prolactin*** stimulates secretion of milk and ensures future supply of breast milk
- Composition of breast milk: Lactose, Casein, Water, Linoleic acid, Electrolytes esp. $Ca^{2+}$, Vitamins (A,B,C,D), IgA.

# 114. Endocrine function of the testes

## Testosterone

– is the major androgen synthesized and secreted by the **Leydig cells**.
– **LH** increases testosterone synthesis by stimulating ***cholesterol desmolase***, the first step in the pathway.
– Accessory sex organs (e.g., prostate) contain 5α-reductase, which converts testosterone to its active form, *dihydrotestosterone*.
– **5α-reductase inhibitors (finasteride)** may be used to treat benign prostatic hyperplasia because they block the activation of testosterone to dihydrotestosterone in the prostate.

Regulation of testes

**1. *Hypothalamic control – GnRH***
– Arcuate nuclei of the hypothalamus secrete GnRH into the hypothalamic-hypophysial portal blood. GnRH stimulates the anterior pituitary to secrete FSH and LH.

**2. *Anterior pituitary – FSH and LH***
– **FSH acts on the Sertoli cells** to maintain spermatogenesis. The Sertoli cells also secrete **inhibin**, which is involved in negative feedback of FSH secretion.
– **LH acts on the Leydig cells** to promote **testosterone synthesis**. Testosterone acts via an intratesticular paracrine mechanism to reinforce the spermatogenic effects of FSH in the Sertoli cells.

**3. *Negative feedback control – testosterone and inhibin***
– **Testosterone inhibits the secretion of LH** by inhibiting the release of GnRH from the hypothalamus and by directly inhibiting the relase of LH from the anterior pituitary.
– **Inhibin** (produced by the Sertoli cells) **inhibits the secretion of FSH** from the anterior pituitary.

## Actions of Testosterone

– Differentiation of epididimys, vas deferens, and seminal vesicles
– Pubertal growth spurt
– Cessation of pubertal growth spurt (epiphyseal closure)
– Libido
– Spermatogenesis in Sertoli cells (paracrine effect)
– Deepening of voice
– Increased muscle mass
– Growth of penis and seminal vesicles
– Negative feedback on anterior pituitary

## Actions of dihydrotestosterone

– Differentiation of penis, scrotum, and prostate
– Male hair pattern
– Male pattern baldness
– Sebaceous gland activity
– Growth of prostate

## 115. Sex reflexes

Coordinated sexual activity depends on a series of reflexes integrated at many neural levels an its absent after cord transection. However, genital manipulation in male spinal animals and humans produces *erection* and even *ejaculation*. In female spinal dogs, vaginal stimulation causes tail deviation and movement of the pelvis into the *copulatory position*.

## 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. Regulatio of constant osmotic pressure

## Osmoregulation

The osmolality of most body fluids is about 290mOsm/kg $H_2O$, 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). $H_2O$ fluctuations in the gastrointestinal tract are monitored by *peripheral osmosensors* in the portal vein region and communicated to the hypothalamus by vagal afferent neurons.

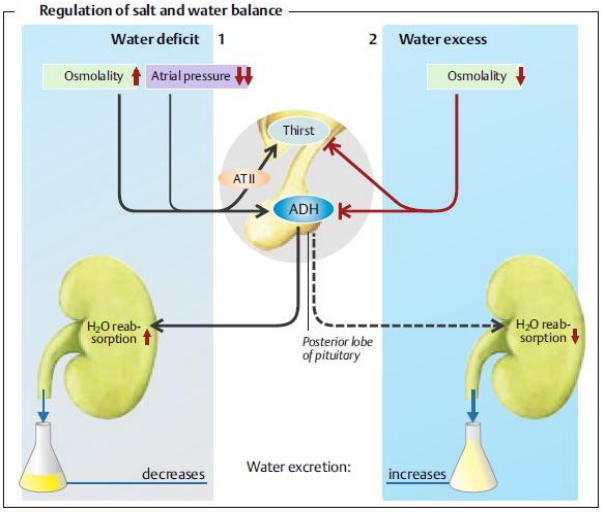
**Water deficit**. Net water losses (hypovolemia) due, for example, to sweating make the ECF hypertonic. Osmolality rises of only 1–2% are sufficient to increase the secretion of **ADH** (antidiuretic hormone = ***vasopressin***), from the posterior lobe of the pituitary. ADH decreases urinary $H_2O$ 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 $\beta_1$-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 [$Ca^{2+}$].
- Is synthesized and secreted by the **chief cells** of the parathyroid glands.

