• Human beings are approximately 70% WATER by body weight. Where is all this water?
• Most of this water is within cells, while a smaller amount is found within:
  A. TISSUE FLUID (surrounds cells)
  B. LYMPH (within lymph vessels)
  C. BLOOD VESSELS
• BLOOD is required by the body to maintain homeostasis. Blood is a liquid connective tissue. Blood functions in a) TRANSPORT (of gases, wastes, and nutrients) b) CLOTTING (to seal injuries) c) INFECTION FIGHTING. Average person has about 5 to 6 liters of blood.
• If blood is allowed to sit in a test tube without clotting, it will divide into TWO MAIN PARTS:
  A. PLASMA (the liquid portion of blood) - makes up about 55% of blood volume. Contains water and organic and inorganic substances (proteins, gases, salts, nutrients, wastes).

<table>
<thead>
<tr>
<th>Plasma Constituent</th>
<th>Function</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Maintains blood volume and transports molecules</td>
<td>Absorbed from large intestine</td>
</tr>
<tr>
<td>Plasma Proteins</td>
<td>All maintain blood osmotic pressure &amp; pH</td>
<td></td>
</tr>
<tr>
<td>a. Albumin</td>
<td>Transport</td>
<td>Liver</td>
</tr>
<tr>
<td>b. Fibrinogen</td>
<td>Clotting</td>
<td>Liver</td>
</tr>
<tr>
<td>c. Globulins</td>
<td>Fight Infection</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Gases</td>
<td>Cellular Respiration</td>
<td></td>
</tr>
<tr>
<td>a. Oxygen</td>
<td>End product of metabolism</td>
<td>Lungs</td>
</tr>
<tr>
<td>b. CO₂</td>
<td></td>
<td>Tissues</td>
</tr>
<tr>
<td>Nutrients: Fats, glucose, amino acids, etc.</td>
<td>Food for cells</td>
<td>Absorbed from intestinal villi</td>
</tr>
<tr>
<td>Salts</td>
<td>Maintain blood osmotic pressure/pH, aid metabolism</td>
<td>Absorbed from intestinal villi</td>
</tr>
<tr>
<td>Wastes</td>
<td>End products of metabolism</td>
<td>Tissues</td>
</tr>
<tr>
<td>Hormones, vitamins etc.</td>
<td>Aid metabolism</td>
<td>Varied</td>
</tr>
</tbody>
</table>

B. FORMED ELEMENTS: the "solid part" of blood, consists of the following parts.
  a. RED BLOOD CELLS (ERYTHROCYTES)
     Transport oxygen, formed in bone marrow. Over 95% of formed elements are erythrocytes.
  b. WHITE BLOOD CELLS (LEUKOCYTES)
     Fight infection, formed in bone marrow and lymphoid tissue.
  c. PLATELETS (THROMBOCYTES)
     Function in blood clotting
• The white blood cells can also be classified according to their appearance.

<table>
<thead>
<tr>
<th>Erythrocytes</th>
<th>Leukocytes</th>
<th>Thrombocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cells</td>
<td>White Blood Cells</td>
<td>Platelets</td>
</tr>
<tr>
<td>Granular Leukocytes</td>
<td>Agranular Leukocytes</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td>Monocytes</td>
<td></td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Here is a micrographs showing formed elements in human blood
Blood Proteins
- Are required for the transport of many molecules. For example, cholesterol is a lipid that is insoluble in plasma. It must be carried by proteins.
- HDL (high-density lipoprotein) is “better” than LDL for binding with cholesterol, according to some studies, in the prevention of atherosclerosis.
- Blood proteins also contribute to the viscosity of blood (“blood is thicker than water”), which aids in transport.
- Blood proteins also contribute to osmotic pressure, which maintains blood volume.

Hemoglobin
- O$_2$ is carried by Hemoglobin, which is made of 4 amino acid chains (2 alpha (α) and 2 beta (β)). Each chain has iron-containing heme group which attaches to oxygen.
- Hemoglobin is an excellent carrier of oxygen because it weakly binds with oxygen in the cool, neutral conditions in the lungs, and easily gives O$_2$ up in the warmer and more acidic tissues.
- Hemoglobin is always contained within red blood cells. Since hemoglobin is a red pigment, red blood cells appear red. This colour can change based on what the hemoglobin is attached to.
- OXYHEMOGLOBIN (hemoglobin bound to oxygen, abbreviated as HbO$_2$) is bright red, while REDUCED HEMOGLOBIN (hemoglobin that has lost its oxygen) is dark purple.
- Carbon Monoxide (CO) is a poison found in car exhaust. It binds to Hb better than oxygen, and stays bound for several hours regardless of the environmental conditions. CO poisoning can lead to death.

