Today's lecture is chapter 11, the hematopoietic and lymphatic systems. All right. So basically, I think you guys understand or know that blood basically is to transport substances to tissues, all right, and what substances? Oxygen, nutrients, hormones, leukocytes, are the white blood cells, the red blood cells, platelets and antibodies. Platelets are produced in the bone marrow and they come from what type of cell? Anybody remember? Anybody?

>> STUDENT: [Inaudible].

>> PROFESSOR: Good. Megakaryocytes. Good. The volume of blood is about five quarts, depending on the size of the individual, and almost half of the blood consists of cellular elements suspended in plasma. So, basically there are stem cells are the precursor cells in bone marrow, and they then differentiate to form blood cells, white cells and platelets. The white cells, I mentioned. Leukocytes are the white cells, and the most common one is the neutrophil. Monocytes, when they leave the capillaries and go into the interstitial tissue, become macrophages. Okay? Also, monocytes coalesce together and form osteoclasts. Anybody know what organ system osteoclasts are in? Bone. Okay. They're responsible for breaking down bone. We'll talk about that in another chapter.

Eosinophils, we talked about that, associated with allergies, lymphocytes and then basophils and platelets. Okay. So the red cells, primarily concerned with transport of oxygen. They survive 128 days, and the precursor is the erythroblast. Once again, the suffix blast, young, immature cell. All right? And what happens is then these cells mature and they contain hemoglobin. Hemoglobin is the oxygen-carrying protein formed by the developing red cell, and there are, let's see -- the leukocytes are less numerous, and of course there's different types.

Lymphocytes, we've talked about before. They can last for several years. Lymphocytes are also produced in the bone marrow, but also in lymph nodes in the spleen, so the neutrophils, most numerous. They make up to 70% of the circulating white cells and they're going to be phagocytic. Monocytes, they're phagocytic. Eosinophils, as I mentioned, they're associated with allergic reactions, and lymphocytes are the next most common leukocytes in adults. They are the predominant leukocyte in children. Lymphocytes tend to be a
little higher percentage when you do a differential of the white blood cells. And of course as you know from our lecture, they take part in cell-mediated and humoral defense reactions.

Platelets from previous chapter, they're essential for blood coagulation. And they are bits of cytoplasm that break off of megakaryocytes. They survive about ten days. People are placed on 30 milligrams of aspirin therapy, have to take it for ten days, and then all the platelets are affected because after ten days, all the platelets only live for ten days.

So now, hematopoiesis refers to the formation of blood cells. And basically, the substances necessary for formation of blood cells, you need protein, you need vitamin B12 and folic acid. And the red cell production is regulated by the oxygen content of the blood, and that is monitored by cells in the kidney, glomerulus, and what happens is if oxygen content goes down, a substance is released called erythropoietin. It goes into the bloodstream, goes to the bone marrow, stimulates production of red blood cells.

All right. We don't have a great understanding of white blood cell production. Okay. Factors that may cause white cell production, or influence it, can be illness, obviously, products of cell necrosis, or hormone secretion by certain glands.

So here's a diagram. Iron's very significant. Okay? Remember I told you iron, folic acid, B-12. So here you have a diagram. You're taking dietary iron, and what happens to it? All right. In the duodenum, it's absorbed and combines with a protein, apoferitin, okay, which is in the mucosa, the lining of the duodenum, to form ferritin. It then gets downed in the blood to a protein transferrin, and from there it can go -- it can be stored, okay, in the bone marrow, used as ferritin later, or it's carried to the marrow and used to make hemoglobin.

All right. When hemoglobin is broken down, all right, the iron is reused. The basically hemoglobin is made up of four units, tetramers, and they're composed of a porphyrin ring, iron molecule and globin chains. So and of course the globin chains are made up of amino acids. So the amino acids are reused, the iron's reused, the porphyrin ring is excreted as bile.

