بسم الله الرحمن الرحيم

Physiology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

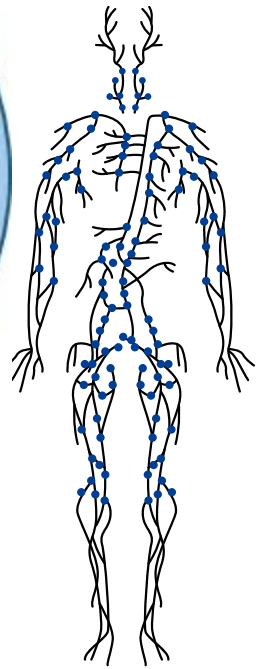
ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

MID | Lecture 8

Blood Types and Transfusion

Written by: Roaa Maakoseh
Sarah Mahasneh

Reviewed by: Sarah Mahasneh



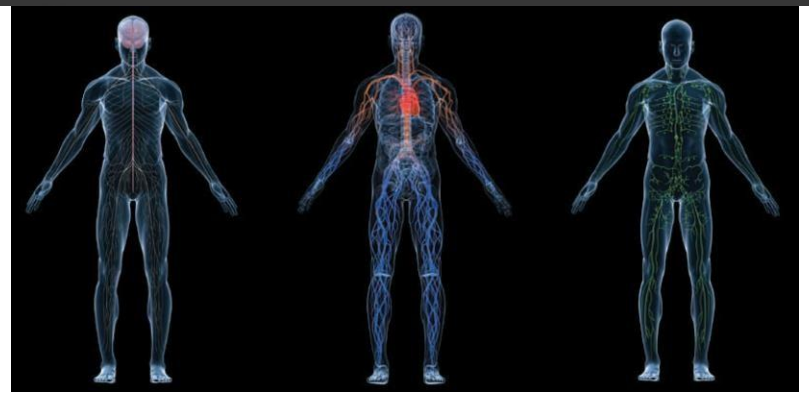
UNIT VI

Chapter 36:

GUYTON AND HALL

TEXTBOOK OF **MEDICAL PHYSIOLOGY**

THIRTEENTH EDITION



Blood Types; Transfusion; Tissue and Organ Transplantation

Ebaa M Alzayadneh, PhD Associate Professor of Physiology

Previously...

· We discussed how T cells become activated and that they cannot recognize antigens directly unless these antigens are presented by antigen-presenting cells (APCs) such as macrophages, dendritic cells, and B lymphocytes.

· These APCs display the processed antigen on their plasma membrane bound to membrane glycoproteins called major histocompatibility complex (MHC) molecules, which are crucial for activating T lymphocytes.
There are two types of MHC molecules:
MHC **class I**, which presents antigens to **cytotoxic ($CD8^+$) T cells.**
MHC **class II,** which presents antigens to **helper ($CD4^+$) T cells.**

○ We also discussed how helper T cells play a central role in coordinating immune responses. For example, AIDS patients have a deficiency of $CD4^+$ T helper cells, which **weakens their immune defenses** and makes them susceptible to persistent and recurrent infections.

Early transfusions

· In the past, physicians performed blood transfusions without understanding the underlying science or the concept of blood group compatibility. They observed that transfusions succeeded in some patients but caused severe, sometimes fatal, reactions in others.

- **Red cell agglutination and lysis**
- **Severe transfusion reactions, often fatal**
- **In other cases, well-tolerated and beneficial**
- **Led to the discovery of red blood cell antigens and the practice of cross-matching**
- **>30 common antigens, many rare ones**

· More than 100 red blood cell antigens have since been identified, but approximately 30 of them are commonly shared among different populations.

The ABO System

- **Red blood cell surface antigens: glycolipids or glycoproteins**
- **Present on all cells in the body, not just blood cells**
- **Agglutinogens "AKA antigens": surface antigens (A,B)**
  - **Genes: A, B, O (maternal, paternal alleles)**
    - **Genotypes: OO, OA, OB, AA, BB, AB**
- **Agglutinins "AKA antibodies" (immunoglobulins): anti-A, anti-B**
- Occurance:

O: 47%

A: 41%

B: 9%

AB: 3%

- **Agglutination** is a reaction that occurs when an antigen binds specifically to its corresponding antibody, resulting in the clumping of red blood cells (RBCs).
- This reaction can be observed either with the naked eye or under a microscope.

