**Lecture topic is…**

**(Slide 1) Lecture 5**

**Physiology of the blood system. Part 2**

**(Slide 2)** Lecture plan:

1. Erythrocytes and Hemoglobin.
2. Platelets.
3. The concept of hemostasis.
4. Blood group systems and Rh factor.

**(Slide 3) The Components of Blood and Their Importance. Video**

**(Slide 4)** The erythrocyte, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and only thousands of leukocytes.

**(Slide 5)** Specifically, males have about 5.4 million erythrocytes per microliter (µL) of blood, and females have approximately 4.8 million per µL. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. They are small cells, with a mean diameter of 7–8 micrometers (µm). The primary function of erythrocytes is to pick up oxygen from the lungs and transport it to the body’s tissues, and to pick up carbon dioxide at the tissues and transport it to the lungs. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.

**(Slide 6)** As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a reticulocyte, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production. Abnormally low or high levels of reticulocytes indicates deviations in the production of these erythrocytes. These organelle remnants are quickly shed, so circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, erythrocytes rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

**(Slide 7)** Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center. Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so small that, despite their own small size, erythrocytes sometimes fold in on themselves to pass through. Fortunately, their structural proteins like spectrin are flexible, allowing them to fold and then spring back again when they enter a wider vessel.

**(Slide 8) Oxygen Transport. Video**

**(Slide 9)** Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of the protein globin, designated alpha 1 and 2, and beta 1 and 2. Each of these globin molecules is bound to a red pigment molecule called heme, which contains an iron ion (Fe2+). Each iron ion in the heme can bind to one oxygen molecule, therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and can bind to and transport up to 1.2 billion oxygen molecules.

**(Slide 10)** In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming **oxyhemoglobin**. The bright red, oxygenated hemoglobin travels to the capillaries of the body tissues, where it releases some of the oxygen molecules, becoming darker red **deoxyhemoglobin**. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely leaves all of its oxygen behind. At the time time, carbon dioxide (CO2) enters the bloodstream. About 76 percent of the CO2 dissolves in the plasma, some of it remaining as dissolved CO2, and the remainder forming bicarbonate. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as **carbaminohemoglobin**. From the capillaries, the hemoglobin carries CO2 back to the lungs.

**(Slide 11) Travel with the red blood cell as it transports oxygen. Video**

**(Slide 12)** In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient’s blood. Clinically this value is commonly referred to simply as “percent sat.” Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient’s finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect hypoxemia, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO2 and is typically recorded in units of millimeters of mercury, mm Hg.

**(Slide 13)** Receptors for oxygenation saturation are found in the kidneys, which is an ideal site to monitor saturation, since the kidneys filter about 180 liters (~380 pints) of blood in an average adult each day. In response to hypoxemia, less oxygen is diffused into the kidney, resulting in hypoxia of the kidney cells where oxygen concentration is actually monitored. Interstitial fibroblasts within the kidney secrete erythropoietin, leading to increased erythrocyte production and eventually restoring oxygen levels. In a negative-feedback loop, as oxygen saturation rises, erythropoietin secretion falls, and vice versa, thereby maintaining homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere, naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few days after their arrival. In response to the hypoxemia, the kidneys secrete erythropoietin to step up the production of erythrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness, mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing elevations to allow erythropoietin levels and, consequently, erythrocyte counts to rise.

**(Slide 14)** Platelets are relatively small, 2–4 µm in diameter, but numerous, with typically 150,000–160,000 per µL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

**(Slide 15)** Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

**(Slide 16) Platelet Activation and Factors for Clot Formation. Video**

**(Slide 17)** Platelets are key players in hemostasis, the process by which the body seals a ruptured blood vessel and prevents further loss of blood. Although rupture of larger vessels usually requires medical intervention, hemostasis is quite effective in dealing with small, simple wounds. There are three steps to the process: vascular spasm, the formation of a platelet plug, and coagulation (blood clotting). Failure of any of these steps will result in hemorrhage—excessive bleeding.

**(Slide 18)** When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In vascular spasm, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

**(Slide 19)** In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing platelet plug.

**(Slide 20)** As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

* adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug;
* serotonin, which maintains vasoconstriction;
* prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals, as discussed next.

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made.

**(Slide 21)** More sophisticated and durable repairs made beyond the plug formation are collectively called coagulation, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of fibrin—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped.

