

Blood

Blood is a liquid tissue. Suspended in the watery **plasma** are seven types of cells and cell fragments.

- **red blood cells** (RBCs) or **erythrocytes**
- **platelets** or **thrombocytes**
- five kinds of **white blood cells** (WBCs) or **leukocytes**
 - Three kinds of **granulocytes**
 - **neutrophils**
 - **eosinophils**
 - **basophils**
 - Two kinds of leukocytes without granules in their cytoplasm
 - **lymphocytes**
 - **monocytes**

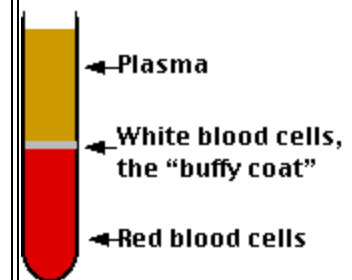
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If one takes a sample of blood, treats it with an agent to prevent clotting, and spins it in a centrifuge,

- the red cells settle to the bottom
- the white cells settle on top of them forming the "buffy coat".

The fraction occupied by the red cells is called the **hematocrit**. Normally it is approximately 45%. Values much lower than this are a sign of **anemia**.



Functions of the blood

Blood performs two major functions:

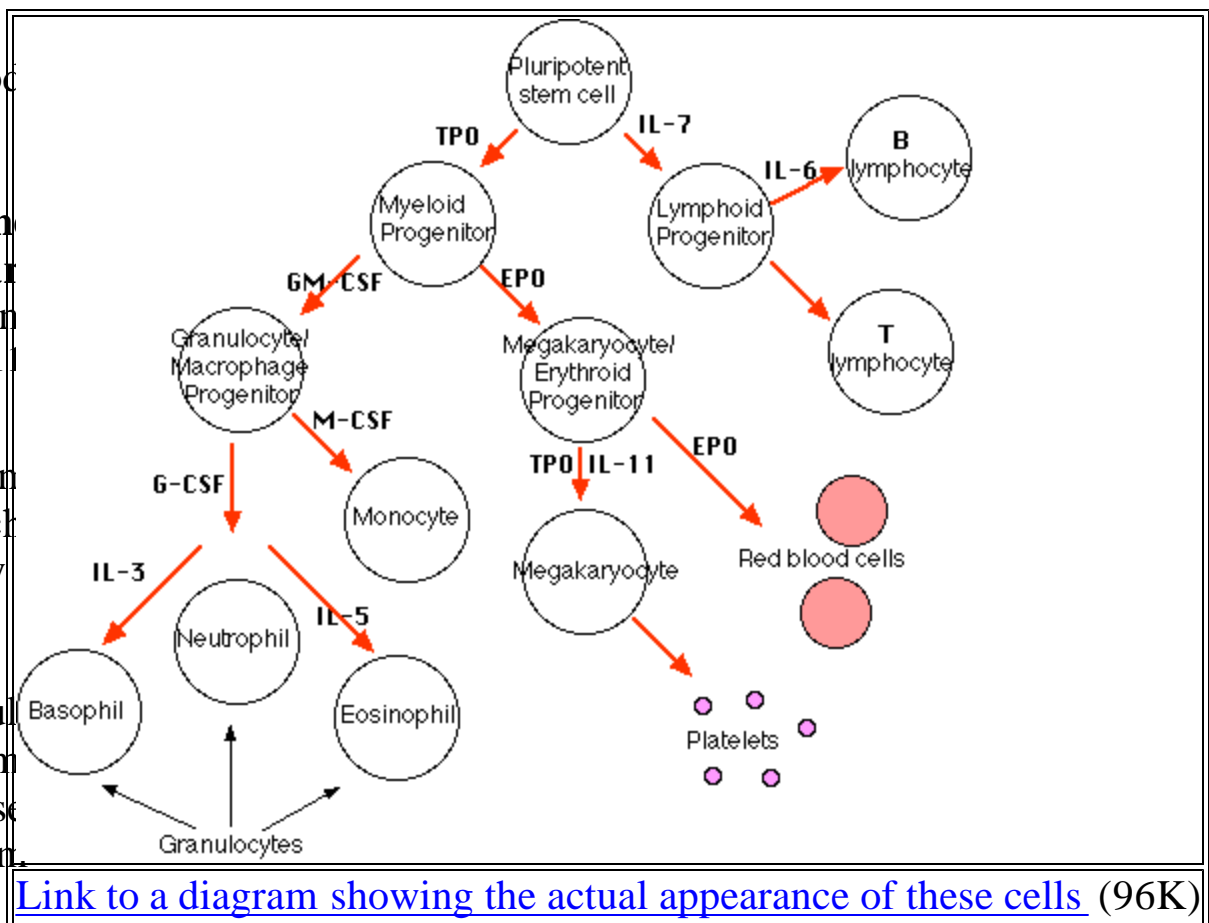
- transport through the body of

- oxygen and carbon dioxide
- food molecules (glucose, lipids, amino acids)
- ions (e.g., Na^+ , Ca^{2+} , HCO_3^-)
- wastes (e.g., urea)
- hormones
- heat
- defense of the body against infections and other foreign materials. All the WBCs participate in these defenses.

The formation of blood cells (cell types and acronyms are defined below)

All the various types of blood cells

- are produced in the bone marrow (some 10¹¹ of them each day in an adult human)
- arise from a single type of cell called a **pluripotent stem cell**.



These stem cells

- are very rare (only about one in 10,000 bone marrow cells);
- are attached (probably by [adherens junctions](#)) to [osteoblasts](#) lining the inner surface of bone cavities;