- Blood type, which is defined by the specific antigen expressed on the surface of red blood cells, is inherited from both parents.

- In the **ABO blood group system**, there are three main alleles – **IA**, **IB**, and **i**.
- Each individual inherits one allele from each parent, and the **combination of these two alleles** determines the person's blood type.

- There are **six** possible genotype combinations in the ABO blood group system.

- Individuals with the genotype **ii** (formerly written as OO) have blood type O, because the **i** allele is recessive and **does not** produce any antigen on the red blood cell surface.
- Individuals with the genotypes **IAi** or **IAIA** have blood type A, since the **IA** allele is **dominant** and produces the A antigen.
- Individuals with the genotype **IAIB** have blood type AB, because **both** alleles are **codominant**, leading to the **expression** of both A and B antigens.
- Individuals with the genotypes **IBi** or **IBIB** have blood type B, because the IB allele is **dominant** and produces the B antigen.

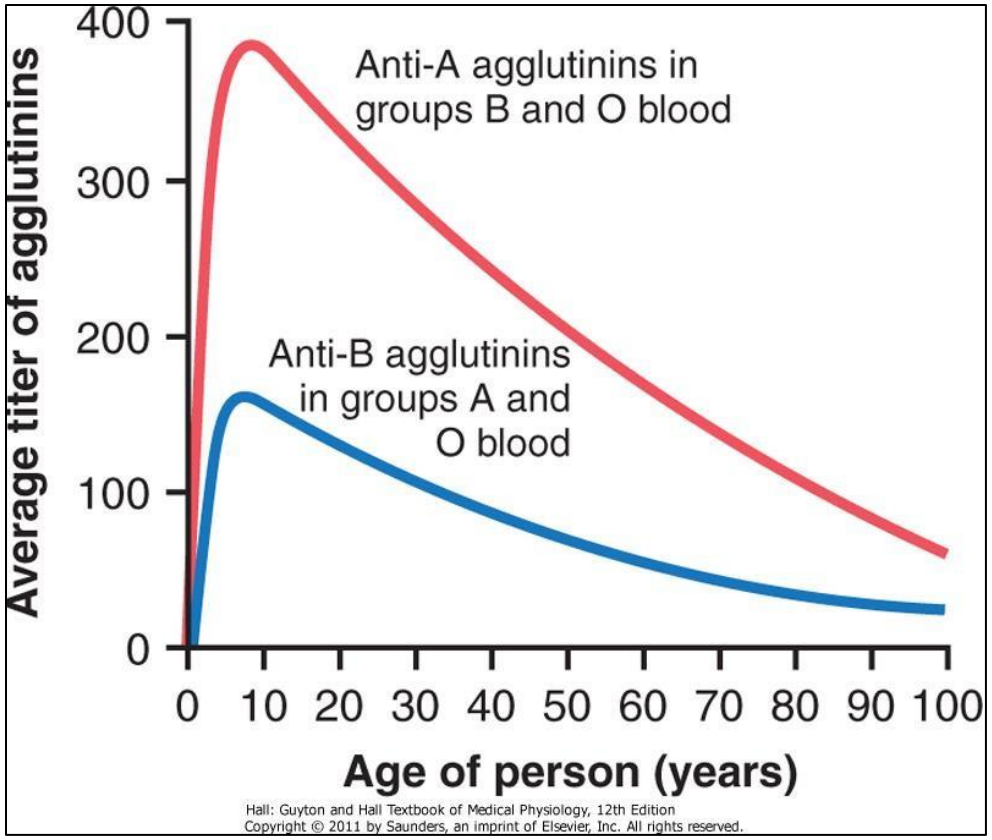
- A key feature of the ABO blood group system is that individuals naturally develop antibodies (**agglutinins**) against the antigens (**agglutinogens**) that they do not possess. These antibodies typically appear within the first few months after birth, without any prior exposure to other blood types.

