HLS

MODIFIED NO. 10

PHYSIOLOGY

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UNIT VI

Chapter 35:

Resistance of the Body to Infection: II. Immunity and Allergy; Innate Immunity

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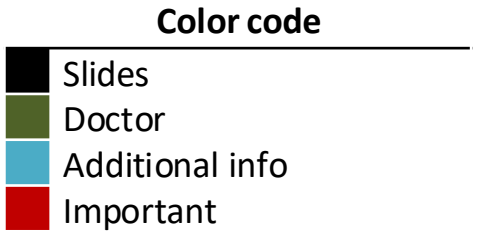


Antibodies: mechanisms of action

- Agglutination
- Precipitation
- Neutralization
- Lysis
- Complement activation

- We talked about the importance of antibodies that are released from activated B cell lymphocyte, they help our body from invading microorganisms by several mechanisms , the 1st one is :

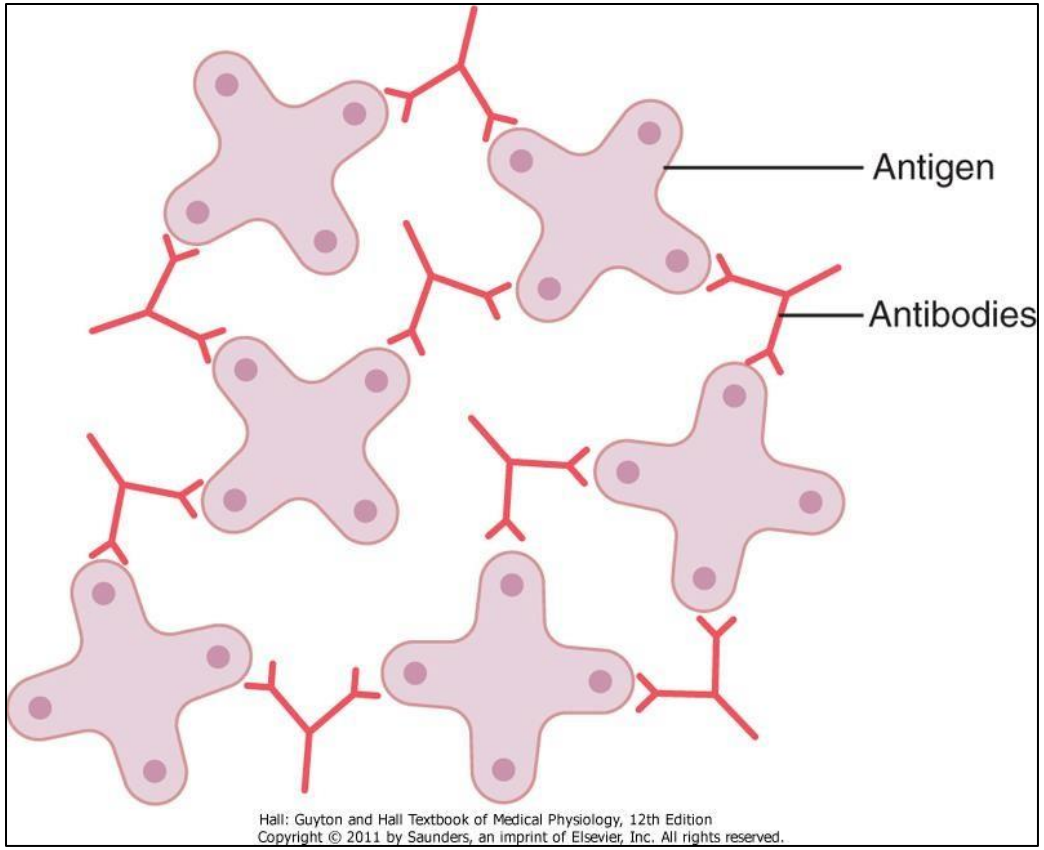
1- Agglutination --> when the antibody binds to the antigen in different places (binding sites) and each antigen is bound to several antibodies this reaction causes clumping of the antigens.

