Blood, Chapter 13
Outline of class notes for Physiology
Objectives:

After studying this chapter you should be able to:

1. Describe the functions of blood and briefly describe its composition.
2. Discuss the components of plasma and explain their importance.
3. Explain the difference between plasma and serum.
4. Describe the characteristics and functions of erythrocytes including a description of how oxygen and carbon dioxide are transported. Be sure to include details of bicarbonate ions, chloride shift, and the Bohr Effect.
5. Explain the process of hematopoiesis, erythropoiesis, and the life cycle of a RBC.
6. Define hematocrit and describe its components.
7. Describe the characteristics and functions of platelets including the mechanism of clot formation in a damaged blood vessel.
8. Explain how aspirin and plavix function to prevent blood clots.
9. Explain ABO blood typing and what the “+” and “-” mean.
10. Discuss the details of hemolytic disease of the newborn (erythroblastosis fetalis).
11. Describe the following disorders: Anemia, sickle-cell disease, hemophilia, and leukemia.
12. Discuss the Clinical Applications from the study guide and assigned Applications to Health.

Cardiovascular System: Blood, Ch 13

- Functions of Blood
  - Blood:
    - Characteristics
    - Components
      - Plasma
      - Formed Elements
  - Blood Cell Formation
  - Types of Blood cells
    - Erythrocytes
    - Leukocytes
    - Platelets (thrombocytes)
  - Preventing Blood Loss
    - Clot formation
  - Blood Grouping
  - Diagnostic Blood Tests

Functions of the Circulatory System

1. Transportation:
   - Blood gases: O2 from the lungs to the body cells and CO2 from the body cells to the lungs.
   - Nutrients:
   - Wastes: Cellular waste products are transported to the liver, kidneys, and skin for elimination.
   - Regulatory molecules: Hormones from endocrine glands are carried to target cells.
2. Regulation:
   • pH:
   • Body Temperature: By absorbing and distributing body heat.
     • During hot ambient temperatures, blood is diverted from deep to superficial
       vessels to cool the body
     • During cold ambient temperatures, blood is diverted from superficial to deeper
       vessels to keep the body core warm.
     • Based on the absorbing and coolant properties of water
   • Fluid Volume and water content of cells: Blood osmotic pressure and in conjunction
     with the urinary system.

3. Protection:
   • Clot Formation:
   • Immune system: Circulating antibodies and WBCs protect
     against infectious microorganisms and toxins.

Physical Characteristics of Blood
   • Color depends on oxygen content.
     – Bright red:
     – Dark red:

   • Blood is 5x more viscous than water
   • Normal Blood pH ranges from 7.35 – 7.45.
     • Slightly alkaline
   • Total blood volume:
     • Females: 4-5 liters (1.2 gal)
     • Males: 5-6 liters (1.5 gal)
   • Salt concentration = 0.9%
     • Females: 4-5 liters (1.2 gal)
     • Males: 5-6 liters (1.5 gal)
     • Makes up ~

Composition of Blood
   • Classified as fluid CT
   • Composed of formed elements (cells and platelets) suspended in a fluid matrix called plasma.
     • Formed elements include:
       • Erythrocytes (red blood cells; RBCs):
       • Leukocytes (white blood cells; WBCs): Function in immune defense
       • Platelets (thrombocytes): Function in blood clotting

Plasma
   • Plasma:
     – Straw-colored liquid that makes up ~55 % of blood volume.
     – Consists of:
       • ~
       • ~
       • ~2% other substances such as enzymes, hormones, metabolites, respiratory gases, nutrients, and electrolytes.
- **Plasma proteins** (7%) divided into 3 classes: Albumins, globulins and clotting proteins
- **Albumins** (~60% of plasma proteins)
  - Produced by
  - Maintain osmotic pressure of the vascular system
    - Function to draw water from the surrounding tissue (interstitial) fluid into the capillaries to maintain blood volume and pressure.
- **Globulins** (~35% of plasma proteins)
  - **Alpha** and **beta globulins**:
    - Produced by the liver; function to transport lipids, steroids, fat-soluble vitamins, and metal ions (iron).
  - **Gamma globulins** (immunoglobulins):
    - Produced by plasma cells (type of leukocyte)
    - Are antibodies which
- **Clotting proteins** (~4% of plasma proteins)
  - Produced by
    - Two examples are thrombin and fibrinogen
  - **Serum**: The yellowish fluid remaining after blood has clotted.
    - Similar to plasma but without the clotting proteins and factors.

