• Organisms must get things in and out of their cells.

• Diffusion is insufficient over distances of more than a few millimeters, because the time it takes for a substance to diffuse to one place to another is proportional to the square of the distance.
  
  • For example, if it takes 1 second for a given quantity of glucose to diffuse 100 microns, it will take 100 seconds for it to diffuse 1 mm and almost three hours to diffuse 1 cm.

• The circulatory system solves this problem by ensuring that no substance must diffuse very far to enter or leave a cell.
2. Most invertebrates have a gastrovascular cavity or a circulatory system for internal transport

- The body plan of a hydra and other cnidarians makes a circulatory system unnecessary.
  - A body wall only two cells thick encloses a central gastrovascular cavity that serves for both digestion and for diffusion of substances throughout the body.
  - Thus, both the inner and outer tissue layers are bathed in fluid.
• In cnidarians like *Aurelia*, the mouth leads to an elaborate gastrovascular cavity that has branches radiating to and from the circular canal.

• The products of digestion in the gastrovascular cavity are directly available to the cells of the inner layer, and it is only a short distance to diffuse to the cells of the outer layer.
• Planarians and most other flatworms also have gastrovascular cavities that exchange materials with the environment through a single opening.

• The flat shape of the body and the branching of the gastrovascular cavity throughout the animal ensure that are cells are bathed by a suitable medium and diffusion distances are short.
In insects, other arthropods, and most mollusks, blood bathes organs directly in an open circulatory system.

There is no distinction between blood and interstitial fluid, collectively called hemolymph.

One or more hearts pump the hemolymph into interconnected sinuses surrounding the organs, allowing exchange between hemolymph and body cells.
• In a **closed circulatory system**, as found in earthworms, squid, octopuses, and vertebrates, 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 organs.

• Materials are exchanged by diffusion between the blood and the interstitial fluid bathing the cells.

![Diagram of closed circulatory system](image-url)
• Arteries and veins are distinguished by the *direction* in which they carry blood, not by the characteristics of the blood they carry.

• All arteries carry blood away from the heart *toward* capillaries.

• Capillaries connect arteries and veins, and they are thin enough for small molecules to get in and out.

• The job of the circulatory system is to get blood to the capillaries; they are *where exchange takes place*.

• Veins return blood to the heart *from* capillaries.
• A fish heart has two main chambers, one atrium and one ventricle.

• Blood is pumped from the ventricle to the gills (the gill circulation) where it picks up oxygen and disposes of carbon dioxide across the capillary walls.

• The gill capillaries converge into a vessel that carries oxygenated blood to capillary beds at the other organs (the systemic circulation) and back to the heart.
- Frogs and other amphibians have a three-chambered heart with two atria and one ventricle.
  - The ventricle pumps blood into a forked artery that splits the ventricle’s output into the **pulmocutaneous** and **systemic circulations**.
• The pulmocutaneous circulation leads to capillaries in the gas-exchange organs (the lungs and skin of a frog), where the blood picks up O₂ and releases CO₂ before returning to the heart’s left atrium.

• Most of the returning blood is pumped into the systemic circulation, which supplies all body organs and then returns oxygen-poor blood to the right atrium via the veins.

• This scheme, called double circulation, provides a vigorous flow of blood to the brain, muscles, and other organs because the blood is pumped a second time after it loses pressure in the capillary beds of the lung or skin.

• More efficient than a fish’s.
• Reptiles also have double circulation with pulmonary (lung) and systemic circuits.
  • However, there is even less mixing of oxygen-rich and oxygen-poor blood than in amphibians.
  • Although the reptilian heart is three-chambered, the ventricle is partially divided.
  • Evolution is tinkering!
• In crocodilians, birds, and mammals, the ventricle is completely divided into separate right and left chambers.

• In this arrangement, the left side of the heart receives and pumps only oxygen-rich blood, while the right side handles only oxygen-poor blood.

• Double circulation restores pressure to the systemic circuit and prevents mixing of oxygen-rich and oxygen-poor blood.

Fig. 42.3c
• The evolution of a powerful four-chambered heart was an essential adaptation in support of the endothermic way of life characteristic of birds and mammals.

• The endotherm circulatory system needs to deliver about ten times as much fuel and O$_2$ to their tissues and remove ten times as much wastes and CO$_2$.