All right. Let's see here all right. So you have the hemoglobin tetramer has four subunits, and they're different chains, okay, of globin. They're designated as alpha, beta, gamma, delta, epsilon, and typically they're made up of two alphas, two betas in the adult, and in the infant, they tend to be made up of gamma chains. The gamma chains are quicker, or they grab on, bind oxygen, okay, greater, and
they're easier to release oxygen. So that helps for the newborn, or actually not the newborn, but the baby inside the utero, where, again, it's exposed to lower oxygen levels from the paternal blood. The porphyrin ring is produced in the mitochondria. The iron is inserted to form heme, and then the globin chains are attached.

All right. So you have four subunits to form the hemoglobin tetramer.

What happens is that the red blood cells do not have nuclei. It's very significant. So the fact that they don't have nuclei, what happens is they have a finite amount of energy and enzymes that can be used to accommodate cellular function, and basically, it lasts for about 120 days, and then it's done. Okay? The red cell dies gets removed from the circulation. And when red blood cells are produced, okay, they are extruded, we use the word extruded, they're extruded from the bone marrow, and at that time, they still have a nucleus, so nucleated red blood cells are called reticulocytes, and they only have a nucleus for a day or so, and then it is -- disintegrates and is removed so that the mature red blood cells don't have a nucleus. So for example in treating anemia, okay, what famous quarterback here in Tampa Bay had, after a football game, had his spleen removed. Chris Simms, right. And evidently he had some abdominal pain and they didn't realize what was going on. He went to the emergency room after the game and here they did a CAT scan and saw he was bleeding into the abdomen. I think his blood pressure started to drop, which is basically he was going into shock, rushed him to surgery and took out his spleen. All right? Large blood loss. So what were the hematologists going to be doing in following him? They were going to check his retic count. Usually a retic count is about 1%. In someone who is recovering from severe anemia, you want the bone marrow to really turn on. You want it to turn on and start producing a lot of red blood cells. All right, because you have to compensate for all that blood that was lost. So ideally, if they've got adequate iron levels and B-12, folic acid, retic count can be up to 4%, 5%. Okay?

So that's why it's significant. So the reticulocyte, young red cell without a nucleus, retains some of the organelles, and it can be identified by a special stain, not strains. 24 hours, the reticulocyte matures and survives in circulation for about four months.

Worn out red cells removed by the spleen. All right. Let's see. The globin chains are broken down and used to make other proteins. The iron's extracted and saved to make new hemoglobin.

All right. The problem with certain types of anemia, we're going to go over types of anemia. Unfortunately, there's a
lot of information to go over in this chapter so I'm talking kind of fast. But one of the problems with anemia is that people lose iron, okay? If they lose iron, then in a greater than usual amount, then it's difficult to take in that amount of iron and to replace it. All right? So anemia results. 

All right. So the red cell production regulated by oxygen content of arterial blood, all right, and the reduced oxygen then stimulates formation of red blood cells, I told you that it's stimulated by erythropoietin, all right, which is produced in the kidneys. 

So classification of anemia. You have reduction of red blood cells, inadequate production of red cells, insufficient raw materials, iron, B-12, folic acid deficiency, or the inability to deliver adequate red cells into the circulation due to the bone marrow. All right? 

Damage or destruction. Maybe cancer. 

My most senior partner, his wife died of an aplastic anemia in four days. All right? Her blood cells -- her bone marrow shut down. It was years ago. And she became -- developed severe anemia and died in four days. He was devastated. It was a horrible loss. They had six young kids. It was terrible. And so -- and they're not really sure exactly what caused her aplastic anemia. 

But they get severe infection and they die. 

So excessive loss of red blood cells. Okay? Hemorrhage, external loss, I mentioned about Chris Simms, that would be an example of an anemia. Shortened survival of red cells in circulation. What can do that? Defective red cells, we'll talk about that, or increased destruction of cells, from antibodies, or mechanical trauma. What type of mechanical trauma? Sometimes heart valves, all right? A heart valve replacement. Someone has, you know, a defective mitral valve, who's had rheumatic fever, and they suffer from aortic regurge, or mitral regurge or mitral stenosis, and they have compromised cardiac output, so they can have the mitral valve replaced by a mechanical valve, but unfortunately, the actual mechanical valve tends to break down red blood cells with a shearing effect, the red blood cells. 

