Overview of Lecture: Circulation, Respiration & Homeostasis

Read: Text ch 42 & 44.

Bullet Points: {lots of facts today!}
- Circulation
- Membrane Transport
- Circulatory Systems:
  - None
  - Open
  - Closed single Loop
  - Closed Double loop
- Hearts & Chambers
- Shunting & Diving
- Capillaries & Control
- Blushing!
- Breathing

Good Circulation Is Essential For Good Health...

...This is especially true for organs that require the most circulation including:
- the heart,
- kidneys,
- liver,
- and healthy functioning sex organs.

CircuLex because...
Every living cell is an open system, importing resources & exporting wastes across the lipid plasma membrane. \(\text{ch 7}\)

Hydrophobic (nonpolar) molecules, such as lipids, carbon dioxide, and oxygen, can dissolve in the lipid bilayer of the plasma membrane and cross it by diffusion. The \(\text{lipid}\) core impedes the diffusion of ions and polar molecules such as glucose and even water.

Channel & Transport proteins built into the membrane play key roles in regulating transport.

- **Passive transport**
  - Diffusion
  - Facilitated diffusion

- **Active transport**
  - Active ATP enzymes pump ions up gradient: \(\text{Na}^+\)-\(\text{K}^+\) exchange pump

hydrophyllic channels facilitate diffusion: water & simple solutes

carrier proteins selectively admit glucose & big stuff

Endo- & exocytosis via membrane-bound vessicles
\(\text{recall secretory epithelial cells}\)

Signals (information) from water-soluble hormones & neurotransmitters relayed by receptor proteins \(\text{ch 11}\)

The Nobel Prize in Chemistry 2012
Robert J. Lefkowitz, Brian K. Kobilka
Diffusion is inefficient over distances of more than a few millimeters; diffusion time is proportional to the square of the distance: if it takes ~1 sec for a given quantity of glucose to diffuse 100 µm, it will take ~100 seconds for it to diffuse 1 mm and almost 3 hours to diffuse 1 cm.

The branching gastrovascular cavities of coelenterates & flatworms → body wall only two cells thick; each cell in direct contact w/ medium; ensuring that ... diffusion distances are short & a circulatory system is unnecessary.

In larger multicellular animals, diffusion is inadequate. The circulatory system solves this problem by bulk transport of the aqueous environment surrounding cells {plasma → interstitial fluid} & the surfaces that exchange gases, nutrients & wastes w/ external env. Diffusion only has to bridge the 1st or last few mm.
For animals with many cell layers, gastrovascular cavities are insufficient. Two types of *mesodermal* circulatory systems have evolved to overcome the limitations of diffusion: open & closed circulatory systems. 3 basic components: a fluid (*blood*), tubes (*blood vessels*), a muscular *pump* (heart).

**In arthropods & most mollusks** (*except active cephalopods*), blood bathes organs directly in an open circulatory system. **There is no distinction between blood and interstitial fluid,** and the body fluid is more correctly termed *hemolymph*. In arthropods, the *heart is an elongated dorsal tube*; it pumps hemolymph through vessels out into sinuses. *{kinda like a “sump pump”}* Instead of lungs, *insects have trachea* that take air directly to cells.

**Earthworms, squids, octopuses, and vertebrates** have closed circulatory systems: blood is confined to vessels and is distinct from the interstitial fluid. One or more hearts pump blood into large vessels that branch into smaller ones coursing through the organs, where **materials are exchanged across capillaries by diffusion between blood and the interstitial fluid bathing the cells.** Note: earthworm ‘lungs’ are just skin capillaries *{‘single loop’}* {amphibians & turtles have some gas exchange through skin}
The ‘heart’ of simple chordates like lancelets is little more than a muscular tube in the main ventral artery that contracts in peristaltic waves. \{like earthworm\}

The closed circulatory system in fishes is a single circuit. The evolution of gills in fish resulted in blood passing through two capillary beds during each circuit \{like hepatic (liver) circulation in mammals - later\} w/ a big drop in pressure across each capillary bed; systemic circulation is quite slow, constraining the delivery of oxygen to body tissues, and hence the maximum aerobic metabolic rate of fishes.