2- This leads to isolation of the pathogen that causes the inflammatory reaction away from being distributed in tissue or outside it, also the immunogloulins bind to the pathogen surface and cover its surface, which leading to neutralization of the microorganism and this actually helps to reduce the microorganisms' effect.

3- Immunoglobulins can cause lysis of the cells (damage , destruction) and activation of the complement system which help in antibodies activation to increase their efficiency against inflammatory response .

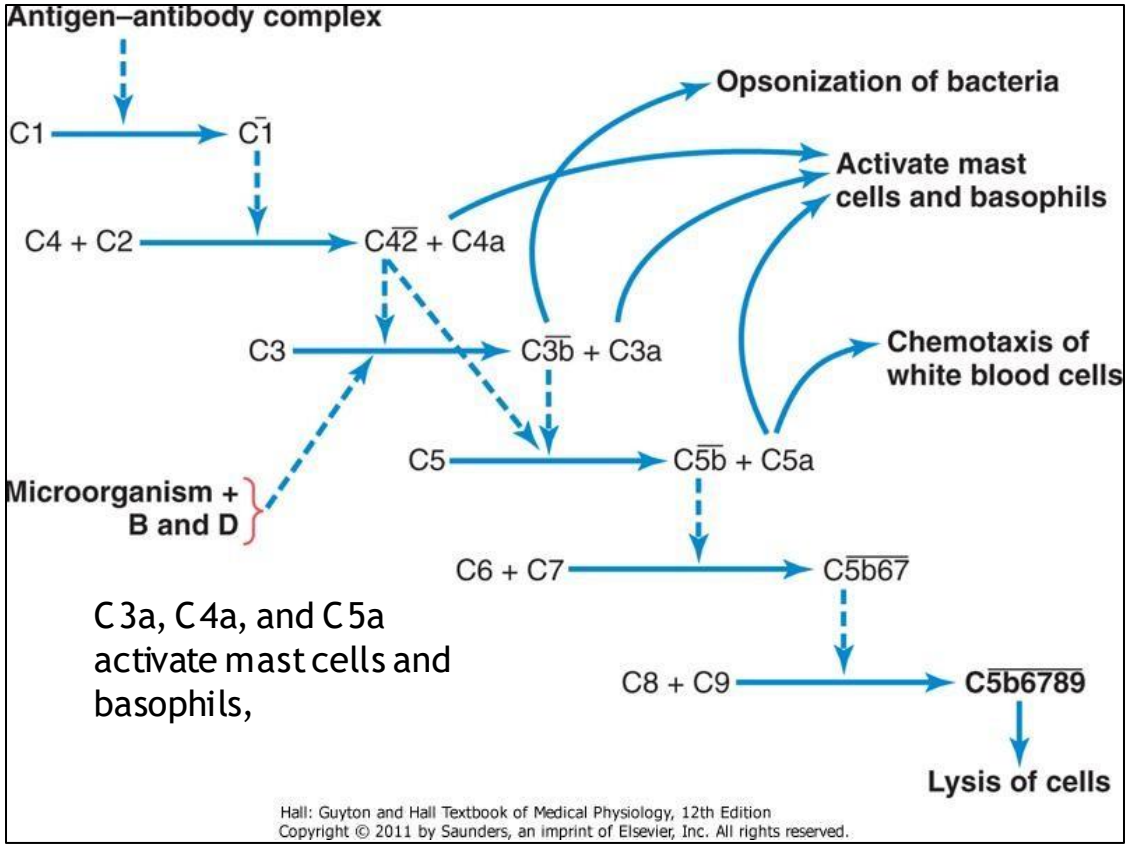
Agglutination

Okay , this is how agglutination occurs as we can see here, clumping will happen because of the many binding sites that each antibody exhibit.
More binding sites --> more clumping



The Complement System

"Complement" (because it's complementary to the roles of antibodies and the immune cells, it helps their function) is a collective term that describes a system of about 20 proteins, many of which are enzyme precursors. The principal actors in this system are 11 proteins designated C1 through C9, B, and D which is the most common component , shown in Figure. All these are present normally among the plasma proteins in the blood are in inactive state as mentioned below , as well as among the proteins that leak out of the capillaries into the tissue spaces. The enzyme precursors are normally inactive, but they can be activated by the so-called classical pathway.



