

Blood

I. Intro

- A. Some introductory questions to get you started: what are formed elements? What is plasma? Name a couple of plasma proteins. Where are most blood proteins made? What do Hb, RBC, and WBC stand for?
- B. Plasma proteins:
 - a. Albumins- these serve a major role in creating osmotic pressure, which holds plasma in the blood, and in buffering the plasma
 - b. Globulins- those made by the liver serve a major role in transporting certain substances through the blood. For example, they transport fatty acids, thyroid hormones, and vitamin A which are all fat-soluble. They also transport Ca^{2+} and Fe^{2+} (remember transferrin?)

Those made by activated B-lymphocytes are antibodies.
 - c. Clotting proteins
 - d. Enzymes, some hormones, non-antibody proteins of the immune system

I. Production of formed elements (erythrocytes, leukocytes, platelets)- occurs in red marrow, called hemopoiesis

A. Hemocytoblasts- are stem cells to all of the formed elements, give rise to Myeloid stem cells and Lymphoid stem cells. Myeloid stem cells will give rise to erythrocytes, platelets, and most leukocytes. Lymphoid stem cells will give rise to a particular leukocyte: lymphocytes.

B. Development of the formed elements- each type of blood cell goes through stages as they mature. Generally, early in their development we call them "blast" cells, then "cyte" cells as they come closer to full maturity.

1. Lymphoid Stem cells: Mature into lymphoblasts, which mature into prolymphocytes, then to fully mature lymphocytes. We will investigate the lymphocytes in more detail when we get to immunity. Remember that lymphocytes are considered leukocytes.
2. Myeloid Stem cells: give rise to RBC, platelets, and the rest of the WBC. Myeloid stem cells first divide into a population of Myeloid Progenitor cells. The progenitor cells will then differentiate into one of the formed elements, depending on the message they get. For example, if they get Erythropoietin, they will become RBC.

- a. Erythrocyte development- You don't need to recite to me exactly what happens on which day, or exactly what happens during which stage. Know how long it takes for a RBC to mature, know the events of maturation in the correct order, and know the correct order of immature erythrocyte names.

Approximate Day	Name of Maturing RBC	Events
1	Myeloid Progenitor Cell – Proerythroblast	Myeloid Progenitor gets a dose of erythropoietin, sending it on the RBC pathway
2-4	Erythroblast – Normoblast	Maturing RBC continue mitosis, make lots of Hb, collect iron, eject organelles. Nucleus ejected in last stage.
5-7	Reticulocyte	RNA, ribosomes and ER degraded by enzymes. Enter circulation.
8 th day – 4 th month	Erythrocyte	Mature. Deliver O ₂ . No mitochondria, rely on anaerobic metabolism. (so, can they use fatty acids?)

b. Platelets- Myeloid stem cell --> Progenitor cell --> Megakaryocyte (huge cell) --> Platelets. Platelets are pinched off pieces of the megakaryocytes, so they are cell fragments rather than actual cells.

c. Leukocytes (other than lymphocytes)- The mature leukocytes are basophils, eosinophils, neutrophils, and monocytes (which we call macrophages). They, like lymphocytes, are involved in immune function. We will discuss them in more detail when we get to immunity.

i. Basophils, eosinophils, and neutrophils- Myeloid Stem Cell --> Progenitor cell --> Myeloblast. The myeloblast will then differentiate into one of the 3 different types.

ii. Monocytes- Myeloid stem cell --> Progenitor cell --> Myeloblast. The myeloblast matures into a monocyte.

II. Erythrocytes, Red Blood Cells

A. General & Background information

1. The hematocrit is the proportion of whole blood that is cellular (including platelets). Since most formed elements in the blood are RBC, the hematocrit is a good estimate of RBC content.
2. Structure- packed with hemoglobin (Hb), doughnut shaped (mmm....), biconcave discs, but not hollow in the middle. Structure is related to function:
 - a. Allows a high surface area:volume; why is this important?
 - b. Allows RBC to stack up end to end through capillaries
 - c. Can easily flex and bend through the tiniest capillaries
3. RBC are the primary factor influencing blood viscosity; the more RBC in relation to plasma, the thicker the blood.

B. RBC function and life span

1. Hemoglobin (Hb)- Approximately 97% of the volume of a RBC is dedicated to Hb molecules (about 250 million molecules of Hb are packed into each RBC). Hb is what actually carries O₂ (each Hb carries four molecules of O₂, so about 1 billion molecules of O₂ can be carried by each RBC). Let's take a look at Hb.

a. A protein composed of 4 subunits (Remember primary, secondary, tertiary and quaternary structure?): two "alpha" chains, and two "beta" chains.

Each chain contains one molecule of the pigment, heme.