- The exact mechanism behind this natural antibody formation is not completely understood, but several hypotheses exist.

- One widely accepted explanation is that after birth, exposure to environmental antigens, such as those present in food or the normal gut microbiota, stimulates the immune system to produce these anti-A or anti-B antibodies.

Agglutinins

- Antibodies, mostly IgM and IgG
- Begin developing age 2-8 months, peak ~age 10 years
- Response to A and B antigens in foods, bacteria; initial exposures are environmental

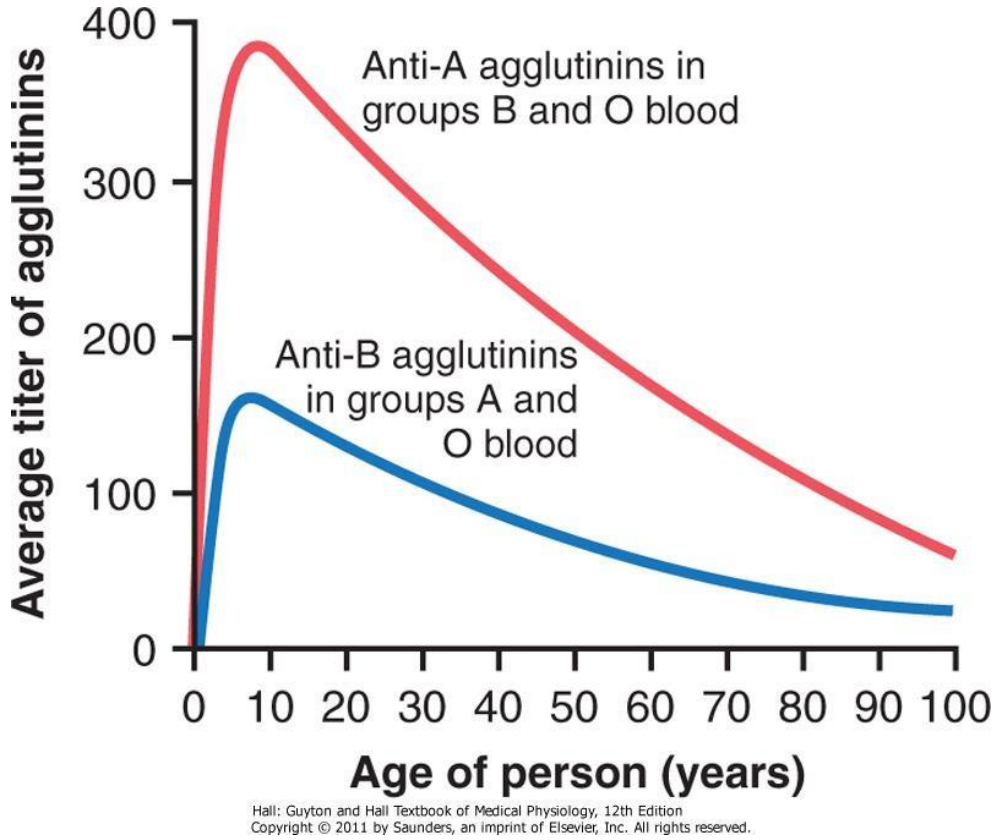


○ As shown in the figure, after birth there is a gradual rise in the **titers of natural antibodies** (**agglutinins**) directed against the ABO antigens that an individual **lack**.

○ Specifically, **anti-A antibodies** develop in individuals with blood types B and O, while **anti-B antibodies** develop in individuals with blood **types A and O**.

○ These **antibody titers** increase during **childhood**, peak around **8-10 years of age**, and then **gradually decline** in the middle of age.

- However, even after this decline, the antibody levels **remain high enough to cause severe transfusion reactions** if incompatible blood is introduced.