•The classical pathway is initiated by an antigen-antibody reaction. That is, when an antibody binds with an antigen, a specific reactive site on the “constant” portion of the antibody becomes uncovered, or “activated,” and this in turn binds directly with the C1 molecule of the complement system, setting into motion a “cascade” of sequential reactions.

1- Opsonization and phagocytosis. One of the products of the complement cascade, C3b, strongly activates phagocytosis by both neutrophils and macrophages, causing these cells to engulf the bacteria to which the antigen-antibody complexes are attached. This process is called opsonization. It often enhances the number of bacteria that can be destroyed by many hundredfold .

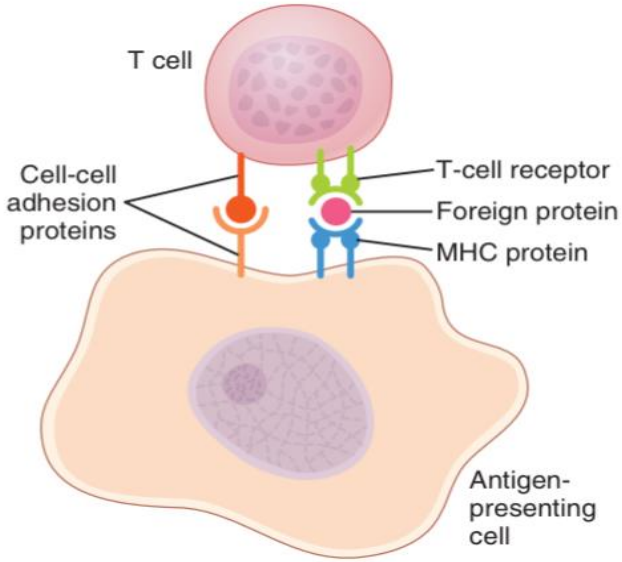
2- Activation of mast cells and basophils. Fragments C3a, C4a, and C5a activate mast cells and basophils.

3- Chemotaxis. Fragment C5a initiates chemotaxis of neutrophils and macrophages, thus causing large numbers of these phagocytes to migrate into the tissue area adjacent to the antigenic agent .

4- Lysis: One of the most important of all the products of the complement cascade is the lytic complex, which is a combination of multiple complement factors and is designated C5b6789. This has a direct effect of rupturing the cell membranes of bacteria or other invading organisms.

T cell activation

- **Binds to cognate antigen presented by antigen-presenting cell**
- **Rapid expansion of T helper (CD4) cells**
- **T helper cells produce cytokines**
- **Drives expansion of both T helper (CD4) the major one in number and function and cytotoxic (CD8) T Cells and T regulatory or suppressor**
- **Both types of cells also generate clonal memory T cells**



• Although B lymphocytes recognize intact antigens, T lymphocytes respond to antigens only when they are
bound to specific molecules called MHC proteins on the surface of antigen-presenting cells in the lymphoid
tissues as shown in the Figure
•T cells to bind to antigen-presenting cells long enough to become activated.
•There are two types of MHC proteins: (1) MHC I proteins, which present antigens to cytotoxic T cells, and
(2) MHC II proteins, which present antigens to T-helper cells. The specific functions of cytotoxic and T-helper cells are discussed later