- express a surface protein designated CD34;
- produce, by mitosis, two kinds of progeny:
 - more stem cells
 - cells that begin to differentiate along the paths leading to the various kinds of blood cells.

Which path is taken is regulated by

- the need for more of that type of blood cell which is, in turn, controlled by appropriate [cytokines](#) and/or hormones.

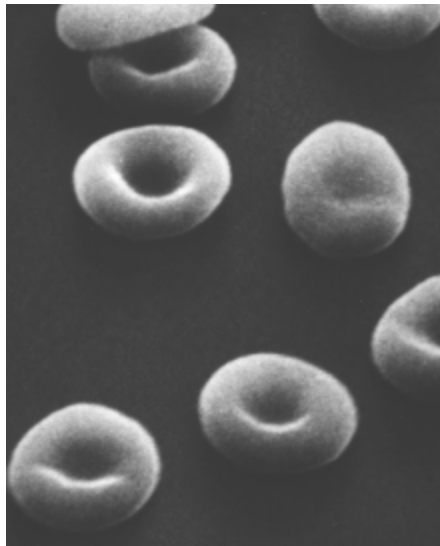
Examples:

- **Interleukin-7 (IL-7)** is the major cytokine in stimulating bone marrow stem cells to start down the path leading to the various [lymphocytes](#) (mostly [B cells](#) and [T cells](#)).
- **Erythropoietin (EPO)**, produced by the kidneys, enhances the production of **red blood cells** (RBCs).
- **Thrombopoietin (TPO)**, assisted by Interleukin-11 (**IL-11**), stimulates the production of **megakaryocytes**. Their fragmentation produces [platelets](#).
- **Granulocyte-monocyte colony-stimulating factor (GM-CSF)**, as its name suggests, sends cells down the path leading to both those cell types. In due course, one path or the other is taken.
 - Under the influence of **granulocyte colony-stimulating factor (G-CSF)**, they differentiate into [neutrophils](#).
 - Further stimulated by interleukin-5 (**IL-5**) they develop into [eosinophils](#).
 - Interleukin-3 (**IL-3**) participates in the differentiation of most of the white blood cells but plays a particularly prominent role in the formation of [basophils](#) (responsible for some [allergies](#)).
 - Stimulated by **macrophage colony-stimulating factor (M-CSF)** the granulocyte/macrophage progenitor cells differentiate into [monocytes](#), the precursors of **macrophages**.

Red Blood Cells (erythrocytes)

The most numerous type in the blood.