**Erythrocytes (Red Blood Cells)**
- Round cells shaped like biconcave discs with a diameter of 7-8 µm.
  - Shape increases
- **Function**: O₂ transport; also plays a minor role in CO₂ transport.
- **Quantity**: 4.5-5.5 million per cubic millimeter (mm³).
  - Have about 260 million RBCs/drop of blood.
- Mature RBCs are **anucleated** and lack mitochondria.
  - No nucleus = more room for hemoglobin molecules
  - No mitochondria = the RBC will not use the oxygen it is transporting.
    - RBCs generate ATP by anaerobic respiration

**Erythrocytes and Hemoglobin**
- **Hemoglobin** molecules function in the transport of oxygen and to a smaller extent, carbon dioxide
  - A hemoglobin molecule consists of: 4 polypeptide (protein) chains called globins and 4 iron containing pigment molecules called hemes.
    - Of the 4 polypeptide chains, 2 are composed of identical **alpha chains**, each 141 amino acids long, and two identical **beta chains**, each 146 amino acids long.
    - Each protein chain is bound to
    - A **heme** group consists of a **porphyrin ring** that holds 1 atom of iron. An iron atom can **reversibly bind to one oxygen molecule (O₂)**.
      - One hemoglobin molecule can combine with 4 molecules of oxygen
      - Each red blood cell contains ~280 million hemoglobin molecules and can thus carry over a billion molecules of oxygen.
- Hemoglobin gives
- Hemoglobin transports 98.5% of blood oxygen with the remaining oxygen transported in the plasma
- Depending on what is bound to hemoglobin will determine its name.
  - **Oxyhemoglobin**: when iron binds to oxygen
  - **Deoxyhemoglobin**: when the oxygen is released
  - **Carboxyhemoglobin**:
- Bond between hemoglobin and carbon monoxide is about 210 Xs stronger than the bond with oxygen and can be fatal.

**Carbon Dioxide Transport**
- Carbon dioxide is transported in the blood in three forms:
  1. As dissolved CO2 in the plasma, ~10%
  2. As carbaminohemoglobin (HbCO2), ~20%. CO2 is attached to an amino acid in the globin portion.
  3.

**Overview of the Transport of Bicarbonate Ions and the Chloride Shift**
- In order to increase the amount of CO2 transport, RBCs convert the CO2 to bicarbonate and H+ at the systemic capillaries.
- So what does the RBC do with the bicarbonate and H+?
  - H+ binds to hemoglobin
  - Bicarbonate diffuses out the RBC as Cl- diffuses onto the RBC. This process is known as the chloride shift and allows bicarbonate to move out of the RBC.
  - In the pulmonary capillaries this process is reversed (reversed chloride shift)
Bicarbonate Ions and the Chloride Shift

- In systemic capillaries, carbon dioxide combines with water to form carbonic acid, but at a slow rate.
  - In RBCs, the enzyme carbonic anhydrase greatly speeds this reaction to form carbonic acid (H2CO3).
  - As carbonic acid builds up it dissociates into

- Most of the hydrogen ions (H+) remain in the RBC and attach to hemoglobin (HbH) while most of the bicarbonate ions diffuse out into the plasma by facilitated diffusion and can serve as a buffer.
- The result is that the

- This attracts chloride ions (CL-), which move into the RBCs as HCO3- move out.

- **Chloride Shift**: This exchange of anions, diffusion of Cl- into RBCs as HCO3- diffuses out of the RBCs, is called the **chloride shift** and occurs in the systemic capillaries.

**Question?**

- How do red blood cells know where to release more oxygen and where less? Or why do they unload more oxygen at all? Why is O2 released in tissues?
- Answer: The higher the levels of CO2 and thus H+ as occurs in actively metabolizing cells, the greater the release of oxygen from hemoglobin in what is known as the **Bohr Effect**.