Here's a diagram which basically shows you exactly what I was talking about. So, let's see, the etiologic classification of anemia. Inadequate production of red cells. What can it be caused by? Inadequate raw materials, all right, it can be caused by impaired function of the bone marrow, all right, aplastic anemia, or possibly the bone marrow being replaced by foreign or abnormal cells. All right. Cancer. It can be. Or you can have excessive loss of red cells. All right. And this is going to be caused by external blood loss or shortened survival of red cells.
All right. Now, what's some examples of defective red blood cells that maybe will have a shortened survival rate? They can have abnormal shape. They can have abnormal hemoglobin. They can have defective hemoglobin synthesis within the red blood cells, or deficient red cell enzymes. The abnormal red cell shape is called hereditary spherocytosis, it's genetically determined. These cells are shaped like spheres and they tend to get broken down much sooner. Another one is abnormal hemoglobin within red blood cells, and we're talking the most common ones, hemoglobin S. All right? And of course people who carry the gene for hemoglobin S, and then they have a gene for another hemoglobin, usually hemoglobin A, we say they carry the trait, and unless they do excessive exercise at high oxygen -- or high altitude levels, so that there's reduced oxygenation, they don't have a problem with sickling of their red blood cells. The problem occurs for people who have two genes for hemoglobin S where all the hemoglobin is hemoglobin S. As a result, then there's a change in shape of the red blood cells. They have a picture of it in the book, and these people end up with sickling. Defective hemoglobin synthesis within red blood cells. The term is thalassemia. There's two types of chains in the hemoglobin, all right, basically A and B are alpha and beta chains in the adult hemoglobin, and what happens is there can be defective synthesis of the chains. So as a result, hemoglobin is reduced in the red blood cells, and we call it alpha thal or beta thal, and beta thal is probably more common, and it can be minor or major. Minor means basically that they carry one gene for it, and the major is two. Very often the -- if people -- if there's the presence of two genes to determine beta thal, it's incompatible with life. These children, if they're born, die at a very early age. I'll never forget. We had one patient, she had beta thalassemia minor. Her husband had beta thalassemia major. And the first child they conceived died two weeks before delivery and diagnosis revealed that the baby had thalassemia major, beta thalassemia major, had gotten both genes. The second pregnancy she had amniocentesis for genetic testing to see if the baby had thalassemia major, which it did not. It had thalassemia minor, and the pregnancy went on to be fine. All right. Also, hostile environment where people get antired cell antibodies, okay? Lupus is an example of that. So the classification can be based on the red cell appearance, and classification of anemia, you have by red cell appearance, we're talking about whether the cells are large, and that would be macrocytic, or if they're small, microcytic, and on top of the size, we also refer or can refer to the staining of the red blood cells, and that are
they hypochromic, which means that they don't stain as red, as intense because they don't have as much hemoglobin. And an example of a microcytic, hypochromic anemia is iron deficiency. Iron deficiency is the most common anemia affecting red blood cell production. And in that, the cells are microcytic, they're smaller than usual when you look under the microscope and their paler stained, or hypochromic. The folic acid deficiency, the vitamin B-12 deficiency, that's a macrocytic anemia. These cells are larger than normal. All right. A normocytic anemia, normal size in appearance. Normocytic anemia would be Chris Simms an hour after surgery. Okay? He would be anemic, all right, he'd have definitely would have low hemoglobin count, but the cells would be normocytic, okay, at the time. Later on, they probably would be a little bit smaller in size because of the fact of the rapid production.

All right. So the hypochromic anemia, reduced hemoglobin content. Hypochromic microcytic anemia, smaller than normal and reduced hemoglobin content.

So the most common type of anemia, as I mentioned, is going to be iron deficiency, and once again, iron's absorbed in the duodenum, and then it's bound to a protein.

All right. Now, what causes that, the most common one is inadequate iron intake in the diet. All right. And, you know, infants, rapid period of growth, adolescents subsisting on inadequate food or diet, or inadequate utilization of iron present in red cells due to chronic blood loss. Okay?