Each heme contains one Fe atom

Fe and O₂ are weakly attracted: when the concentration of O₂ is high, they bind. When the concentration of O₂ is low, they let go.

b. Hb can also bind CO₂, so in tissues, it picks up some CO₂. Upon reaching the lungs, the CO₂ will be released. (Not all of the CO₂ in tissues is carried back to the lungs on Hb; in fact, most will get there another way, which we will discuss in the vessels chapter).

Hb carrying O₂ is referred to as "oxyhemoglobin"

Hb NOT carrying O₂: "deoxyhemoglobin"

Hb carrying CO₂: "carbaminohemoglobin," which is almost as much fun to say as supercalafragalisticexpialadocious.

2. The life of an RBC and its Hb-

a. Birth- "erythropoiesis"- where does this occur? What are the stages of development of an RBC? What hormone is the major hormone affecting erythropoiesis? Where does that hormone come from?

The release of Erythropoietin (EPO) is regulated by blood O₂ levels.

Approximately 3 million new RBC enter the blood each minute, so there's some serious cell division and protein production going on!

Anything that affects cell division, energy utilization and protein production can have a major effect on erythropoiesis, and the proper development of blood cells. For example, the B vitamins folate and B₁₂ support proper cell division and maturation. A deficiency of either vitamin can result in a type of anemia in which immature (nonfunctional) RBC enter circulation, called megaloblastic anemia (we call it pernicious if it's B₁₂ because of a combination of other symptoms).

b. School and Work- RBC are released to the blood as immature reticulocytes. They spend a couple of days degrading their RNA and ribosomes, and continuing to make Hb. Once they've done so they are fully mature, fully functional erythrocytes. Each lives about 120 days.

c. Death- most old RBC are ingested by phagocytes. Some burst before being phagocytized. Each carries a very valuable estate: lots of Fe and protein, and the body wants to hang onto them to recycle in new RBC. Let's look at what happens to iron when RBC burst on their own and when they are phagocytized:

i. If they burst on their own, some of the fragments will be picked up by phagocytes for recycling. Some of it, however, will be lost to the urine.

ii. If they are phagocytized,

The proteins will be hydrolyzed into amino acids, which will enter blood circulation for other cells to use

Iron will be attached to the protein "transferrin," which will carry it through the blood to bone marrow (to incorporate into new RBC) or to the liver (for storage).

Heme will be converted to the pigment bilirubin*, which is released to the blood. Bilirubin will be excreted by the kidneys or the liver. If it is excreted by the kidneys, it will come out in urine and make it yellow. If it is excreted by the liver, the liver will dump it into the small intestine with bile. From there it will enter the large intestine, come out with feces, and contribute to the yellowish/brownish color of feces.

*there are actually a couple of conversions before and after bilirubin, but I have chosen to simplify the explanation.

C. Blood typing

I. Background information/ Definitions

a. Antigens- structures (often glycoproteins) that extend from the exterior of a cell membrane, which can be used for self-identification; more importantly, they can be recognized as foreign by another organism. So, for example, if a bacterium enters your body, immune cells can recognize it as foreign because it has unfamiliar antigens. Antigens are substances that can trigger an immune response; for example, our immune system responds to the foreign antigens of the bacterium and attacks it.

RBC contain identifying antigens. We call the antigens of RBC "agglutinogens." The agglutinogens that cause the most problems with blood transfusions are A, B, and Rh.

b. Antibodies- are proteins made by immune cells that attach to invaders and slow them down for capture by immune cells.

Antibodies are made for specific antigens. For example, if you were exposed to Mononucleosis as a child, your immune cells made antibodies custom fit for that pathogen's antigens.

The antibodies that attack foreign blood agglutinogens are called "agglutinins." They grab onto a bunch of foreign RBC, and cause clumping, or agglutination.

2. What blood types are: Your blood type represents the type of antigens (agglutinogens) you have on your RBC. For example, if you are type A, then you have the A antigen sticking off your RBC, but you do not have the B antigen.

- a. The ABO system- Antigens A and B are coded for by a gene (O just means the absence of both) . Whether you have A, B, both, or neither is genetic. The interesting thing about this system is that you make antibodies for whichever antigen you don't have; so, if you are type B, you make antibodies against the A antigen. If you are exposed to type A blood, you will have a reaction.

Complete the following table:

If you are type	Then you will have antigen	And you will make antibodies that attack antigen	And you can receive	And you can donate to
A	A	B		
B	B	A		
AB	A and B	Neither		
O	Neither	both		

Which blood type would you prefer to be if you need blood in a pinch?

Which would you prefer to be if you wanted to help as many people as possible?