• Birds and mammals evolved from different reptilian ancestors, and their powerful four-chambered hearts evolved independently - an example of convergent evolution.

• Can we do a vertebrate cladogram?
To trace the double circulation pattern of the mammalian cardiovascular system, we’ll start with the pulmonary (lung) circuit.
Fig. 42.5

Pulmonary artery

Anterior vena cava

Right atrium

Pulmonary veins

Semilunar valve

Atrioventricular valve

Posterior vena cava

Aorta

Pulmonary artery

Left atrium

Pulmonary veins

Semilunar valve

Atrioventricular valve

Right ventricle

Left ventricle

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• A **cardiac cycle** is one complete sequence of the heart contracting and relaxing.

• The contraction phase is called **systole**, and the relaxation phase is called **diastole**.

• See it here
• Cardiac output depends on two factors: the rate of contraction or **heart rate** (number of beats per minute) and **stroke volume**, the amount of blood pumped by the left ventricle in each contraction.

  • The average stroke volume for a human is about 75 mL.
  • The typical resting cardiac output, about 5.25 L / min, is about equivalent to the total volume of blood in the human body.
  • Cardiac output can increase about fivefold during heavy exercise.
• Four valves in the heart, consisting of flaps of connective tissue, prevent backflow and keep blood moving in the correct direction.
• Their closing is responsible for the sound of a heartbeat.
• Look here.
• Several mechanisms have evolved that assure the continuity and control of heartbeat.

• Certain cells of vertebrate cardiac muscle are self-excitabile, meaning they contract without any signal from the nervous system. This ability of muscles to generate their own contraction is what is meant by the adjective myogenic.
  
  • Each cell has its own intrinsic contraction rhythm.
  
  • However, these cells are synchronized by the sinoatrial (SA) node, or pacemaker, which sets the rate and timing at which all cardiac muscle cells contract.
  
  • The SA node is in the wall of the right atrium.
• The cardiac cycle is regulated by electrical impulses that radiate throughout the heart.

• Cardiac muscle cells are electrically coupled by intercalated disks between adjacent cells.
While the SA node sets the tempo for the entire heart, it is influenced by a variety of physiological cues.

- Two sets of nerves affect heart rate with one set speeding up the pacemaker and the other set slowing it down.
  - Heart rate is a compromise regulated by the opposing actions of these two sets of nerves.
- The pacemaker is also influenced by hormones.
  - For example, epinephrine from the adrenal glands increases heart rate.
- The rate of impulse generation by the pacemaker increases in response to increases in body temperature and with exercise.
• Structural differences result in the different functions of arteries, veins, and capillaries.

• Capillaries lack the two outer layers and their very thin walls consist of only endothelium and its basement membrane, thus enhancing exchange.
• Arteries have thicker middle and outer layers than veins.

• The thicker walls of arteries provide strength to accommodate blood pumped rapidly and at high pressure by the heart.

• Their elasticity (elastic recoil) helps maintain blood pressure even when the heart relaxes.

• Thickness, thinness, the presence of smooth, circular muscles, the presence of elastic tissues, etc. are all structural aspects that contribute to the function of these blood vessels.
• The thinner-walled veins convey blood back to the heart at low velocity and pressure.

• Blood flows mostly as a result of skeletal muscle contractions when we move that squeeze blood in veins.

• Within larger veins, flaps of tissues act as one-way valves that allow blood to flow only toward the heart.
• A sphygmomanometer, an inflatable cuff attached to a pressure gauge, measures blood pressure fluctuations in the brachial artery of the arm over the cardiac cycle.

• The arterial blood pressure of a healthy human oscillates between about 120 mm Hg at systole and 70 mm Hg at diastole; thus a blood pressure # of 120/70.
Cardiac output is adjusted in concert with changes in peripheral resistance.

For example, during heavy exercise the arterioles in the working muscles dilate, admitting a greater flow of oxygen-rich blood to the muscles and decreasing peripheral resistance.