Blood Groups

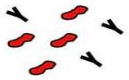
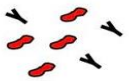
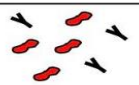
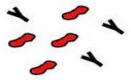
- The main principle of blood transfusion compatibility is to **avoid transfusing red blood cells (RBCs) that possess antigens recognized by the recipient's antibodies.**

- Both the **donor and recipient** have **RBC antigens** and **plasma antibodies**, but it is the **recipient's immune system** that determines whether a **transfusion reaction** will occur.

- Therefore, **the donor's RBC antigens must not include any antigens that the recipient's antibodies can recognize,** thereby **preventing immune-mediated hemolytic reactions.**

Genotype	Blood Type	Agglutinogens	Agglutinins
OO	O	------	ANTI-A and ANTI-B
OA or AA	A	A	ANTI-B
OB or BB	B	B	ANTI-A
AB	AB	AB	------

Blood Typing

Blood Type	Anti-A	Anti-B
O		
A		
B		
AB		

-The **principle of ABO blood typing is based on agglutination reactions** that occur when **specific antibodies in the test sera bind to their corresponding antigens on red blood cells.**

-Two types of antisera are used:
one containing anti-A antibodies and the other containing anti-B antibodies.

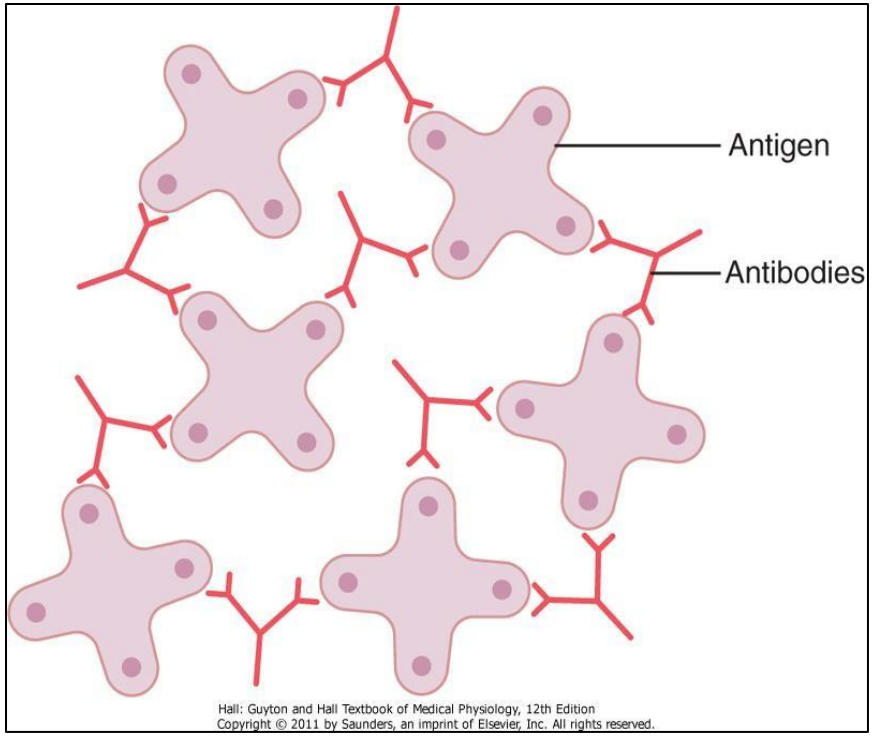
A small blood sample is mixed separately with each antiserum, and the presence or absence of agglutination (clumping) is observed:
Agglutination with anti-A serum only → Blood type A (**A** antigen **present**).
Agglutination with anti-B serum only → Blood type B (**B** antigen **present**).
Agglutination with both sera → Blood type AB (**both** A and B antigens **present**).
No agglutination with either serum → Blood type O (**no A** or **B** antigens **present**).

Transfusion reactions

○ Each antibody molecule has two or more antigen-binding sites, allowing it to attach to more than one RBC at a time. As a result, each red blood cell becomes linked to several antibodies, and each antibody connects multiple cells, forming a network of cross-linked cells that appears as visible clumps.