**Bohr Effect**

- **Bohr Effect**: The unloading of oxygen from oxyhemoglobin is increased by the bonding of H+ (released from carbonic acid) to oxyhemoglobin due to a
  - It results in increased conversion of oxyhemoglobin to deoxyhemoglobin liberating more O2 in the tissues.
  - Thus, carbon dioxide increases oxygen unloading
  - **Bohr Effect**: The effect of decreased pH promotes

**Reverse Chloride Shift**

- In the pulmonary capillaries oxygen binds to deoxyhemoglobin and becomes oxyhemoglobin.
- H+ doesn’t bind well to oxyhemoglobin and

- The H+ attracts bicarbonate (HCO3-) from the plasma, which combines with H+ to form carbonic acid and Cl- moves out of the RBC into the plasma.
- Under low CO2 concentrations, as occurs in the lungs, **carbonic anhydrase** converts carbonic acid to H2O and CO2 which is exhaled.
Hematopoiesis
- **Hematopoiesis** (hemopoiesis) is the generation of new blood cells and occurs in the red bone marrow
  - Hemocytoblast:
- **Hematopoiesis Includes:**
  - **Leukopoiesis:** Formation of leukocytes (white blood cells)
  - **Erythropoiesis:** Formation of erythroctes (red blood cells)
  - **Thrombopoiesis:** Formation of platelets (thrombocytes) – technically not a cell.

Erythropoiesis
- **Erythropoiesis is the formation of RBCs**
  - Occurs in the bone marrow at a rate of ~ 2 million/second to replace the worn out RBCs that are continuously destroyed by the spleen and liver.
  - During the process, hemoglobin is synthesized and levels are built up within the future RBC.
    - Each erythrocyte consists of ~280 million molecules of hemoglobin
  - Near the end of the developmental sequence the nucleus is ejected and the cell becomes a **reticulocyte** which still some organelles such as mitochondria, ribosomes, and endoplasmic reticulum.
    - **Loss of the nucleus** causes the center of the cell to

  - **Reticulocytes** are then released into the circulation, loose their mitochondria, ribosomes, and endoplasmic reticulum and develop into erythrocytes within 1-2 days

Clinical Significance of Reticulocytes
- **Reticulocytes** normally make up about 1 to 2% of the RBCs in the human body. A **reticulocyte count** or **Retic Count** measures the
  - A reticulocyte percentage that is higher or lower than "normal" can help in the determination of the type of **anemia and/or health of the bone marrow** because it represents recent production.
• **Increased reticulocyte count:** Can occur when there is an increased production of red blood cells to overcome chronic or severe loss of red blood cells, such as in a **hemolytic anemia** or **hemorrhage**.

• **Decreased reticulocyte count:** Can be attributed to anemia due to poor RBC production as in aplastic anemia or pernicious anemia. Can occur due to chemotherapy, bone marrow malignancies, and various vitamin or mineral deficiencies (B\textsubscript{9}, B\textsubscript{12}, iron),

**Control of Erythropoiesis**
- Normally RBC production and destruction proceed at the same pace.
- **Erythropoietin (EPO):**
  - EPO production is increased by:
    - **Hypoxia** due to decreased RBC count
    - Decreased availability of oxygen to blood
    - Increased tissue demands for oxygen.
  - What would happen if oxygen content increased?

**Question?**
- Why is fecal (Laymen term: poop) matter brown and urine (Laymen term: pee) yellow?
**Answer:**

**Life Cycle of a Typical RBC**
- RBCs have
  - Formed in the red bone marrow by erythropoiesis.
  - Old and damaged RBCs are engulfed by **macrophages** in the **spleen, liver, and bone marrow**.
- **Hemoglobin** is disassembled into heme and globin portions.
  - The **globin** proteins are broken down into amino acids for reuse.
  - **Heme** units are striped of their **iron** and the iron is reused in **erythropoiesis**.
  - The remainder of the heme is converted into a pigment called **biliverdin (green color)** and then to **bilirubin (yellow color)**
  - Most of the **bilirubin** is excreted by the liver into the bile; the remainder by the kidneys
    - Bilirubin and urobilins gives urine its characteristic yellow color.
  - Inside the large intestine, bacterial convert the **bilirubin** into other forms that give feces its characteristic brown color.
Hematocrit

- **Hematocrit (Hct):**
  - Average normal Hct in females is 42 ± 5% and in males is 47 ± 5%.