A fish heart is basically just a tube w/ 4 chambers the Sinus Venosus & Atrium collect venus blood the Ventricle & Conus Arteriosus pump it in a peristaltic wave to capillary beds in the exchange surfaces. \{the SV & CA are ~ muscular vessels (as is ‘heart’)}

The Sinus Venosus \{SV\} serves as ‘pacemaker’ of peristaltic waves; in mammals homolog is sinoatrial (SA) node
The evolution of lungs in **amphibians** (lost in thin ‘lungless’ salamanders) is associated with two separate circuits: the **pulmocutaneous circuit** to the lungs & skin and the **systemic circuit** to the other tissues. (double loop w/ single capillary bed per loop)

Amphibians have a **three-chambered heart**: the **Right Atrium** (& sinus venosus) collect O₂ depleted systemic blood, the **Left Atrium** collects O₂ rich pulmonary blood. The pulmonary and systemic blood mixes {a little} in the **single Ventricle**.

Most of the oxygen-rich blood from the left atrium is diverted into the systemic circulation by ridges.

**Turtles, snakes & lizards also have double circulation** with pulmonary (lung) and systemic circuits, but one ventricle w/ some mixing.

Ridges (septa) & valves allow shunting of blood from one circuit to the other: right aorta captures blood from right pulmonary artery. {note: this shunting from pulmonary to systemic happens in fetuses of placental mammals, but isn’t supposed to happen in adults – later}

Birds and mammals have independently evolved a four-chambered heart. The division of blood flow also allows the pressure to vary between the pulmonary and systemic circulatory systems. High pressures of blood in the lungs could cause fluid to leak across the respiratory membranes.

The crocodilian heart is an interesting mosaic:
- It is four chambered *like endothermic birds & mammals*.
- But it also has a shunting system *as if 3-chambered; shunts blood away from systemic periphery, similar to Mammalian Dive Reflex: heart slows, peripheral vasoconstriction reallocates systemic blood, O₂ & heat to brain & visceral core*.

Seymour *et al.* propose that the ancestors of modern alligators and crocodiles were endothermic & required a four-chambered heart for pressure separation, and that it has since re-evolved *ectothermy and* a shunting system.

The crocodilian ancestors from the Triassic were rather small (< 2 metres long), completely terrestrial animals that are thought to have had an active lifestyle. In the Jurassic, larger, fully aquatic crocodilian forms evolved, and presumably adopted the same sit-and-wait predatory strategy that characterizes modern crocs.

Because heat loss in water can be many times higher than that in air, there would have been considerable selective pressure against endothermy during this return to the water.
Birds and mammals descended from different reptilian ancestors; their four-chambered hearts evolved independently, an example of convergent evolution.

In fetal mammals, the lungs are nonfunctional & the pulmonary circuit is bypassed. Systemic venous blood entering the right atrium, it is shunted directly into the left atrium through an opening called the foramen ovale, which is supposed to close at birth, when the pulmonary circuit opens.

The evolution of double circulation w/ a four-chambered heart was essential to support endothermy \{‘warm-blooded’\}.

Cohort study of multiple brain lesions in sport divers: role of a patent \{not completely closed\} foramen ovale.
Note: the two circuits are in series, so volume flow at $2 = 6$ - lymph

note hepatic portal system: 2 capillary beds in series
Each day the average heart beats 100,000 times & pumps about 2,000 gallons of blood. In a 70-year lifetime, an average human heart beats more than 2.5 billion times.

The normal ECG has the following features:
- P wave - atrial depolarisation
- PR interval - delay at the AV node
- QRS complex - ventricular depolarisation
- T wave - ventricular repolarisation

see: http://www.anaesthetist.com/icu/organs/heart/ecg/

**note: how bundle branches & purkinji fibers reverse direction of contraction: atria top down ventricles bottom up**

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"Natural" heart pacemakers made from human stem cells have been successfully tested in pigs.

The best way to correct some types of bradycardia (slower than normal heartbeat) is with a heart pacemaker. Pacemakers have helped thousands of people of all ages and all walks of life overcome problems associated with serious arrhythmias.
The Law of Continuity states that a liquid is incompressible and the same volume must pass each cross-section per unit time. Therefore, as the cross-section increases, the velocity decreases.

Still waters run deep, indicating that the biggest pressure drop through Arterioles (with a big increase in area) is the main control point.

Blood pressure & flow (flow ~ pressure/resistance ~ pressure X area)

Note many capillary beds in parallel: if 1 dilates, pressure drops for all & flow redirected to the low-resistance channel.

Relate arterial pulses to blood pressure cuff:

Note: no pressure in veins to push blood up to heart! Contracting skeletal muscles squeeze the veins. Flaps within the veins act as one-way valves that keep blood moving only toward the heart.

If we sit or stand too long, the lack of muscular activity causes our feet to swell with stranded blood. {note valves in veins on back of hand!}
Humans are circulating ~5 liters (~10.6 pints) of blood through ~60,000 miles of capillaries with a total surface of ~1000 m². 5l of blood cannot fill the heart, arteries, veins and all the capillaries at once; tissue capillary beds take turns “time sharing” blood; prioritizing by need.