- Women average about 4.8 million of these cells per cubic millimeter (mm^3 ; which is the same as a microliter [μl]) of blood.
- Men average about 5.4×10^6 per μl .
- These values can vary over quite a range depending on such factors as health and altitude. (Peruvians living at 18,000 feet may have as many as 8.3×10^6 RBCs per μl .)



As RBC precursors mature in the bone marrow,

- they manufacture hemoglobin until it accounts for some 90% of the dry weight of the cell.
- The nucleus is squeezed out of the cell. Nearby macrophages ingest the extruded nuclei and break down their DNA.

This scanning electron micrograph (courtesy of Dr. Marion J. Barnhart) shows the characteristic biconcave shape of red blood cells.

Thus RBCs are terminally differentiated; that is, they can never divide. They live about 120 days and then are ingested by phagocytic cells in the liver and spleen. Most of the iron in their hemoglobin is reclaimed for reuse. The remainder of the heme portion of the molecule is degraded into bile pigments and excreted by the liver. Some 3 million RBCs die and are scavenged by the liver each second.

Red blood cells are responsible for the transport of **oxygen** and **carbon dioxide**.

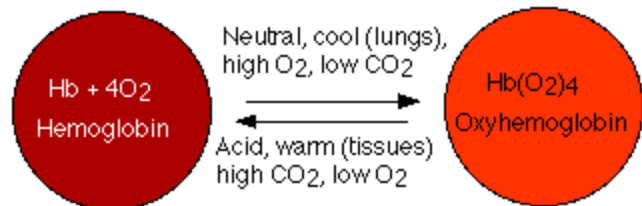
Oxygen Transport

The hemoglobin (Hb) molecule

- consists of four polypeptides.
- Each of these is attached the [prosthetic group heme](#).
- There is one atom of iron at the center of each heme.
- One molecule of oxygen can bind to each heme.

The reaction is reversible.

- Under the conditions of lower temperature, higher pH, and increased oxygen pressure in the capillaries of the lungs, the reaction proceeds to the right. The purple-red deoxygenated hemoglobin of the venous blood becomes the bright-red **oxyhemoglobin** of the arterial blood.
- Under the conditions of higher temperature, lower pH, and lower oxygen pressure in the tissues, the reverse reaction is promoted and oxyhemoglobin gives up its oxygen.



Carbon Dioxide Transport

Carbon dioxide (CO_2) combines with water forming carbonic acid, which dissociates into a hydrogen ion (H^+) and a [bicarbonate ions](#):



95% of the CO_2 generated in the tissues is carried in the red blood cells:

- It probably enters (and leaves) the cell by diffusing through transmembrane channels in the plasma membrane. (One of the proteins that forms the channel is the **D antigen** that is the most important factor in the [Rh system](#) of blood groups.)
- Once inside, about one-half of the CO_2 is directly bound to hemoglobin (at a site different from the one that binds oxygen).
- The rest is converted — following the equation above — by the enzyme **carbonic anhydrase** into
 - bicarbonate ions that diffuse back out into the plasma and

- hydrogen ions (H^+) that bind to the protein portion of the hemoglobin (thus having no effect on pH).

Only about 5% of the CO_2 generated in the tissues dissolves directly in the plasma. (A good thing, too: if all the CO_2 we make were carried this way, the pH of the blood would drop from its normal 7.4 to an instantly-fatal 4.5!)

When the red cells reach the lungs, these reactions are reversed and CO_2 is released to the air of the alveoli.

Anemia

Anemia is a shortage of

- RBCs and/or
- the amount of hemoglobin in them.

Anemia has many causes. One of the most common is an inadequate intake of [iron](#) in the diet.

Blood Groups

Red blood cells have surface antigens that differ between people and that create the so-called blood groups such as the **ABO** system and the **Rh** system.

[Link to a discussion of blood groups.](#)

White Blood Cells (leukocytes)

White blood cells

- are much less numerous than red (the ratio between the two is around 1:700),
- have nuclei,
- participate in protecting the body from infection,
- consist of **lymphocytes** and **monocytes** with relatively clear cytoplasm, and three types of **granulocytes**, whose cytoplasm is filled with granules.