- **Hematocrit determination:**
  A blood sample is centrifuged; blood separates into two layers.
  - **Bottom Layer (~45%):** Composed of formed elements
    - **RBCs** make up 99% of the formed elements
    - **WBCs** and **Platelets** make up less than 1% of the formed elements and form a thin layer (buffy coat) between the RBCs and plasma.
  - **Top Layer (~55%):** Plasma; straw-colored layer.

**Test Your Knowledge**
If Arthur has a hematocrit of 49%, then approximately what % of his blood is composed of plasma?

- a. 49%  
- b. 51%  
- c. 90%  
- d. Cannot be determined
Details of Leukocytes will be covered during the immune system.

Platelets
- **Platelets (thrombocytes)** are cell fragments produced by the megakaryocyte in the bone marrow.
  - Thrombopoiesis:
- Function in clot formation and blood vessel repair.
  - Contain chemicals vital to coagulation (blood clots).

**Mechanism of Clot Formation in a Damaged Blood Vessel**
- Blood loss from a damaged vessel involves three steps: 1) vascular spasm 2) formation of a platelet plug, and 3) Production of a fibrin web - clot formation.
  1) **Vascular spasm:**
    - A cut or torn vessel immediately constricts and reduces blood flow through the vessel.
  2) **Formation of a platelet plug:**
    - Breakage of the endothelial lining of a vessel exposes collagen fibers from the basement membrane of the endothelium.
    - **Collagen fibers** activate platelets to change shape (spiky processes) and become sticky which causes them to bind with the collagen fibers and other platelets to form a platelet plug.
    - Endothelial cells in the injured area produce a protein called von Willebrand’s factor which binds to both collagen and platelets holding them together.
    - Activated platelets release several chemicals from their storage granules including adenosine diphosphate (ADP) and thromboxane A₂ (TxA₂). Both of which activate other platelets.
    - Thromboxane A₂ (a prostaglandin) is also a powerful vasoconstrictor which reinforces vascular spasms.
    - Platelets also release chemicals to
3) Production of a fibrin web - clot formation: Blood clotting is the transformation of blood from a liquid into a solid structure that strengthens the platelet plug.

- The **final step in clot formation** is the conversion of **fibrinogen**, a soluble protein produced by the liver and normally present in the blood to **fibrin**, an insoluble threadlike molecule. Actually fibrin monomers attach to produce a fibrin polymer.
  
  - **Fibrin** molecules adhere to the damaged blood vessels surface forming a netlike meshwork that traps blood cells – the resulting **mass of platelets, blood cells, and fibrin becomes the blood clot**.
  
  - **Thrombin** is the enzyme that **converts fibrinogen to fibrin** at the injury site.
    - **Prothrombin**, produced by the liver and normally present in the blood, is converted to **thrombin** by factor X (prothrombinase), which was activated by a cascade of a number of clotting factors including thromboplastin and Ca$^{2+}$.
Dissolution of Clots
• During the healing process the fibrin meshwork is dissolved by a fibrin splitting enzyme called plasmin.
  – Plasminogen, the inactive form of plasmin, is activated by a number of plasminogen activators found within the body including urokinase, kallikerin and tissue plasminogen activator (TPA).
  – Clinically, TPA and urokinase, produced by genetically engineered bacteria, and streptokinase, a natural bacterial product, can be injected into the blood stream to dissolve blood clots such as in pulmonary embolism, myocardial infarction, stroke, and thrombus formation.
    • TPA, urokinase and Streptokinase activate the conversion of