- **Red cells agglutinate**
- **Plug small vessels**
- **Physical**

  distortion, phagocytic attack → hemolysis
- **In some cases, immediate, complement-dependent hemolysis (depends on Ig type…IgM "hemolysins")**



· Although agglutination may look similar to clotting, it is not the same process – **no fibrin is formed**, and the mixture typically appears as a grainy or slightly cloudy fluid.

● Hemolysis resulted from red blood cell (RBC) agglutination can be immediate or delayed, depending on the underlying **immune mechanism**.

○ If hemolysis is caused by **macrophage** activation and phagocytosis of **antibody-coated RBCs**, it is considered **delayed** hemolysis, which usually develops over several hours to days.

○ In contrast, **immediate** hemolysis occurs when antibody binding activates the **complement** system, leading to **rapid destruction** of RBCs **within minutes**.

○ This reaction depends on the **antibody type and titer** – when **IgM** levels are **high**, there is a greater likelihood of immediate, complement-mediated hemolysis during transfusion reactions.

- Hemoglobin released from RBCs is phagocytosed by macrophages, mainly in the liver and spleen, and broken down into bilirubin, which may cause jaundice.
○ However, the main concern is the **activation of the immune system**: macrophages release cytokines, initiating an inflammatory response. This inflammation causes **vasodilation** and increased vascular **permeability**, allowing fluid to leak into tissues and reducing blood volume, which can lead to circulatory shock. Severe hypotension decreases blood flow to vital organs such as the brain, and RBC agglutination can obstruct microcirculation, especially in the kidneys.

The Rh (rhesus) antigens

- **Requires prior exposure to incompatible blood**
- **Six common antigens ("Rh factors")**
  C, D, E, c, d, e

  - Each person is CDE, CDe, Cde, CdE, cDE, cDe, or cde
- **D ("Rh positive") is prevalent (85% EA, 100% Africans) and particularly antigenic**
- **C and E can also cause transfusion reactions, generally milder**

○ In the Rh system, an **Rh-negative** person does not initially have anti-D antibodies, so the first exposure to Rh-positive blood usually does not cause an immediate reaction. However, **the first exposure sensitizes the immune system, producing anti-D antibodies**. A subsequent exposure can then trigger a hemolytic transfusion reaction.

Anti-Rh Transfusion Reactions

- **Rh+ blood into Rh- recipient:**

  -delayed mild transfusion reaction (Can be unnoticeable)
  -sensitization to further Rh+ transfusion
  - agglutinins peak after 2-4 months

- **50% of Rh- are sensitized by 1st exposure**
  - 20% after a second exposure
  - 30% are non-responders

- **Rh matching to prevent immunization**

Anti-Rh Transfusion Reactions

- **Naïve Rh- recipient**

  → usually no reaction initially

- **Within 2-4 weeks sufficient Ig for agglutination**

  → delayed reaction, usually mild hemolysis within tissue macrophages

- **Any subsequent transfusion with Rh+ blood**

  → potentially severe transfusion reaction

Clinical Perspective

Hemolytic Disease of the Newborn (Erythroblastosis fetalis)