Lymphocytes

There are several kinds of lymphocytes (although they all look alike under the microscope), each with different functions to perform . The most common types of lymphocytes are

- **B lymphocytes** ("B cells"). These are responsible for making antibodies.
- **T lymphocytes** ("T cells"). There are several subsets of these:
 - **inflammatory T cells** that recruit macrophages and neutrophils to the site of infection or other tissue damage
 - **cytotoxic T lymphocytes** (CTLs) that kill virus-infected and, perhaps, tumor cells
 - **helper T cells** that enhance the production of antibodies by B cells

Although bone marrow is the ultimate source of lymphocytes, the lymphocytes that will become T cells migrate from the bone marrow to the **thymus** [\[View\]](#) where they mature. Both B cells and T cells also take up residence in lymph nodes, the spleen and other tissues where they

- encounter antigens;
- continue to divide by mitosis;
- mature into fully functional cells.

Monocytes

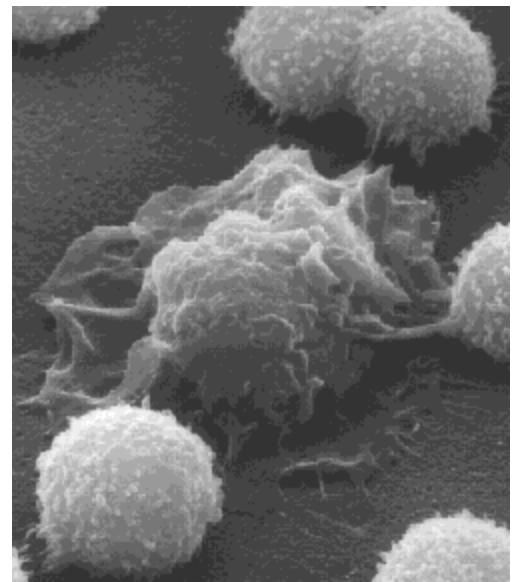
Monocytes leave the blood and become **macrophages**.

This scanning electron micrograph (courtesy of Drs. Jan M. Orenstein and Emma Shelton) shows a single macrophage surrounded by several lymphocytes.

Macrophages are large, phagocytic cells that engulf

- foreign material (antigens) that enter the body
- dead and dying cells of the body.

Neutrophils



The most abundant of the WBCs. This photomicrograph shows a single neutrophil surrounded by red blood cells.

Neutrophils squeeze through the capillary walls and into infected tissue where they kill the invaders (e.g., bacteria) and then engulf the remnants by [phagocytosis](#).

This is a never-ending task, even in healthy people: Our throat, nasal passages, and colon harbor vast numbers of bacteria. Most of these are [commensals](#), and do us no harm. But that is because neutrophils keep them in check.

However,

- heavy doses of radiation
- chemotherapy
- and many other forms of stress

can reduce the numbers of neutrophils so that formerly harmless bacteria begin to proliferate. The resulting **opportunistic infection** can be life-threatening.

Eosinophils

The number of eosinophils in the blood is normally quite low (0–450/ μ l). However, their numbers increase sharply in certain diseases, especially infections by parasitic worms. Eosinophils are cytotoxic, releasing the contents of their granules on the invader.

Basophils

The number of basophils also increases during infection. Basophils leave the blood and accumulate at the site of infection or other inflammation. There they discharge the contents of their granules, releasing a variety of mediators such as:

- histamine
- [serotonin](#)
- [prostaglandins and leukotrienes](#)

which increase the blood flow to the area and in other ways add to the inflammatory process. The mediators released by basophils also play an important part in some allergic responses such as

- hay fever and
- an [anaphylactic response](#) to insect stings.

Platelets

Platelets are cell fragments produced from **megakaryocytes**.

Blood normally contains 150,000–350,000 per microliter (μl) or cubic millimeter (mm^3). This number is normally maintained by a homeostatic (negative-feedback) mechanism [[Link](#)].

If this value should drop much below 50,000/ μl , there is a danger of uncontrolled bleeding because of the essential role that platelets have in blood clotting.

Some causes:

- certain drugs and herbal remedies;
- autoimmunity. [[Link](#)]

When blood vessels are cut or damaged, the loss of blood from the system must be stopped before [shock](#) and possible death occur. This is accomplished by solidification of the blood, a process called **coagulation** or clotting.