- b. The Rh system- Antigen Rh is coded for by another gene, but there aren't variations like with ABO. You either have the Rh antigen (Rh+) or you don't (Rh-). Since ABO and Rh are coded for by separate genes, you can have both an A or B and an Rh, depending on your genetics. If you are A+, that means you have both the A antigen and the Rh antigen. If you are A-, you have A but not Rh.

If you are Rh-, you don't make enough antibody against Rh to have a reaction if you are exposed once. However, once you are exposed, then you start making the antibody. If you are exposed a second time, then you will have a reaction. Exposure to Rh could come through a blood transfusion, or through a pregnancy, if your child is Rh+.

If you are AB+, you can receive any blood type. Why is that?

If you are O-, you can only receive O- blood...but, anyone can receive your blood safely. Why is that?

D. Anemia- refers to a variety of conditions in which oxygen delivery to cells is impaired. The term anemia refers to a set of symptoms. Since O₂ is required by most cells to make enough ATP to function, you can imagine that the symptoms are wide-ranging. What are some common symptoms of anemia? Some specific anemias:

1. Iron-deficiency- Why would O₂ delivery be impaired?
2. Sickle-cell- a genetic disease- one of the amino acids in one of the types of hemoglobin chains is different than in normal hemoglobin. This simple change causes the cells to take on a different shape, sickled, or half-moon shaped. Since we know that RBC shape is vital to their function, this shape change causes problems; for example, the RBC do not move easily through capillaries and get stuck.
3. Megaloblastic- caused by a deficiency of folate or B₁₂. RBC don't mature beyond the proerythrocyte stage (but do enter circulation). These immature cells do not function properly.

III. WBC, Leukocytes: Overview (more detail in the immunity chapter)

A. Some general info

Move by amoeboid movement. Are not restricted to the blood, can migrate out of capillaries and in-between cells in tissues. Damaged tissues release chemicals that attract WBC to the site.

Some are phagocytic, some produce antibodies.

B. General functions of specific leukocytes

1. Neutrophils-phagocytic, engulf pathogens and debris.
2. Eosinophils- attack larger pathogens (ex, worms) in addition to bacteria.
3. Basophils- Hang out in tissues, packed with histamine and heparin. When tissues are damaged, histamine keeps local vessels dilated to keep blood coming into the local area, and heparin prevents clotting in the local area. Allows WBC, O₂ and nutrients to make it to the damaged tissue. (Clotting will occur around the area, as we will see soon).
4. Monocytes- Huge phagocytic cells. We also call them macrophages (technically, monocytes are immature macrophages). Some set up residence in tissues for extended periods of time. When they do, we give

them special names; what were the names of the macrophages that hang out in the epidermis? In the CNS?

5. Lymphocytes- T cells, B cells and NK (natural killer) cells. T and B cells work together to target specific pathogens (they learn to recognize the unique identity...because of antigens...of each specific pathogen they encounter). B cells produce antibodies. T cells kill pathogens.

NK cells kill abnormal self cells, like cancerous cells.

IV. Platelets- cell fragments (what cell pinches off, giving rise to platelets?). Platelets aggregate at the site of vessel damage, creating a plug. They contain actin and myosin, and pull the cut ends of vessels together. They also release chemicals that coordinate the clotting process.

V. Clotting: Hemostasis (blood-stopping)

A. Background info

The clotting process is complex and involves positive feedback; once it starts, it speeds up.

There are a series of clotting factors (procoagulants) in the blood that exist as inactive forms when no damage has occurred. These clotting factors are activated when they encounter damaged tissues.

In addition, there are anticoagulants in the blood. Some of these are inactive as well, and will be activated by chemicals released during clotting.

So, a delicate balance is maintained; clotting is necessary to prevent blood loss from vessels, but clots need to be dissolved as soon as the damage is adequately repaired. Why is clot clean up important?

The process involves 3 phases, which overlap and merge into each other. As far as the body is concerned, there are no phases, just a continuous process. We humans talk about phases because we can generally see the process doing certain things at certain times, and it's easier for us to remember if we can categorize the events.

Remember that "endothelium" refers to the inner, epithelial lining of cells in blood vessels. What type of epithelium is it, again?

B. The Process:

i. The Vascular Phase (vascular spasms)

a. When a vessel is damaged, the smooth muscle lining the endothelium constricts, closing (or reducing the size of) the hole.

b. In addition, the endothelial cells themselves do a few things:

They contract (the cytoskeleton is responsible for this), which exposes the basement membrane underneath them. The basement membrane, as you recall, has a ton of collagen (remember, this is the area that "ties" the epithelial layer to the underlying connective tissue layer). The importance of exposed collagen will be revealed soon, my patient readers.