So if you're evaluating anemia, what do you do if you get blood tests back that show that the hemoglobin count is low, or the hematocrit is low, you're going to measure serum ferritin, which is iron binding, serum iron, and then the iron binding capacity. The iron binding capacity is a protein, okay, it's a test to measure the binding sites that are available in the proteins, okay, that are in the blood that are used to carry iron. Iron has -- travels basically in the blood bound to protein.

So if the TIBC, total iron binding capacity, is low, then that's another way of saying that probably, or suggesting, that it's an iron deficiency anemia. If you've got anemia, and the TIBC is -- I'm sorry. I meant the reverse. If an iron deficiency anemia, the total iron binding capacity is going to be low. There's going to be a lot of sites available -- no, I'm sorry. It's going to be the iron binding capacity is going to be high because it's going to be a lot of sites available, open to bind iron. Okay?

If the iron binding capacity is going to be low, then that means a lot of those sites are filled up with iron. So there's going to be not many binding sites available.

So characteristic laboratory profile will be basically
higher than normal serum iron binding protein capacity.
All right. Let's see here. So basically, treatment is usually administering supplementary iron. For really severe anemia, what they'll do is not -- iron is not absorbed real well by the mouth, and so it can be given as a shot. All right? As an intramuscular shot. It's a depo type of shot where you give them the shot of iron, and it serves as just a reservoir for iron.
Now, let's see. Another example for chronic blood loss, people with an ulcer, okay, or colon cancer. Women also who have really heavy menses, menstrual blood loss that last a long -- cycles that last a long time, menstrual bleeding for a long time, will have low blood count.
All right. So we got normal red blood cells here. And here, we have hypochromic microcytic anemia. See how pale staining these red blood cells are.
And then for vitamin B-12. Vitamin B-12 is very interesting because it's in made, liver, foods, all right. Vitamin B-12, to be absorbed, has to be bound to a protein called intrinsic factor. The intrinsic factor is in the lining of the stomach, so when it's taken in, it's bound to the intrinsic factor. It then goes in the GI tract. It then is absorbed in the last section of the small intestine called the ileum. So people who have regional enteritis, which is basically ulcers of the ileum, sometimes they have to have a segment of their bowel removed, the ileum. If so, they can be deficient in B-12. Folic acid also is in green, leafy vegetables, and that's required for normal hematopoiesis also. So B-12 is responsible for structural and functional integrity of the nervous system, so people who have B-12 deficiency will be anemic and they can have some neurologic changes. They tend to lose vibratory sensation on their shins and other disturbances.
So once again, the absence or deficiency of vitamin B-12 or folic acid interferes with the red cell maturation. You have large cells, and then you develop anemia.
Pernicious anemia refers to lack of the intrinsic factor. As a result, when they don't have the intrinsic factor, they don't absorb B-12.
And things that can cause it is, you know, gastric resection, or bowel resection, as I mentioned. All right. And sometimes there's antibodies, auto antibodies that are directed against the gastric lining that interfere with the production of the intrinsic factor.
Folic acid deficiency, it's relatively common. All right. And it's usually due to inadequate diet, lack of green, leafy vegetables, very common in alcoholics.
All right. So diagnostic and evaluation of anemia. You do a history and physical. Do you the complete blood count. Now, when you have a complete blood count, they look at the
total number of white blood cells, red blood cells. The two indices they use a lot are the hemoglobin and the hematocrit. And typically maybe the hemoglobin is around 16, and the hematocrit, what the hematocrit is we've gone to the doctor. How many have gone to the doctor here and they stick your finger and then they have those really narrow little tubes, and as the blood comes out of the spot where they prick your finger, the blood goes into those narrow capillary tubes. Anybody have that? Okay. That's called a finger stick hematocrit. And what happens is those little a capillary tubes are sealed. They're spun down. And when they're put in the spun down, what happens is you take the capillary tube out, and you can read it, and basically the top half of the tube is clear fluid, all right, and then the bottom half is going to be red blood cells. And so what they do is they measure by the percentage of the total volume in that capillary tube, percentage of red blood cells, which are at the bottom, against the total volume, and that's your hematocrit. So it's a percentage of red blood cells of the total blood volume.