**(Slide 22)** In the coagulation cascade, chemicals called clotting factors (or coagulation factors) prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

1. The extrinsic pathway, which normally is triggered by trauma.
2. The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

**(Slide 23)** Both of these merge into a third pathway, referred to as the common pathway. All three pathways are dependent upon the 12 known clotting factors, including Ca2+ and vitamin K. Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

**(Slide 24)** The quicker responding and more direct extrinsic pathway (also known as the tissue factor pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin). Sequentially, Ca2+ then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

**(Slide 25)** The intrinsic pathway (also known as the contact activation pathway) is longer and more complex. In this case, the factors involved are intrinsic to (present within) the bloodstream. The pathway can be prompted by damage to the tissues, resulting from internal factors such as arterial disease; however, it is most often initiated when factor XII (Hageman factor) comes into contact with foreign materials, such as when a blood sample is put into a glass test tube. Within the body, factor XII is typically activated when it encounters negatively charged molecules, such as inorganic polymers and phosphate produced earlier in the series of intrinsic pathway reactions. Factor XII sets off a series of reactions that in turn activates factor XI (antihemolytic factor C or plasma thromboplastin antecedent) then factor IX (antihemolytic factor B or plasma thromboplasmin). In the meantime, chemicals released by the platelets increase the rate of these activation reactions. Finally, factor VIII (antihemolytic factor A) from the platelets and endothelial cells combines with factor IX (antihemolytic factor B or plasma thromboplasmin) to form an enzyme complex that activates factor X (Stuart–Prower factor or thrombokinase), leading to the common pathway. The events in the intrinsic pathway are completed in a few minutes.

**(Slide 26) Coagulation Cascade Animation - Physiology of Hemostasis. Video**

**(Slide 27)** The stabilized clot is acted upon by contractile proteins within the platelets. As these proteins contract, they pull on the fibrin threads, bringing the edges of the clot more tightly together, somewhat as we do when tightening loose shoelaces. This process also wrings out of the clot a small amount of fluid called serum, which is blood plasma without its clotting factors.

**(Slide 28)** To restore normal blood flow as the vessel heals, the clot must eventually be removed. Fibrinolysis is the gradual degradation of the clot. Again, there is a fairly complicated series of reactions that involves factor XII and protein-catabolizing enzymes. During this process, the inactive protein plasminogen is converted into the active plasmin, which gradually breaks down the fibrin of the clot. Additionally, bradykinin, a vasodilator, is released, reversing the effects of the serotonin and prostaglandins from the platelets. This allows the smooth muscle in the walls of the vessels to relax and helps to restore the circulation.

**(Slide 29)** Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient’s own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

**(Slide 30)** Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following a transfusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the transfused erythrocytes and cause them to adhere to one another.

**(Slide 31)** Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of erythrocytes. This process is called agglutination. The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.

**(Slide 32)** As the erythrocyte clumps are degraded, in a process called hemolysis, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney’s capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.

**(Slide 33)** Although the ABO blood group name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

**(Slide 34)** Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

**(Slide 35)** The Rh blood group is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified, only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of people − are described as Rh positive (Rh+) and those who lack it are Rh negative (Rh−). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient’s blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A+) means ABO group A blood with the Rh antigen present, and AB negative (AB−) means ABO group AB blood without the Rh antigen.

**(Slide 36)** In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh− individuals after exposure to the antigen. This process, called sensitization, occurs following a transfusion with Rh-incompatible blood or, more commonly, with the birth of an Rh+ baby to an Rh− mother. Problems are rare in a first pregnancy, since the baby’s Rh+ cells rarely cross the placenta (the organ of gas and nutrient exchange between the baby and the mother). However, during or immediately after birth, the Rh− mother can be exposed to the baby’s Rh+ cells (Figure 18.6.1). Research has shown that this occurs in about 13−14 percent of such pregnancies. After exposure, the mother’s immune system begins to generate anti-Rh antibodies. If the mother should then conceive another Rh+ baby, the Rh antibodies she has produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as hemolytic disease of the newborn (HDN) or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

**(Slide 37)** To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B+ recipient should ideally receive blood only from a type B+ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient’s life, there may not be time for cross matching to identify blood type. In these cases, blood from a universal donor − an individual with type O− blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient’s blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. Ideally, the transfusion is not whole blood, but only red blood cells and saline, avoiding the problem of type A or type B antibodies in the donor’s plasma being transfused to the patient. If whole blood is transfused instead, and the the O− donor had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood would introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient’s own blood, the adverse effects of the relatively few infused plasma antibodies are typically limited. For these reasons, it is preferable to cross match a patient’s blood before transfusing, or only transfuse red blood cells and saline. In a true life-threatening emergency situation, this is not always possible, and the universal donor (O-) whole blood could be used.

**(Slide 38)** A patient with blood type AB+ is known as the universal recipient. This patient can theoretically receive any type of blood, because the patient’s own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh+ patient can receive both Rh+ and Rh− blood.

Lauralee Sherwood. Fundamentals of Human Physiology. P. 299 – 309.

**Questions that we will analyze for a lesson on this topic:**

1. Red blood cells and their function.
2. Hemoglobin, amount in the blood, its structure, its compounds.
3. Primary or vascular platelet hemostasis: sequence of processes, the role of platelets.
4. Secondary (coagulation) hemostasis: sequence of processes, phases of coagulation hemostasis.
5. Fibrinolysis mechanisms.
6. Anticoagulant system.
7. Blood groups of ABO systems.
8. Rhesus factor.
9. Blood transfusion rules.

Finish for today

The full lecture is at the indicated website.

**Thank you for attention**