A blood clot consists of

- a **plug of platelets** enmeshed in a
- network of insoluble **fibrin** molecules.

Details of the clotting process are in a separate page. Link to it.

Plasma

Plasma is the straw-colored liquid in which the blood cells are suspended.

Composition of blood plasma

Component	Percent
Water	~92
Proteins	6–8
Salts	0.8
Lipids	0.6
Glucose (blood sugar)	0.1

Plasma transports materials needed by cells and materials that must be removed from cells:

- various ions (Na^+ , Ca^{2+} , HCO_3^- , etc.
- glucose and traces of other sugars
- amino acids
- other organic acids
- cholesterol and other lipids
- hormones
- urea and other wastes

Most of these materials are in transit from a place where they are added to the blood (a "source")

- exchange organs like the intestine
- depots of materials like the liver

to places ("sinks") where they will be removed from the blood.

- every cell
- exchange organs like the kidney, and skin.

Serum Proteins

Proteins make up 6–8% of the blood. They are about equally divided between **serum albumin** and a great variety of **serum globulins**.

After blood is withdrawn from a vein and allowed to clot, the clot slowly

shrinks. As it does so, a clear fluid called serum is squeezed out. Thus:

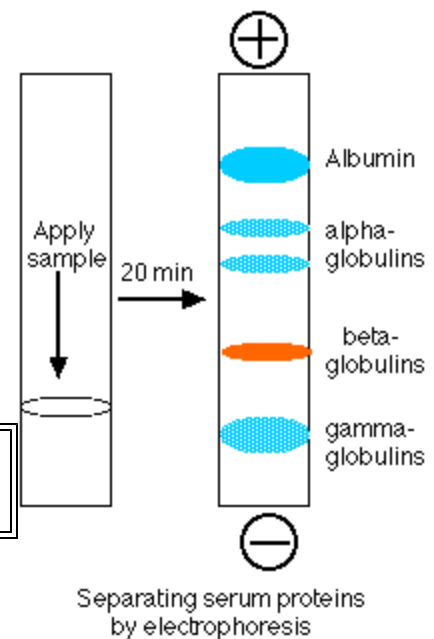
Serum is blood plasma without fibrinogen and other clotting factors.

The serum proteins can be separated by **electrophoresis**.

- A drop of serum is applied in a band to a thin sheet of supporting material, like paper, that has been soaked in a slightly-alkaline salt solution.
- At pH 8.6, which is commonly used, all the proteins are negatively charged, but some more strongly than others.

[Link to an explanation of how pH affects the net charge on proteins.](#)

- A direct current can flow through the paper because of the conductivity of the buffer with which it is moistened.
- As the current flows, the serum proteins move toward the positive electrode.
- The stronger the negative charge on a protein, the faster it migrates.
- After a time (typically 20 min), the current is turned off and the proteins stained to make them visible (most are otherwise colorless).
- The separated proteins appear as distinct bands.
- The most prominent of these and the one that moves closest to the positive electrode is **serum albumin**.
- Serum albumin
 - is made in the liver
 - binds many small molecules for transport through the blood
 - helps maintain the [osmotic pressure](#) of the blood
- The other proteins are the various serum globulins.
- They migrate in the order
 - **alpha globulins** (e.g., the proteins that transport [thyroxine](#) and [retinol](#) [vitamin A])
 - **beta globulins** (e.g., the iron-transporting protein **transferrin**)
 - **gamma globulins**.
 - Gamma globulins are the least negatively-charged serum proteins. (They are so weakly charged, in fact, that some are

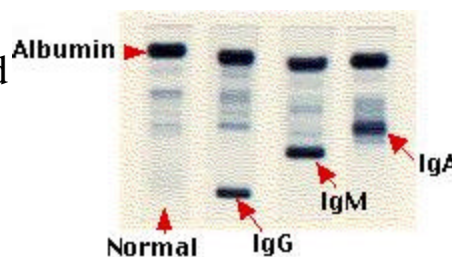


swept in the flow of buffer back toward the negative electrode.)