Blood Clot Prevention - Aspirin and Plavix
• Thromboxane A₂ is a prostaglandin required for platelet aggregation and is a potent vasoconstrictor. The formation of thromboxane A₂ is catalyzed by the cyclooxygenase-1 (COX-1) enzyme.
  – Aspirin is a COX-1 and COX-2 inhibitor and thus reduces platelet aggregation by inhibiting thromboxane A₂ production.
  – Since platelets are not compete cells, they cannot regenerate new enzymes and thus the COX-1 enzyme is inhibited for the life of the platelet (~10 days). Note: aspirin can significantly increase bleeding times.
• Plavix inhibits platelet activation by blocking the receptors for ADP on the platelet plasma membrane.
Blood Grouping (Typing)

- General information
  - A blood type (also called a blood group) is a classification of blood based on the presence or absence of inherited antigenic substances on the surface of red blood cells (RBCs).
    - About 33 human blood group systems are now known.
    - Two major blood group classifications are ABO and Rh antigens; they determine the person’s blood type (A, B, AB, and O with + and – indicating Rh status).

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<thead>
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<th>Antigen B</th>
<th>Antigens A and B</th>
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<tbody>
<tr>
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<td>Anti-A antibody</td>
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</tr>
<tr>
<td>Type A</td>
<td>Type B</td>
<td>Type AB</td>
<td>Type O</td>
</tr>
<tr>
<td>Red blood cells with type A surface antigens and plasma with anti-B antibodies</td>
<td>Red blood cells with type B surface antigen and plasma with anti-A antibodies</td>
<td>Red blood cells with both type A and type B surface antigens, and neither anti-A nor anti-B plasma antibodies</td>
<td>Red blood cells with neither type A nor type B surface antigens, but both anti-A and anti-B plasma antibodies</td>
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Basis of the ABO Blood Group

- ABO blood types are based on the presence or absence of two specific glycoprotein antigens known as type A and type B, found on the RBC’s external surface.
  - Glycoprotein: A molecule that consists of a carbohydrate plus a protein – functions as cell markers for cell recognition.
  - An antigen (abbreviation for antibody generator) is anything the body perceives as foreign and generates an immune response to.
    - Commonly known antigens are toxins and molecules on the surfaces of bacteria, viruses, cancer cells, and mismatched RBCs.
    - Type A blood has only the A antigen
    - Type B blood has only the B antigen
    - Type AB blood has both A and B antigens on the RBCs
    - Type O blood has neither A or B antigens on the RBCs

Figure 1. ABO antigen specificity. The ABO antigens differ by just one sugar at the antigen terminus. Only the carbohydrate portion of the antigen is illustrated.
Antibodies of the ABO Blood Groups

- Unique to the ABO blood groups is the presence of **naturally occurring antibodies** found in the plasma. “**Naturally occurring**” antibodies are those produced without known exposure to the antigen.
  - These antibodies (agglutinins) act against RBCs carrying ABO antigens that are not present on a person’s own RBCs
- **A newborn lacks these antibodies**, however they begin to appear in the plasma within 2-6 months after birth.
  - The “naturally occurring antibodies” are now known to be produced in response to the development of the normal gut flora as there are ‘A’ and ‘B’ like **antigens associated with common intestinal bacteria**.
- **Antibodies found in the plasma is a follows**:
  - Type A blood contains **anti-B antibodies**
  - Type B blood contains **anti-A antibodies**
  - Type AB blood contains **neither anti-A or anti-B antibodies**
  - Type O blood contains **both anti-A and anti-B antibodies**

- If the wrong blood type is transfused into a person the RBC surface glycoproteins will be recognized as foreign and antibodies will bind to and **clump (agglutinate)** the cells together and destroy them.
  - Since RBC antigens promote **agglutination (clumping)**, they can also be called **agglutinogens**.
- Although there are about 30 different groups of RBC antigens, the ABO and Rh blood groups are the most important because of the presence of naturally occurring antibodies and the chance of a **transfusion reaction**.