Orthostatic {Postural} Hypotension
The gravitational stress of sudden standing normally causes pooling of blood in the venous capacitance vessels of the legs and trunk. The subsequent transient decrease in venous return results in reduced BP. {when you stand up, blood pools in your legs, you get dizzy and fall down!}

A g-suit is worn by pilots subject to high levels of acceleration (g); to prevent Loss Of Consciousness due to the blood pooling in the lower body.

Baroreceptors in the aortic arch and carotid bodies activate autonomic reflexes that rapidly normalize BP by causing a transient increase in heart rate. These changes reflect primarily the sympathetic {nerves} mediated increase in {neurotransmitter} levels, which increases heart rate {see Fig 49.8} and enhances arterial and venous vasoconstriction.

When portions of the autonomic reflex arc are impaired by diseases or drugs, these homeostatic mechanisms may be inadequate to restore the lowered BP.

Many astronauts experience postflight orthostatic hypotension, The Jobst stocking provides leg compression ...
Transfer of substances between the blood and the interstitial fluid occurs only across the thin walls of capillaries. At any given time, only about 5-10% of the body’s capillaries have blood flowing through them. Capillaries in the brain, heart, kidneys, and liver are usually filled to capacity, but in many other sites, like the muscles and gut, the blood supply varies over time as blood is diverted from one destination to another.

Contraction of the smooth muscles in the walls of arterioles and rings of precapillary sphincters controls the flow of blood between arterioles and venules.

In anaphylactic shock, a hyper-allergic reaction results in massive release of histamines which constrict bronchiole airways & dilate too many capillaries, dropping blood pressure. Epinephrine should be given to open the airways, and to raise the blood pressure by constricting blood vessels in guts.
Flow follows need.

The competition between the **parasympathetic** and **sympathetic** nervous systems {Fig 49.8} to direct energy either to storage {digestion} or to skeletal muscle {“fight or flight”} is also played out in the circulatory system.

During relaxation, the **parasympathetic** dominates. Blood flow to visceral organs is abundant.

**Sympathetic** arousal changes the priority of distributing energy in favor of skeletal muscle. Blood vessels to the viscera are constricted and an increased proportion of blood flows to the body wall and limbs.

**Individual tissues** have the ability to **signal their own needs for increased blood**. {paracrine signals: local cell-to-cell – Fig 45.2}

The messenger molecule nitric oxide (NO) is synthesized by endothelial tissues in need of oxygen and diffuses across cell membranes. It **causes the smooth muscle of the arteriole walls and precapillary sphincters to relax and the vessels to dilate**.

This interplay of oxygen and NO represents a negative feedback system that can be specific to individual capillary beds and small areas of tissue.

http://biology.uindy.edu/Biol504/1review/circulation.htmD
Good Circulation Is Essential For Good Health...

...This is especially true for organs that require the most circulation including:

- the heart,
- kidneys,
- liver,
- and healthy functioning sex organs.

CircuLex because...
Is That A Bottle In Your Pocket…?

Viagra \textit{\{Sildenafil\}} was originally investigated as a potential \textit{\{heart pain\}} medication, based on its ability to increase blood flow to the heart. Although Viagra failed as a heart medication, researchers became excited when many of the men in the clinical trials reported the frequent occurrence of ...

Vascular smooth muscle (VSM) cells surround arteries and arterioles, contracting and relaxing the arteries to regulate blood pressure. ...

Normally, in the presence of sexual stimulation, blood flow is directed into ...

The resulting inflow of blood leads to ...

This … is triggered by \textit{nitric oxide (NO)} ... activates an enzyme that manufactures cyclic guanosine monophosphate (cGMP).

\textit{cGMP, directs the smooth muscle cells to relax, leading to the dilation of … arteries.}

However, \textit{immediately following release of NO and production of cGMP; another enzyme, cGMP phosphodiesterase type 5 (PDE-5), is activated.}

\textit{PDE-5 destroys cGMP.} The result of this is a rapid decrease in ...

How Viagra Works \textit{\{“When the time is right”\}}

Unfortunately, as we age, cellular concentrations of cGMP decrease.