- Most antibodies are gamma globulins.
- Therefore gamma globulins become more abundant following infections or immunizations.

If an antibody-secreting cell — called a [plasma cell](#) — becomes cancerous, it grows into a [clone](#) secreting a **single kind of antibody molecule**.

The image (courtesy of Beckman Instruments, Inc.) shows — from left to right — the electrophoretic separation of:



1. **normal** human serum with its diffuse band of gamma globulins;
2. serum from a patient with **multiple myeloma** producing an **IgG myeloma protein**;
3. serum from a patient with Waldenström's macroglobulinemia where the cancerous clone secretes an **IgM** antibody;
4. serum with an **IgA** myeloma protein.

[Discussion of the 5 classes of antibody molecules.](#)

- Gamma globulins can be harvested from donated blood (usually pooled from several thousand donors) and injected into persons exposed to certain diseases such as chicken pox and hepatitis. Because such preparations of **immune globulin** contain antibodies against most common infectious diseases, the patient gains temporary protection against the disease. [[More](#)]

Serum Lipids

Because of their relationship to cardiovascular disease, the analysis of serum lipids has become an important health measure.

The table shows the range of typical values as well as the values above (or below) which the subject may be at increased risk of developing [atherosclerosis](#).

LIPID	Typical values (mg/dl)	Desirable (mg/dl)

Cholesterol (total)	170–210	<200
LDL cholesterol	60–140	<100
HDL cholesterol	35–85	>40
Triglycerides	40–160	<160

- Total cholesterol is the sum of
 - HDL cholesterol
 - LDL cholesterol and
 - 20% of the triglyceride value
- Note that
 - **high LDL** values are **bad**, but
 - **high HDL** values are **good**.
- Using the various values, one can calculate a **cardiac risk ratio** = **total cholesterol** divided by **HDL cholesterol**
- A cardiac risk ratio greater than 7 is considered a warning.

[More on cholesterol](#) [How cholesterol is taken into cells.](#)

Blood Transfusions

In the United States, in 2001, some 15 million "units" (~475 ml) of blood were collected from blood donors.

- Some of these units ("whole blood") were transfused directly into patients (e.g., to replace blood lost by trauma or during surgery).
- Most were further fractionated into components, including:
 - RBCs. When refrigerated these can be used for up to 42 days.
 - platelets. These must be stored at room temperature and thus can be saved for only 5 days.
 - plasma. This can be frozen and stored for up to a year.

Ensuring the safety of donated blood

A variety of infectious agents can be present in blood.

- viruses (e.g., [HIV-1](#), [hepatitis B](#) and C, [HTLV](#), West Nile virus)
- bacteria like the spirochete of [syphilis](#)

- protozoans like the agents of [malaria](#) and babesiosis
- **prions** (e.g., the agent of [variant Crueutzfeldt-Jakob disease](#))

and could be transmitted to recipients. To minimize these risks,

- donors are questioned about their possible exposure to these agents;
- each unit of blood is tested for a variety of infectious agents.

Most of these tests are performed with enzyme immunoassays (EIA) — [Link](#) — and detect **antibodies** against the agents. However, it takes a period of time for the immune system to produce antibodies following infection, and during this period ("window"), infectious virus is present in the blood. For this reason, blood is now also checked for the presence of the RNA of these RNA viruses:

- HIV-1
- hepatitis C
- West Nile virus

by the so-called **nucleic acid-amplification test** (NAT).

Thanks to all these precautions, the risk of acquiring an infection from any of these agents is vanishingly small. Despite this, some people — in anticipation of need — donate their own blood ("autologous blood donation") prior to surgery.

Blood Typing

Donated blood must also be tested for certain cell-surface antigens that might cause a dangerous transfusion reaction in an improperly-matched recipient. This is discussed in a separate page — [link to it](#).

Blood Substitutes

Years of research have gone into trying to avoid the problems of blood perishability and safety by developing blood substitutes. Most of these have focused on materials that will transport adequate amounts of oxygen to the tissues.

- Some are totally synthetic substances.

- Others are derivatives of hemoglobin.

Although some have reached [clinical testing](#), none has as yet proved acceptable for routine use.

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8 October 2004