All right. And those are basically the indices that they use.

Also, like I said, they'll measure platelets. Usually comes back the platelets are adequate, and they just look at a glass slide. And leukopenia refers to low blood count. All right. So when they do the blood smear, they're going to look at platelet numbers, they're going to look at the red blood cells. Are they normocytic, macrocytic, hypochromic or microcytic. They do the reticulocyte count, which I mentioned, they'll measure iron, B-12, folic acid, and then if worse comes to worse and they're not sure, they'll do a bone marrow study, looking for abnormalities in the marrow cells, and then sometimes they need to be evaluated for GI tract blood loss. Do they have an ulcer? Do they have a cancer of the colon? Colon cancer basically of the ascending portion of the colon presents with anemia. If it's a cancer of the colon and it's the descending portion, then that usually presents with obstruction. So that's why it's important for people, older age group, they get a rectal exam, and they do a stool for occult blood and what they're looking for is blood in the stool, which could be related to ulcer or it could be related to a colon cancer.

Bone marrow suppression. What conditions can depression bone marrow function? All right. Chronic disease, aplastic anemia, which we mentioned. The bone marrow can be injured by radiation, anticancer drugs, chemicals or antibodies. I think I told you about the one student of mine who had lupus, and her blood count went really down really low, and she had to go stay out of class and she was put on prednisone because what happened is the autoantibodies
caused her to develop severe anemia. And with cancer, the marrow can be infiltrated by tumor or replaced by fibrous tissue. So treatment's going to depend on the cause. You can give blood, you can give platelets, prednisone, bone marrow transplant, very risky.

All right. Hemolytic anemia, hereditary. Hemolytic anemia, it's a genetic abnormality, prevents normal survival. I mentioned already about hereditary spherocytosis. We talked about abnormal hemoglobin S, defective synthesis, the thalassemias, the major and the minor, and what that refers to basically is that the chains are normal, but the formation of the chains is defective. It's decreased. So as a result, there's anemia.

One thing I did not talk about is the enzyme defect, glucose-6 phosphatase, dehydrogenase. It's an enzyme within the red blood cell. And remember I told you, there's sufficient amount of enzymes, and glucose and energy for the cell for 120 days. And a deficiency of this cell, okay -- I'm sorry, of this enzyme, what it does is it can shorten the life span of the red blood cell, and there are certain drugs that can be taken that shorten the life span of the red blood cell even more due to the enzyme problem. So we call that G6PD deficiency.

Acquired hemolytic anemia is normal red blood cells, but they're unable to survive due to a hostile environment. It can be antibodies, mechanical trauma, and a large spleen. Here you have cells that basically contain the hemoglobin S and they're sickling. And then we have a greater magnification, you can see the sickling of the red blood cells.

All right. And here's cells that are very round, hereditary spherocytosis.

Polycythemia, okay, is an increase in red blood cells. There's primary and secondary. Primary is known as primary polycythemia is known as polycythemia vera, and we don't know what causes it. Okay? And it's of unknown etiology, and that's why we say vera. Anybody know what vera means in Latin? True. Right. So it's true polycythemia vera. You can call it idiopathic. We don't know what causes it. It happens.

Secondary polycythemia is caused by increased red blood cell production for a cause, and usually it's due to the reduced arterial saturation, okay, low oxygen content in the red blood cells and therefore increased production of erythropoietin in the kidney. And pulmonary diagnoses can do that, emphysema, pulmonary fibrosis, congenital heart disease. Can anybody think of any type of congenital heart disease that might cause production of increased number of red blood cells or polycythemia? What type of situation
would there be?

>> STUDENT: [Inaudible].

>> PROFESSOR: More specific than an enlarged heart. Okay? Because most people who have an enlarged heart on x-ray, all right, left ventricular hypertrophy don't have polycythemia. I'll give you a slight hint. It's a congenital issue that I'm thinking about.