At the same time, cardiac output increases, maintaining blood pressure and supporting the necessary increase in blood flow.
8. The lymphatic system returns fluid to the blood and aids in body defense

- Fluids and some blood proteins that leak from the capillaries into the interstitial fluid are returned to the blood via the **lymphatic system**.
  - Fluid enters this system by diffusing into tiny lymph capillaries intermingled among capillaries of the cardiovascular system.
  - Once inside the lymphatic system, the fluid is called **lymph**, with a composition similar to the interstitial fluid.
  - The lymphatic system drains into the circulatory system near the junction of the venae cavae with the right atrium.
• Lymph vessels, like veins, have valves that prevent the backflow of fluid toward the capillaries.

• Rhythmic contraction of the vessel walls help draw fluid into lymphatic capillaries.

• Also like veins, lymph vessels depend mainly on the movement of skeletal muscle to squeeze fluid toward the heart.
• Along a lymph vessels are organs called **lymph nodes**.

• The lymph nodes filter the lymph.

• Inside a lymph node is a honeycomb of connective tissue with spaces filled with white blood cells specialized for defense.

  • When the body is fighting an infection, these cells multiply, and the lymph nodes become swollen.

• In addition to defending against infection and maintaining the volume and protein concentration of the blood, the lymphatic system transports fats from the digestive tract to the circulatory system.
9. Blood is a connective tissue with cells suspended in plasma

• However, blood in the closed circulatory systems of vertebrates is a specialized connective tissue consisting of several kinds of cells suspended in a liquid matrix called plasma.

• The plasma, about 55% of the blood volume, consists of water, ions, various plasma proteins, nutrients, waste products like urea, respiratory gases, and hormones, while the cellular elements include red and white blood cells and platelets.
### Plasma 55%

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Major functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Solvent for carrying other substances</td>
</tr>
<tr>
<td>Ions</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Plasma proteins</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins (antibodies)</td>
<td></td>
</tr>
<tr>
<td>Substances transported by blood</td>
<td>Nutrients (e.g., glucose, fatty acids, vitamins)</td>
</tr>
<tr>
<td></td>
<td>Waste products of metabolism</td>
</tr>
<tr>
<td></td>
<td>Respiratory gases ($O_2$ and $CO_2$)</td>
</tr>
<tr>
<td></td>
<td>Hormones</td>
</tr>
</tbody>
</table>

### Cellular elements 45%

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Number (per mm$^3$ of blood)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes (red blood cells)</td>
<td>5–6 million</td>
<td>Transport oxygen and help transport carbon dioxide</td>
</tr>
<tr>
<td>Leukocytes (white blood cells)</td>
<td>5000–10,000</td>
<td>Defense and immunity</td>
</tr>
<tr>
<td>Basophil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>250,000–400,000</td>
<td>Blood clotting</td>
</tr>
</tbody>
</table>

Fig. 42.14
• Mammalian erythrocytes lack nuclei, an unusual characteristic that leaves more space in the tiny cells for hemoglobin, the iron-containing protein that transports oxygen.

• Red blood cells also lack mitochondria and generate their ATP exclusively by anaerobic metabolism.
• Erythrocytes, leukocytes, and platelets all develop from a single population of cells, pluripotent stem cells, in the red marrow of bones, particularly the ribs, vertebrae, breastbone, and pelvis.

• “Pluripotent” means that these cells have the potential to differentiate into any type of blood cells or cells that produce platelets.

• This population renews itself (by mitosis) while replenishing the blood with cellular elements.
Fig. 42.13
• A negative-feedback mechanism, sensitive to the amount of oxygen reaching the tissues via the blood, controls erythrocyte production.

  • If the tissues do not contain enough oxygen, the kidney converts a plasma protein to a hormone called erythropoietin (EPO), which stimulates production of erythrocytes.

  • If blood is delivering more oxygen than the tissues can use, the level of EPO is reduced, and erythrocyte production slows.

  • Some endurance athletes take EPO (illegally) to increase their aerobic capacity.
• Through a recent breakthrough in isolating and culturing pluripotent stem cells, researchers may soon have effective treatments for a number of human diseases, such as leukemia.

• Individuals with leukemia have a cancerous line of stem cells that produce leukocytes.

• These cancerous cells crowd out cells that make red blood cells and produce an unusually high number of leukocytes, many of which are abnormal.