Hemoglobin picks O$_2$ up in the lungs and releases O$_2$ in tissues. Meanwhile, CO$_2$ and wastes diffuse out of cells. What this means is that there are all sorts of diffusing molecules going in and out of the blood and cells. We should understand how this works and what drives the movement of molecules. The main answer lies in battle of blood pressure versus osmotic pressure. The pressure of blood in blood vessel would tend to push molecules out of the blood. Osmotic pressure is the opposing force trying to force molecules into the blood. Osmotic pressure is basically constant, but blood pressure varies considerable around a capillary bed. This causes some natural movement of molecules.
- At the arterial side of a capillary, blood pressure is higher than the osmotic pressure and therefore water, oxygen and glucose tend to leave the bloodstream.
- At the venous end of a capillary, the osmotic pressure is higher than the blood pressure and, therefore, water, ammonia, and carbon dioxide tend to enter the bloodstream.
- Reduced hemoglobin can now pick up CO$_2$ to form carbaminohemoglobin (HbCO$_2$).
- However, most CO$_2$ transported as BICARBONATE ION ( = HCO$_3^-$), which is formed after CO$_2$ combines with water, forming carbonic acid which then dissociates. Note the following reaction:
  \[
  \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \]
- The enzyme CARBONIC ANHYDRASE speeds up this reaction.
• The H⁺ released by the above reaction could wreak havoc on blood pH. To prevent this H⁺ is picked up by the globin portion of hemoglobin (to become HHb) so that pH is maintained.

Red Blood Cells
• There are close to 30 trillion blood cells in an adult. Each cubic millimeter of blood contains from 4 1/2 to 5 1/2 million red blood cells and an average total of 7,500 white blood cells. In humans, red blood cells are small, biconcave, disk-shaped cells without nuclei.
• Red blood cells are made by cells called “STEM CELLS” in red bone marrow (over 2 million per second!) of the skull, ribs, vertebrae, and ends of the long bones. Here, Stem Cells continuously divide. During the maturation process, a red blood cell loses its nucleus and gets much smaller.
• Oxygen levels in blood determine the rate of RBC formation. When oxygen tension is low, the kidneys produce a chemical called renal erythropoietic factor (REF) that, after combining with globulin from the liver, causes the bone marrow to produce more RBC.
• RBC live for only 120 days and then are destroyed in the liver and spleen. The iron is recovered from the hemoglobin and sent to the bones, while the heme portion is chemically degraded and is excreted by the liver in the bile as bile pigments.

BLOOD CLOTTING
• After an injury, coagulation "or clotting" takes place to prevent excessive blood loss.
• This requires the action of 1) platelets 2) prothrombin, and 3) fibrinogen.
• Platelets result from fragmentation of large cells called megakaryocytes in red bone marrow. You have more than a trillion in your blood.
• Fibrinogen and prothrombin are plasma proteins manufactured and deposited in the blood by the liver (vitamin K is required for the production of prothrombin)
• Here is a simplified summary of the steps involved in clot formation:
  1. Platelets clump at the site of the puncture and partially seal the leak.
  2. Platelets and injured tissues release the enzyme prothrombin activator that activates prothrombin to thrombin. Calcium ions (Ca++) are necessary for this step.
  3. Thrombin acts as an enzyme and severs two short a.a. chains from each fibrinogen molecule.
  4. These activated chains join end to end to form long ends of fibrin.
  5. Fibrin threads entangle red cells and platelets in the damaged area and form the framework of the clot.
• Red cells trapped in the clot give it its red colour.
• Clotting takes place faster at warmer temperatures than cold because it is
controlled by enzymes.

- Serum is plasma from which the fibrinogen has been removed due to clotting.
- A fibrin clot is only a temporary repair. Eventually, an enzyme called plasmin destroys the fibrin network and restores the fluidity of plasma.