- **ABO incompatibility (O mother and A or B fetus)**

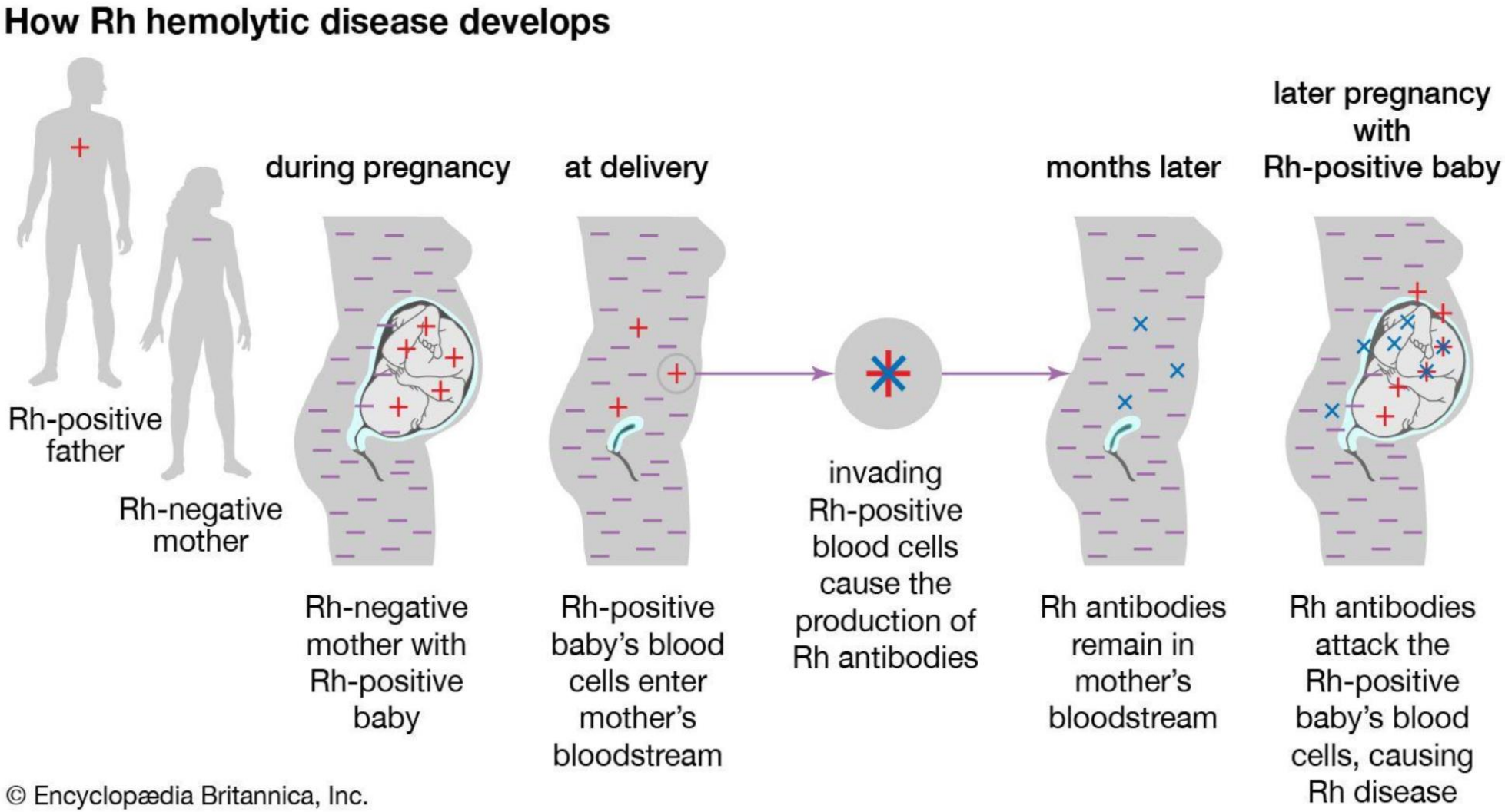
  - **Unusual:**
    - **Most anti-A is IgM, does not cross placenta**
    - **ABO antigens not well developed in fetus**

- **Rh incompatibility (RhD+ fetus and Rh- mother)** more common

  - **Immunization due to fetal-maternal bleeding during delivery**
  - **Mother develops Anti-D agglutinins**
  - **Usually not a problem with first pregnancy**
  - **Worse with subsequent pregnancies**
    (3% EF second pregnancy, 10% with third)

· This condition becomes concerning when an Rh-negative mother and an Rh-positive father conceive a child, because the baby may be Rh-positive, potentially triggering maternal sensitization and hemolytic disease in future pregnancies.

Hemolytic Disease of the Newborn
(Erythroblastosis fetalis)



○ **First Pregnancy (Sensitization):** When an **Rh-negative** (**Rh-**) mother carries an **Rh-positive** (**Rh+**) baby, **fetal RBCs do not cross the placenta** during gestation. The mother is usually exposed and **sensitized** only at **delivery**. The resulting slow **primary immune response** does not produce enough antibodies to harm the first baby.