• One strategy now being used experimentally for treating leukemia is to remove pluripotent stem cells from a patient, destroy the bone marrow, and restock it with noncancerous pluripotent cells.
• Blood contains a self-sealing material that plugs leaks from cuts and scrapes.
  • A clot forms when the inactive form of the plasma protein \textit{fibrinogen} is converted to \textit{fibrin}, which aggregates into threads that form the framework of the clot.
  • The clotting mechanism begins with the release of \textit{clotting factors} from platelets.
  • An inherited defect in any step of the clotting process causes \textit{hemophilia}, a disease characterized by excessive bleeding from even minor cuts and bruises.
  • Remember Queen Victoria, Rasputin, sex-linked recessive, etc.?
1. Injury to lining of blood vessel exposes connective tissue; platelets adhere

2. Platelet plug forms

3. Fibrin clot with trapped cells

- Collagen fibers
- Platelet releases chemicals that make nearby platelets sticky
- Platelet plug

Clotting factors from:
- Platelets
- Damaged cells
- Plasma (factors include calcium, vitamin K)

Prothrombin → Thrombin

Fibrinogen → Fibrin

Fig. 42.16
10. Cardiovascular diseases are the leading cause of death in the U.S. and most other developed nations

- More than half the deaths in the United States are caused by **cardiovascular diseases**, diseases of the heart and blood vessels.

- The final blow is usually a heart attack or stroke.
  - A **heart attack** is the death of cardiac muscle tissue resulting from prolonged blockage of one or more coronary arteries, the vessels that supply oxygen-rich blood to the heart.
  - A **stroke** is the death of nervous tissue in the brain.
Heart attacks and strokes frequently result from a thrombus that clogs a coronary artery or an artery in the brain.

- The thrombus may originate at the site of blockage or it may develop elsewhere and be transported (now called an embolus) until it becomes lodged in an artery too narrow for it to pass.

- Cardiac or brain tissue downstream of the blockage may die from oxygen deprivation.

- The effects of a stroke and the individual’s chance of survival depend on the extent and location of the damaged brain tissue.
• If damage in the heart interrupts the conduction of electrical impulses through cardiac muscle, heart rate may change drastically or the heart may stop beating altogether.

• Still, the victim may survive if heartbeat is restored by cardiopulmonary resuscitation (CPR) or some other emergency procedure within a few minutes of the attack.

• Very important to know this!!!!
• The suddenness of a heart attack or stroke belies the fact that the arteries of most victims had become gradually impaired by a chronic cardiovascular disease known as **atherosclerosis**.

• Growths called plaques develop in the inner wall of the arteries, narrowing their bore.
• At plaque sites, the smooth muscle layer of an artery thickens abnormally and becomes infiltrated with fibrous connective tissue and lipids such as cholesterol.

• In some cases, plaques also become hardened by calcium deposits, leading to arteriosclerosis, commonly known as hardening of the arteries.

• Vessels that have been narrowed are more likely to trap an embolus and are common sites for thrombus formation.
• **Hypertension** (high blood pressure) promotes atherosclerosis and increases the risk of heart disease and stroke.

• According to one hypothesis, high blood pressure causes chronic damage to the endothelium that lines arteries, promoting plaque formation.

• Hypertension is simple to diagnose and can usually be controlled by diet, exercise, medication, or a combination of these.
• To some extent, the tendency to develop hypertension and atherosclerosis is inherited.

• Nongenetic factors include smoking, lack of exercise, a diet rich in animal fat, and abnormally high levels of cholesterol in the blood.

• One measure of an individual’s cardiovascular health or risk of arterial plaques can be gauged by the ratio of low-density lipoproteins (LDLs) to high-density lipoproteins (HDLs) in the blood.
  
  • LDL is associated with depositing of cholesterol in arterial plaques. Watch and Watch here.
  
  • HDL may reduce cholesterol deposition, as these transport cholesterol out of blood and into cells.
Oh, gosh, what am I doing to myself???

- Listen to **My Poor Veins**

- **Breaking news (7/12/13)!!!** A mutation in a gene called PCSK9 was found to lead to high LDL levels, but then a different mutation led to lower levels. Two people have been found who are homozygous for the good mutation, and their LDL levels are around 15 (you should worry if yours is over 100). Three drug companies are in a huge race to get FDA approval for a drug that mimics the PCSK9 mutation’s effect.  
  See [here](#).