**INFECTION FIGHTING: another major function of blood**

- The body's first line of defense against invading pathogens like bacteria and viruses is the skin.
- The second line of defense is the blood: specifically, white blood cells and gamma globulins.

**WHITE BLOOD CELLS**

- White blood cells are usually larger than RBC (8 - 20 μm), have a nucleus, and appear white (if not stained - when stained, they appear bluish).
- Much less numerous than RBC (only 7,000 to 8,000 cells per cubic millimeter). White blood cells, called leukocytes, are outnumbered by the red blood cells 600 to 1.

There are two main types of Leukocytes:

1. **Granulocytes**: have granules in the cytoplasm and a many-lobed nucleus joined by nuclear threads (called "polymorphonuclear"). The granulocytes include Neutrophils (phagocytizes primarily bacteria), Eosinophils (phagocytizes and destroys antigen-antibody complexes), and Basophils (congregates in tissues, releases histamine when stimulated). Formed in the red bone marrow. The granules of a neutrophil are lysosomes.

2. **Agranulocytes**: Include Lymphocytes and Monocytes. They don't have granules, and have a circular (lymphocytes) or indented (monocytes) nucleus. They are produced in lymphoid tissue found in the spleen, lymph nodes, and tonsils. Type B lymphocytes produce antibodies in blood and lymph, Type T lymphocytes kill virus-containing cells. Monocytes become macrophages.
- Infection fighting by white cells is primarily dependent on the neutrophils, which comprise 60 to 70% of all leukocytes, and the lymphocytes (which make up 25 to 30%).
- Neutrophils, monocytes, and eosinophils are phagocytic. They engulf invaders at the site of infection.
- Lymphocytes don't work this way. They secrete a class of gamma globulins (proteins) called IMMUNOGLOBULINS (=ANTIBODIES), which combine with foreign substances to inactivate them.
- Lymphocytes are the smallest white blood cells. When microbes invade the body, lymphocytes begin to multiply and they become transformed plasma cells. Each microbe stimulates only one type of lymphocyte to multiply and form one type of plasma cell. The type of plasma cell formed is the type that can make a specific antibody to destroy the particular microbe that has invaded the body.
- Red bone marrow continually produces white blood cells, except lymphocytes and monocytes, and keeps a reserve ready in case of need. Lymphocytes and monocytes are produced by lymphatic tissue located in the lymph nodes and spleen. When a parasite or virus invades and begins to colonize, the reserves of white blood cells are released and the manufacturing of large quantities of the appropriate white cells begins. It is this increased production that causes fever. Because white blood cells are very specific for various illnesses, their count can help doctors diagnose patients.

**ANTIBODIES: very specific proteins that attach to invading pathogens**

- Lymphocytes produce antibodies in response to invading pathogens.
- Each lymphocyte produces one type of antibody that is specific for one type of antigen. An antigen is a foreign substance (usually a protein, sometimes a carbohydrate) that stimulates the release of antibodies to it. e.g. an antigen could be protein coat of a virus.
- Antibodies combine with antigens in such a way that the antigens are rendered harmless. Each antibody fits its antigen like a lock and key.
- An individual is immune to an antigen if he/she has antibodies to that particular antigens.
- The blood in the individual contains lymphocytes that can remain in the system for years, ready to produce antibodies if that antigen is detected.
Exposure to the antigen, either naturally or by way of a vaccine, can cause active immunity to develop. Diseases will often cause an increase in a particular type of white cell. e.g. **mononucleosis** characterized by greater #s of dark staining lymphocytes. **Leukemia** is a form of cancer characterized by uncontrolled production of abnormal white cells, which accumulate in the bone marrow, lymph nodes, spleen, and liver, causing them to malfunction. Leukemia patients often have severe anemia, clotting difficulties, and succumb to many infections.

**THE INFLAMMATORY REACTION**

Whenever the skin is broken due to a minor injury, a series of events occur that are known as the **inflammatory response** because there is swelling and reddening at the site of the injury. This response is designed to **get the body's defenses marshaled as quickly as possible at the site where they are needed**.

1. When blood vessels and tissue cells get ruptured by an injury, they release precursors of **BRADYKININ**, a chemical with several jobs: 1) it initiates nerve impulses --- this results in PAIN 2) bradykinin causes **MAST CELLS** (a type of cell that resides in tissues that is derived from Basophils) to release histamine, which together with bradykinin causes a capillary to become enlarged and more permeable.