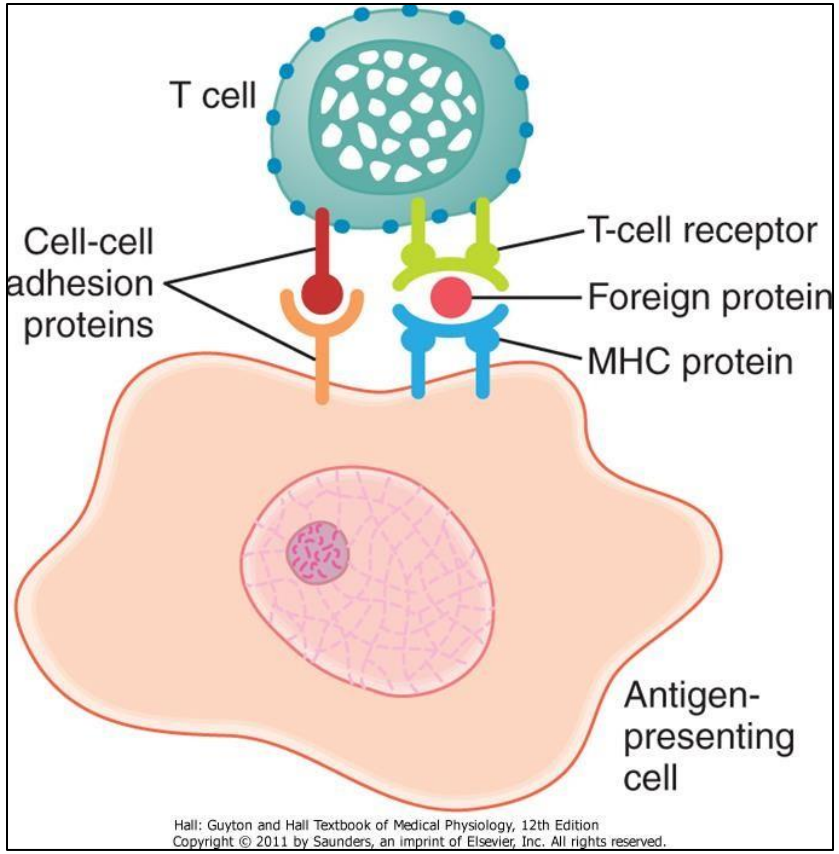
• T helper cells secrete lymphokinse that can affect on the function of various types of immune cells and this leads to expansion and proliferation of cytotoxic T cells as well as the T helper cells, and both types will save a copy that is going to be called memory T cells, similar to B memory cells, are going to be distributed in all body lymphoid tissue, making the 2nd response greater faster.

MHC Proteins

- **B cell surface and secreted antibodies recognize intact antigen**

- **T cells only recognize antigen fragments that are presented by MHC molecules of antigen presenting cells…**
  - **macrophages**
  - **B lymphocytes**
  - **dendritic cells**

Antigen Presentation



MHC Molecules

- **Encoded by the Major Histocompatibility Complex**
  - **MHC I – Present to cytotoxic T cells (CD8)**
  - **MHC II – Present to helper T cells (CD4)**
- **Antigen in the context of MHC is recognized by as many as 100,000 T cell receptors per cell**

Helper (CD4) T cells

- **~ 75% of all T cells**
- **Regulate functions of other immunologic cells by producing cytokines…**
  - **Interleukin (IL-) 2, 3, 4, 5, 6, GM-CSF, Interferon-gamma**

Table 35-1 Subsets of T-helper Cells

	T_H1	T_H2	T_H17
Lymphokines that induce subset	IFN-γ, IL-12	Il-4	TGF-β, Il-1, Il-6, IL-23
Major lymphokines/ factors produced	IFN-γ, Il-2 TNF-α, GM-CSF	IL-4, IL-5, Il-6, IL-10, Il-13	Il-17, IL-22
Major immune reactions	Macrophage activation, Stimulate IgG antibody production	Stimulate IgE production, Activation of mast cells and eosinophils	Recruitment of neutrophils and monocytes