>>>> They poke out sticky cytoplasmic extensions (kind of like reaching out), which helps the endothelial cells to stick together. This will help to close off the damaged vessel.

They release local hormones and factors (chemicals of unknown structure) that will: activate clotting factors, stimulate repair of vessels (for ex, by stimulating mitosis), attract WBC, and activate anticoagulants.

2. The Platelet Phase- a few seconds later, passing platelets bump into the exposed collagen of the basement membrane, and the sticky extensions of the endothelium. At last, the purpose of the exposed collagen can be revealed! What happens to the platelets that encounter collagen and cytoplasmic extensions?

First, the platelets get stuck, and form a plug (called a platelet plug)

Then, they send out extensions of their own, attaching neighboring platelets and trapping more platelets.

They also release chemicals which will have similar functions as those released by endothelial cells. Some of them are the same as those released by endothelial cells.

*Side note: some examples of chemicals released by endothelial cells and platelets-

>ADP (Adenosine DiPhosphate)- encourages platelet aggregation

>Clotting factors- these are some of the proteins required for the cascade of reactions that will lead to a full-on clot; some are already present in the blood in inactive form. Some released by platelets and endothelial cells will activate them.

>Ca²⁺- It's amazing how much Ca²⁺ comes up, isn't it? If I were you, I'd expect a couple of questions about the many roles of Ca²⁺. This is actually one of the clotting factors (we'll see how shortly). It is also involved with other aspects of the clotting process.

>Serotonin- so now we see that serotonin can also be used as a local hormone. Serotonin induces vascular spasms.

>Von Willebrand Factor- binds platelets to exposed collagen

*End of side note

3. The Coagulation Phase (full-on clot is formed): the goal is to convert fibrinogen to fibrin. Fibrinogen is an inactive, soluble protein floating around in the blood. Fibrin is non-soluble, and forms a mesh-like complex, which will close off the damaged area.

a. A blood clot will form when Clotting Factor X (that's "10", as in Bo Derek, not "x", as in Hugh Jackman) is activated. For now, let's consider what happens once CFX (inactive in the blood) is activated. We'll go back in time and consider how it is activated in the next section.

>When CFX is activated, it is converted to Prothrombinase (also called prothrombin activator)

>Prothrombinase then activates Prothrombin, which is another inactive clotting factor in the blood. When Prothrombin is activated, it is converted to Thrombin.

>Thrombin then activates Fibrinogen, which is an inactive protein in the blood. When Fibrinogen is activated, it is converted to Fibrin.

Fibrin is a structural protein that forms a mesh around the injury, and causes the plasma in the local area to thicken and become gel-like. It traps platelets and anything else that has congregated in the area, forming a very effective barrier and preventing the loss of blood.

*The process just described is called the Common Pathway. It is the final stage in the production of a clot, and all prior events lead to the Common Pathway.

b. Now let's go back in time and consider how CFX gets activated. There are two methods: i) by chemicals released by platelets (called the Intrinsic Pathway) and ii) by chemicals released by endothelial cells (called the Extrinsic Pathway).

>>>>The goal of both pathways is to activate Clotting Factor X. Both pathways consist of a series of activations, wherein one clotting factor gets activated, it activates the next, which activates the next, and so forth, until CFX gets activated.

The Extrinsic Pathway has fewer steps and is faster. Still, both start activating Factor X within about 30 seconds, and a clot will start to form in minutes.

c. At some point during all this activity, actin and myosin cause the platelets to contract, pulling damaged vessel ends closer together. This is called **clot retraction**.

C. The role of Vitamin K and Ca^{2+} : Vitamin K is required for the synthesis of many of the clotting factors (for example, CF X), and Ca^{2+} is required for many of the steps in the clotting process.

D. Clot control and clean-up- Some factors that prevent clotting, restrict over-clotting, and promote clean-up:

1. Fibrinolysis: The formation of plasmin, an enzyme that breaks down fibrin. Plasminogen is an inactive blood protein. Plasminogen is activated to plasmin, by a protein released by damaged cells, and indirectly by thrombin!
2. A prostaglandin (prostacyclin/ PGI_2) released by intact endothelial cells around the damaged area. Prostacyclin inhibits platelet aggregation.
3. Heparin released by basophils that migrate to the area
4. Some compounds released at the initial stages of hemostasis build in concentration. At low concentrations, they may enhance hemostasis. At high concentrations, however, they enhance clean-up. Ex. serotonin, at high concentrations, inhibits ADP

5. Clot retraction, which localizes the clot and allows blood to flow around it; brings in more anticoagulants, etc.

6. Enzymes in the blood that break down or inactivate ADP and stray activated clotting factors (example: Protein C is activated by thrombin, and inactivates CF V and CF VIII)