○ **Second Pregnancy** (Pathology): A subsequent **Rh+** pregnancy triggers a rapid **secondary immune response,** resulting in high levels of **IgG anti-Rh antibodies**. **IgG antibodies cross the placenta, enter the fetal circulation, and cause massive hemolysis (RBC destruction).**

- This destruction leads to **severe anemia** and **hyperbilirubinemia**. Unconjugated bilirubin accumulation in the brain can cause kernicterus (**mental retardation**).
- The fetus attempts to compensate through blood production in the liver and spleen (extramedullary hematopoiesis), leading to the **disorder known as Erythroblastosis Fetalis.**

Hemolytic Disease of the Newborn

(Erythroblastosis fetalis)

- **Maternal antibodies cross the placenta and cause agglutination and lysis of fetal erythrocytes**
- **Fetal macrophages convert hemoglobin to bilirubin → jaundice**
- **Anemic at birth; continued hemolysis 1-2 months**
- **Hepato- splenomegaly from extramedullary erythropoiesis**
- **May have permanent neurologic damage from deposition of bilirubin in neural tissues ("kernicterus")**

Clinical Perspective

Hemolytic Disease of the Newborn: Treatment

- **Exchange transfusion involves the repeated removal of Rh-positive blood and its replacement with Rh-negative blood, performed either before birth or shortly after delivery (typically about 400 mL exchanged over 60–90 minutes).**

  ○ It is replaced with Rh-negative blood because maternal anti-Rh antibodies in the newborn's circulation attack Rh-positive red cells.This procedure reduces hemolysis and bilirubin production, although some tissue damage may have already occurred before treatment.

- **May be done several times over a few weeks**

- **Long-term replacement isn't needed because maternal antibodies disappear within 1–2 months, so Rh-positive cells are no longer attacked.**

Clinical Perspective

Hemolytic Disease of the Newborn: **Prevention**

- **Provide exogenous anti-D antibodies to the mother in late pregnancy that don't cross the placenta and just after birth**

- **These bind to D antigenic sites on fetal erythrocytes that enter the mother's circulation, preventing an immune response**

○ **Why is there usually no concern about ABO incompatibility between the mother and the fetus, for example, when the mother is blood type O and the baby is blood type B?**

<u>That's because:</u>

1. The mother's anti-A and anti-B antibodies are mainly IgM, which are **large molecules that cannot cross the placenta,** so they cannot reach the baby's blood.

2. The A and B antigens on the fetal red blood cells are **not fully developed**, making them less reactive even if a small amount of maternal IgG crosses the placenta.

Clinical Perspective

Blood Component Transfusion

- **Single donation is 450 ml**
- **Processed into components**
  - **Packed Red Cells; Stored ~30- 40 days**
  - **Plasma (clotting factors); Frozen**
  - **Platelets; Stored for 8-10 days**
  - **White blood cells; Rarely used**

Clinical Perspective

Transfusion Reactions

- Occur because of mismatched blood
- Recipient antibodies react against donor antigens
- Either immediate or delayed agglutination and hemolysis
- Fever, chills, shortness of breath; potentially shock, renal shutdown
- Macrophages produce bilirubin
- With normal liver function, no jaundice unless ≥400 ml blood hemolyzed in <1 day

- During blood transfusion, our main concern is that the **recipient** must **not have antibodies against the donor's red blood cell antigens**, since this can cause hemolysis.
- When type O blood is given to a recipient with type A or B blood, there is generally **no problem** because type O red cells lack both A and B antigens, making them compatible with all blood types. Although type O plasma contains anti-A and anti-B antibodies that could theoretically react with the recipient's antigens, the amount of donor plasma in **one** or **two** units of whole blood is very small compared to the recipient's total blood volume. These donor antibodies **become highly diluted**, so even if some hemolysis occurs, it is **minimal** and clinically insignificant.

Clinical Perspective

Acute Renal Failure After **Transfusion Reaction**

- **Products of hemolysis cause powerful renal vasoconstriction**
- **Immune-mediated circulatory shock**
- **Free hemoglobin can leak through glomerular membranes into tubules→high quantities may block tubules**
- **May require acute or even chronic hemodialysis**

Physiology Quiz 8

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			