**1.** ***Secretion of PTH***

- is controlled by serum [$Ca^{2+}$] through negative feedback. **Decreased serum [$Ca^{2+}$] increases PTH secretion**.
- Mild decreases in serum [$Mg^{2+}$] stimulate PTH secretion.
- Severe secretion in serum [$Mg^{2+}$] 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 [$Ca^{2+}$]** and a **decrease in serum [phosphate]**.
- The second messenger for PTH actions on its target tissues is **cAMP**.

e. ***PTH increases bone resorption***, which brings both $Ca^{2+}$ and phosphate from the bone mineral into the ECF. Alone, this effect on bone would not increase the serum ionized [$Ca^{2+}$] because phosphate complexes $Ca^{2+}$.

f. ***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 [$Ca^{2+}$] to increase.

g. ***PTH increases renal $Ca^{2+}$ reabsorption*** in the distal tubule. Which also increases the serum [$Ca^{2+}$].

h. ***PTH increases intestinal $Ca^{2+}$ absorption*** indirectly by stimulating the production of 1.25-dihydrocholecalciferol in the kidney.

### *Vitamin D*

- Provides $Ca^{2+}$ 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 [$Ca^{2+}$] and [phosphate]** in ECF to **mineralize new bone**.

**b.** ***Increases intestinal $Ca^{2+}$ absorption***. Vitamin D-dependent $Ca^{2+}$-binding protein (**calbindin D-28K**) is induced by 1,25-dihydroxycholecalciferol.
> PTH increases intestinal $Ca^{2+}$ 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 $Ca^{2+}$ and phosphate***

**d.** ***Increase bone resorption***, which provides $Ca^{2+}$ 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 [$Ca^{2+}$]
- acts primarily to **inhibit bone resorption**.
- can be used to **treat hypercalcemia**.

# 119. Regulation of glycaemia

**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.

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.

## *Hormones that influence blood glucose level*

| Hormone | Tissue of Origin | Metabolic Effect | Effect on Blood Glucose |
|---|---|---|---|
| Insulin | Pancreatic β Cells | 1) Enhances entry of glucose into cells; 2) Enhances storage of glucose as glycogen, or conversion to fatty acids; 3) Enhances synthesis of fatty acids and proteins; 4) Suppresses breakdown of proteins into amino acids, of adipose tissue into free fatty acids. | Lowers |
| Somatostatin | Pancreatic D Cells | 1) Suppresses glucagon release from α cells (acts locally); 2) Suppresses release of Insulin, Pituitary tropic hormones, gastrin and secretin. | Raises |
| Glucagon | Pancreatic α cells | 1) Enhances release of glucose from glycogen; 2) Enhances synthesis of glucose from amino acids or fatty acids. | Raises |
| Epinephrine | Adrenal medulla | 1) Enhances release of glucose from glycogen; 2) Enhances release of fatty acids from adipose tissue. | Raises |
| Cortisol | Adrenal cortex | 1) Enhances gluconeogenesis; 2) Antagonizes Insulin. | Raises |
| ACTH | Anterior pituitary | 1) Enhances release of cortisol; 2) Enhances release of fatty acids from adipose tissue. | Raises |
| Growth Hormone | Anterior pituitary | Antagonizes Insulin | Raises |
| Thyroxine | Thyroid | 1) Enhances release of glucose from glycogen; 2) Enhances absorption of sugars from intestine | Raises |

## *Food and blood sugar regulation*

Some edible mushrooms are noted for the ability to lower blood sugar levels.

# 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 midnight).

**(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.

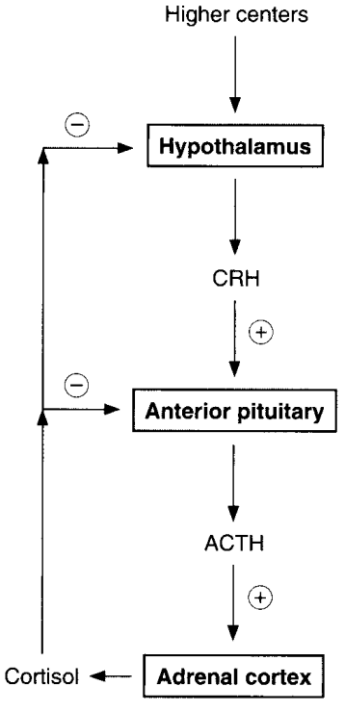
– CRH binds to receptors on corticotrophs of the anterior pituitary and directs them to **synthesize POMC** (the precursor to ACTH) and **secrete ACTH.**

– 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 the 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** from the anterior pituitary.

– When cortisol (glucocorticoid) levels are chronically elevated, the secretion of CRH and ACTH is inhibited by negative feedback.

– The **dexamethasone suppression test** is based on the ability of dexamethasone (a potent synthetic glucocorticoid) to inhibit ACTH secretion. If the hypothalamic-pituitary-adrenocortical axis is normal, then the administration of dexamethasone 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 II** by **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 $K^+$ secretion, restoring blood $[K^+]$ to normal.