Rh Blood Typing

- Rh blood typing determines whether the Rh antigen is **present (Rh+) or absent (Rh-)**
  - Most people (85% of Caucasian population) are Rh+ and lack the anti-Rh antibodies.
  - Rh factor is named for the

<table>
<thead>
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<th>O-</th>
<th>A-</th>
<th>B-</th>
<th>AB-</th>
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- An individual is either **positive or negative** for the **Rh factor**; this is denoted by a ‘+’ or ‘−’ after their ABO type.
  - Blood that is Rh-negative can be transfused into a person who is Rh-positive, but an Rh-negative should not receive Rh-positive blood as the recipient can create antibodies for Rh-positive RBCs.
- **Anti-Rh antibodies** are produced only in people who come into contact with the **Rh+ blood cells** such as during a **transfusion or pregnancy**; an Rh- female who carries a Rh+ fetus can become sensitized and threaten the health of the fetus.
Universal Blood Donors and Recipients

• Type O- is the universal donor
  – Since type O- individuals have no A B, or Rh antigens so no other blood type will reject it.

• Type AB+ is the universal recipient
  – Since type AB+ individuals lack both anti-A, anti-B and anti-Rh antibodies and can receive they can accept donor blood of any other blood type.

Transfusion Reactions

• Transfusion reactions involve the clumping and hemolysis (rupture) of the donated (transfused) RBCs.
  – Clumped RBCs can plug up small blood vessels preventing the delivery of oxygen and removal of waste products.
  – Hemolysis cause the release of hemoglobin which if high enough, will precipitate in the kidneys and block the urine-forming structures leading to acute kidney failure.

• The most serious consequences arise from the effect of antibodies in the recipient’s plasma on the incoming door RBCs.
  – The effect of the donor’s antibodies on the recipient’s RBCs is minor unless a large amount of blood is transfused, because the donor’s antibodies are diluted by the recipient’s plasma.
  – Note: Unless the person needs a large amount of blood, the transfused blood is in the form of “packed red blood cells” which is whole blood minus the plasma portion.

Identification of ABO Blood Groups

• RBC clumping (agglutination) in the typing serum determines the antigens present on the RBC
Percentage of Blood types in the United States

- Each person’s blood belongs to one of four groups. The following population percentages are from the United States.
  - **Type A blood** has
    - About 42% of people have type A blood, with 6% having A-negative (A-) blood and 36% having A-positive (A+) blood.
  - **Type B blood** has antigen B and anti-A antibodies in its plasma
    - About 10% of people have type B blood, with 2% having B-negative (B-) blood and 8% having B-positive (B+) blood.
  - **Type AB blood** has both antigen A and antigen B and lacks both anti-A and anti-B antibodies.
    - Is the rarest, about 4% of people have type AB blood, with 1% having AB-negative (AB-) blood and 3% having AB-positive (AB+) blood.
    - AB+ is called the **universal recipient** because they may receive blood from any other ABO blood type.
  - **Type O blood** lacks both A and B antigens and contains both anti-A and anti-B antibodies.
    - Most common, about 44% of people have type O blood, with 7% having O-negative (O-) blood and 37% having O-positive (O+) blood.
    - O- is called the **universal donor** because their blood may be given to any other ABO type.

<table>
<thead>
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<th>Blood Type</th>
<th>Antigens</th>
<th>Antibodies in plasma</th>
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<th>Can receive blood from</th>
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</table>
Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)

- Disorder can occur when an Rh- female who carries an Rh+ fetus develops anti-Rh antibodies that destroy fetal RBCs.
- Normally fetal and maternal blood are kept separate across the placenta and do not mix. At time of birth there may be tears in the placenta and exposure of Rh+ blood cells from the fetus can cause the Rh- mother’s immune system to become sensitized and produce antibodies against the Rh-antigen.
- Anti-Rh antibodies can move across the placenta and destroy RBCs, causing hemolytic anemia (erythroblastosis fetalis or hemolytic disease of the newborn).
- Usually takes one pregnancy to become sensitized.
- The greatest chance of the blood mixing is during an abortion, miscarriage, or delivery.
- Injecting the Rh- mother with an antibody preparation against the Rh factor can prevent erythroblastosis fetalis.
- Administered before and soon after delivery, miscarriage, or abortion.
- Antibodies bind to and inactivate the fetal Rh antigens before the mother’s immune system can respond to the foreign antigens.
- Trade name for this antibody preparation is

Most people (85% of Caucasian population) are Rh+ and lack the anti-Rh antibodies.