2. the enlarged capillary causes the skin to **redden** and its increased permeability allows **proteins and fluids to escape** so that swelling results.

3. Meanwhile, **bacteria** and **viruses** are also entering through the rupture.

4. Lymphocytes release antibodies that attack the invading pathogens, preparing them for **phagocytosis** by neutrophils or monocytes.

5. Once monocytes have arrived on the scene, they swell up to five to ten times their original size and become **macrophages** (large phagocytic cells that are able to devour a hundred invaders and still survive).

- **Dead neutrophils plus cells, bacteria, and WBC form pus**, a thick yellowish fluid.
BLOOD TYPING

- Human blood is classified according to the **antigens** present on the surface of the red blood cells. The most common blood types belong to the **ABO Grouping**.
- Two antigens that may be present on the red cells are called "A" and "B". An individual may have one of these antigens present (in which case they will have type A or type B blood), or both (type AB) or neither (type O). Therefore, there are four blood types in the ABO Grouping.
- Each individual also carries antibodies in his/her plasma to the antigens **not** present on that individual's red cells. e.g. Type A blood has antibody b, Type AB blood has **no** antibodies.
- If the same antigen and antibody are present, **AGGLUTINATION** (or clumping) of red cells will occur (can cause death).
- Blood recipients may only receive donated blood for which they have no antibodies in their plasma.

anti-A    anti-B    anti-Rh

This test indicates is B+ blood type.

**TYPE “A” BLOOD**
- has type “A” **antigens**
- makes type b **antibodies** (antibodies that attack B antigens)

**TYPE “B” BLOOD**
- has type “B” **antigens**
- makes type a **antibodies** (antibodies that attack A antigens)

**TYPE “AB” BLOOD**
- has both “A” & “B” **antigens**
- makes **NO ANTIBODIES** to A or B antigens.

**TYPE “O” BLOOD**
- has neither A nor B **antigens**
- makes both type a and type b **antibodies**

**Rhesus Antigen (Rh factor)**
- Rh factor is another antigen that can be present on RBC.
- Either you have it (“+”) or you don’t (“−”)
- If you are Rh negative, you **don’t make antibodies** to Rh unless you have been exposed to it.
- The person above is Rh+
Another important antigen in matching blood types is the Rh factor (another antigen found on red blood cells)

- People with this particular antigen on the red cells are **Rh positive**; those without it are **Rh negative**.
- Rh negative individuals **do not normally make antibodies to the Rh factor**, but they will make them **when exposed to the Rh factor**. It is possible to extract these antibodies and use them for blood type testing, since Rh positive blood will agglutinate when mixed with Rh antibodies.
- The Rh factor is very important during **pregnancy**. If the **mother is Rh negative** and the **father is Rh positive**, the child **may be Rh positive**. During gestation, it is **normal that a few red cells from the child will find their way into the mother's system** -- **she will then produce Rh antibodies**.
- If the **mother becomes pregnant with another Rh positive baby**, Rh antibodies cross the placenta and destroy the child's red cells. This is called **FETAL ERYTHROBLASTOSIS**.
- **Current treatment**: give Rh- women an Rh immune globulin injection (like an injection of antibodies) called **RhoGAM** just **after** the birth of any Rh+ child. This injection will **DESTROY ANY RED CELLS** left over from the baby, **BEFORE** the mother has a chance to start producing her own antibodies.
- The injection won't work if the woman has already started to produce her own antibodies.

### The Rh System

- **Type** | **Antigen** | **Antibody** | **%U.S. Black** | **%U.S. Caucasian**
--- | --- | --- | --- | ---
A | A | b | 25 | 41
B | B | a | 20 | 7
AB | A,B | none | 4 | 2
O | none | a,b | 51 | 50

**For Example**: A- mother X O+ father could produce A+ baby.

- A few of baby’s blood cells get into mother just before or during childbirth.
- Mom then produces antibodies to the Rh factor

If she gets pregnant with another Rh+ baby, her anti-Rh antibodies can cross placenta during pregnancy and cause agglutination of baby’s RBC -- can seriously harm or kill the baby.

**Treatment**: immediately after birth of Rh+ baby, give mother injection of RhoGAM. It contains Rh antibodies that **destroy any of the baby’s RBC** left in the mother **before she can produce antibodies to Rh factor**.