All right. A septal defect, specifically a ventricular septal defect, okay, because what happens is if it's really major, then a lot of the oxygenated red blood cell -- the oxygenated red blood cells that are in the left ventricle didn't get over to the right, right ventricle, so as a result, there may be decreased oxygenation of the tissues. It's possible.

All right. Let's go on. Complications of polycythemia vera, if the red blood cell count is increased, all right, there may be slowing of blood through traveling through veins and capillaries due to the increased viscosity. As a result, a clot can form.

All right. So how do you treat polycythemia? You can give medication to suppress bone marrow function, or also what they do is they'll periodically remove all the excess blood. Hemochromatosis is an autosomal recessive, and what that is is it refers to the accumulation of iron in tissues, and it is also recessive. These people don't develop symptoms until they're usually in their 40s, so what happens is they're already have children, so they pass that gene on. And as they accumulate iron, specifically in certain tissues, they develop secondary diseases. They can accumulate iron in the heart, can interfere with the conducting mechanism, it can also be accumulated in the liver. They get cirrhosis, it accumulates in their skin, and that's called hemochromatosis. All right. So then what needs to happen is they need to remove blood. One of the ways to treat it is to remove blood from the circulation so that when you remove the blood, the increased amount of iron stores are then mobilized to form red blood cells.

Thrombocytopenia refers to a low platelet count. And basically, there's damage to the bone marrow from drugs or chemicals, and or can be infiltrated by leukemic cells, metastatic carcinoma. That's going to be secondary. Primary, okay, thrombocytopenic purpura, usually caused by platelet antibodies. Okay? It can be chronic in adults.

All right. The lymph system, this section, and then I think we're going to be done for this unit. Primary function is provide immunologic defenses against the foreign material. We already talked about the immune system, you have your cell-mediated immunity and the humoral defense mechanisms. Of course the humoral defense mechanisms relate to the B cells. They produce antibodies. The cell-mediated immunity
refers to the T-cells. So basically the lymph nodes. They're bean-shaped structures consisting of massive lymphocytes, and they're supported by a mesh work of reticular fibers. They're very fine fibers, and they're scattered throughout the body, in specific locations and they contain phagocytic cells. And then as the lymph flows through the nodes, the phagocytic cells filter out and destroy the microorganisms.

Spleen is specialized to filter blood, contains a tremendous amount of lymphocytes. It's involved in antibody formation, and the lymphoid tissue is also going to be present in the thymus. The thymus is a very small gland in the neck. It is the largest at the time of birth. And gradually, as the child grows older, it becomes very, very small. Tonsils also contain a lot -- the adenoids also contain lymphatic tissue.

All right. And let's see, so lymphatic system disease. You have inflammation of the lymph nodes, okay, they get enlarged. Mono, infectious mono is a disease caused by the Epstein Barr virus, and they get enlarged lymph nodes and they get a very painful sore throat. That's typically how it presents. And so the infection of the lymphocytes causes hyperplasia in the lymph nodes. The concern is when people have mono, they have to be careful if they have an enlarged spleen. You don't want to have any type of abdominal trauma. They should refrain from sports because you don't want to do anything that could cause a ruptured spleen.

All right. The cytotoxic CD8 lymphocytes and antibodies produced by the plasma cells destroyed most of the infected B cells.

It is usually transmitted orally, through kissing or sharing glasses, and as I mentioned, you need to avoid contact sports.

All right. Also, metastatic tumors, breast, lung, colon, other sites can metastasize to the nodes. We talked before about Hodgkin's, non-Hodgkin's lymphoma. You also can have the lymphocytic leukemia, it can be acute or chronic.

All right. Here you have a large lymphocyte, okay, from someone with infectious mono. Look how large that is compared to the red blood cell.

So spleen, I mentioned, will destroy red blood cells, it's phagocytic, involved in antibody formation, and let's see. All right. I mentioned to you about hereditary spherocytosis. Genetically determined sphere -- the red blood cells are sphere-shaped, and they have a shortened life span because they're broken down in the spleen. So the treatment, all right, for this can be removal of the spleen. They do a splenectomy, and as a result, the spherocytes last longer.