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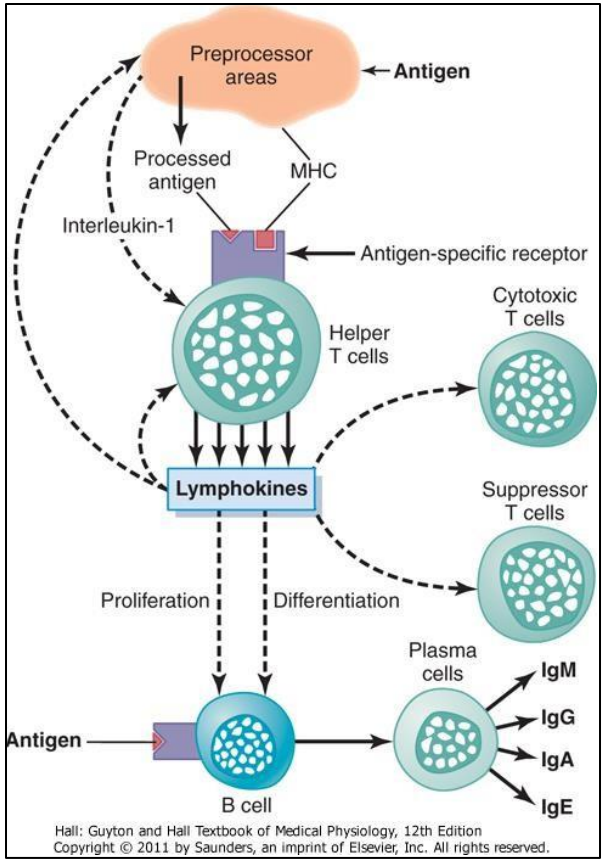
The T-helper cells are by far the most numerous type of T cells, usually constituting more than three quarters of all of them. As their name implies, they help in the functions of the immune system, and they do so in many ways. In fact, they serve as the major regulator of virtually all immune functions. They do this by forming a series of protein mediators, called lymphokines, that act on other cells of the immune system, as well as on bone marrow cells. Among the most important lymphokines secreted by the T-helper cells are the following:
Interleukin-2
Interleukin-3
Interleukin-4
Interleukin-5
Interleukin-6
Granulocyte-monocyte colony stimulating factor Interferon-γ

T cell help for immune response

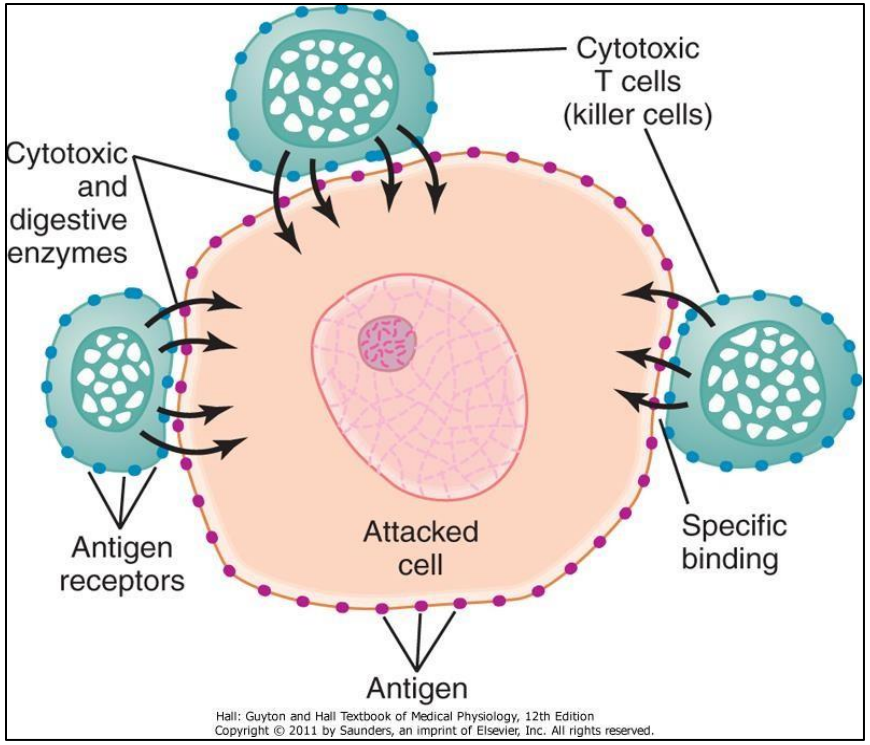
- **Positive feedback for helper T cells (IL-2)**
- **Stimulation of cytotoxic T cells (IL-2, other cytokines)**
- **Stimulation of B cells (IL-4, 5, 6 (BCGFs))**
- **Macrophage accumulation, activation, enhanced killing**