\textit{Viagra … selectively inhibits the cGMP-destroying actions of PDE-5.} \{note “double negative”\}

FDA and Pfizer have warned against taking Viagra with any nitrate-based cardiac medications (i.e., sublingual nitroglycerin tablets, nitroglycerin patches, etc.). There have been cases where patients who received both drugs have died after developing irreversible ... hypotension

\begin{center}
\textbf{Biochemistry: Second signal}
\end{center}


... nitric oxide helps cells to communicate at a molecular level.
Blushing is the most peculiar and the most human of all expressions. Monkeys redden from passion, but it would require an overwhelming amount of evidence to make us believe that any animal could blush. The reddening of the face from a blush is due to the relaxation of the muscular coats of the small arteries, by which the capillaries become filled with blood; arteriole & sphincter smooth muscle relaxed via sympathetic (‘involuntary’) nerves. …as a general rule, with English women, blushing does not extend beneath the neck and upper part of the chest. {data?} The small vessels of the face become filled with blood, from the emotion of shame, in almost all the races of man, We have now to consider, why should the thought that others are thinking about us affect our capillary circulation? {consider the idea of an ‘involuntary’ signal from your subconscious to your social partners via your autonomic nervous system and facial capillary beds!}
Blood is a connective tissue with cells suspended in plasma. Plasma is about 90% water w/ many ionic solutes = electrolytes. Blood normally has a pH of 7.4 {hyperventilation blows off CO₂ & less carbonic acid raises pH} The kidney regulates electrolytes. Various plasma proteins {albumins} escort water-insoluble lipids; immunoglobulins attack antigens; fibrinogens are clotting factors. Blood plasma that has had these clotting factors removed is called serum.

Two classes of cells are suspended in blood plasma (see Fig 42.19):
- red blood cells (erythrocytes) transport oxygen, and white blood cells function in defense.

A third cellular element, platelets, are pieces of cells involved in clotting (Fig 42.18). Mammalian erythrocytes lack mitochondria & nuclei: more space for hemoglobin.

There are several types of leukocyte white blood cells (Ch 43). monocytes, neutrophils, eosinophils & basophils are phagocytes; lymphocytes develop into B cells and T cells, which produce the specific immune response (ch 43).

Blood Groups: http://www.nobelprize.org/educational/medicine/landsteiner/readmore.html
Chronic Obstructive Pulmonary Disease

**Emphysema** is characterized by abnormal permanent enlargement of the airspaces distal to the terminal bronchioles with destruction of their walls {greatly reducing S/V & gas exchange}

The incidence of emphysema, the fourth leading cause of death in the United States, is up more than 40% since 1982.

To observe the recovery of heat & moisture in sinuses: slowly exhale onto wrist via (a) mouth, then (b) nose.
Most O₂ is carried by hemoglobin in red blood cells: ~200ml/l

{Erythropoietin EPO is a hormone that controls red blood cell production}

The sigmoid oxyhemoglobin dissociation curve serves several useful functions:

- Big reserve in veins at rest
- Big dump in capillaries with exercise & demand & low Pₐ₂ in plasma
CO₂ transport & exchange

CO₂ diffuses from cells → interstitial fluid → plasma

~10% of CO₂ is transported in solution in plasma

~70% is converted to carbonic acid H₂CO₃, which dissociates into bicarbonate HCO₃⁻ and hydrogen ions H⁺. Carbonic acid lowers & buffers pH of blood.

Respiratory alkalosis is brought on by rapid, deep breathing called hyperventilation, which causes carbon dioxide in the blood to drop below normal range, causing the blood to become more alkaline (basic; higher pH).

~20% is bound to protein part of hemoglobin; this changes the conformation of hemoglobin & lowers its affinity for O₂ – ‘Bohr shift’

This, and a similar shift w/ temperature increases the efficiency of hemoglobin: more O₂ dumped in lower pH tissue capillaries, more O₂ picked up in higher pH lungs.
Breathing control: Each breath is initiated by neurons in the respiratory control center in the medulla oblongata, which sends motor neurons to diaphragm & rib "skeletal" muscles (see Fig 42.26)

Chemosensors in the brain monitor pH of cerebrospinal fluid, which depends on plasma CO₂. When medulla control center registers a slight ↓ in pH (↑ in CO₂) it increases the depth & rate of breathing, and the excess CO₂ is eliminated in exhaled air.

Peripheral chemoreceptors: carotid & aortic bodies also monitor pH

CO \{carbon monoxide\} is a lethal poison that is colorless, tasteless, odorless … it can overcome the exposed person without warning.

CO poisons by tightly binding to hemoglobin, replacing oxygen, and reducing the oxygen-carrying capacity of the blood.

CO has little effect on plasma CO₂ concentrations & pH so sensors can’t tell that hemoglobin not delivering O₂

Also – carbon monoxide binds to the same sites on heme proteins as nitric oxide, displacing NO into solution, creating damaging levels oxidants and free radicals.