- This is a helper T cell , it has been activated by an antigen-presenting cell, this leads to lymphokines synthesis, which activate the same helper cells, which make a positive feedback on T helper cells .
- leukotriene 2 released can also activates cytotoxic T cells as well as T suppressor cells which accelerate, activate their function .
- B cells (IL- 4, 5, 6 (BCGFs)) which are released by T helper cells, those can activate the activated B lymphocytes , these three interleukins have such potent effects on the B cells that they have been called B-cell stimulating factors.
- Activation of the Macrophage System. The lymphokines also affect the macrophages. First, they slow or stop the migration of the macrophages after they have been chemotactically attracted into the inflamed tissue area, thus causing great accumulation of macrophages. Second, they activate the macrophages to cause far more efficient phagocytosis, allowing them to attack and destroy increasing numbers of invading bacteria or other tissue-destroying agents.

Killing by cytotoxic T cells

- **Virus-infected cells**
- **Cancer cells**
- **Transplanted organs and tissues**



- The cytotoxic T cell is a direct-attack cell that is capable of killing microorganisms and, at times, even some of the body's own cells. For this reason, these cells are called killer cells. The receptor proteins on the surfaces of the cytotoxic cells cause them to bind tightly to the organisms or cells that contain the appropriate binding-specific antigen.
- After binding, the cytotoxic T cell secretes hole-forming proteins, called perforins, that literally punch round holes in the membrane of the attacked cell. Then fluid flows rapidly into the cell from the interstitial space.
- Some of the cytotoxic T cells are especially lethal to tissue cells that have been invaded by viruses, also play an important role in destroying cancer cells, transplanted organs -grafts-, or other types of cells that are foreign to the person's own body.

Immunologic Tolerance

- **Host defense employs powerful destructive mechanisms**
- **These must be directed at pathogens while protecting host tissues from damage**
- **“Tolerance” in acquired immunity is achieved mainly by clonal selection of T cells in the thymus and B cells in the bone marrow**
  - **clones that bind host antigens with high affinity are induced to undergo apoptosis, and are deleted**

- Suppressor T Cells :We have less informations about the suppressor T cells than others types, but they are capable of suppressing the functions of both cytotoxic and T-helper cells. These suppressor functions are believed to prevent the cytotoxic cells from causing excessive immune reactions that might be damaging to the body’s own tissues
- So tolerance means that immune cells don't fight our own tissues
- Immunological tolerance, is the process by which immune cells are made unresponsive to self-antigens to prevent damage to healthy tissues.

Failure of tolerance produces autoimmunity

- **Rheumatic feverin** which the body becomes immunized against tissues in the joints and heart **(cross-reactivity with streptococcal antigens)**
- **Post-streptococcal glomerulonephritis** in which the person becomes immunized against the basement membranes of glomeruli
- **Myasthenia gravis** in which immunity develops against the acetylcholine receptor proteins of the neuromuscular junction, causing paralysis **(antibodies to acetylcholine receptors)**
- **Systemic lupus erythematosis** in which the person becomes immunized against many different body tissues at the same time, a disease that causes extensive damage and even death when SLE is severe **(auto-immunity to multiple tissues)**

- Sometimes cross reactivity occurs between generated immunoglobulins and self antigens and causes autoimmune disease

Immunization

- Injecting killed organisms or their products…that are no longer capable of causing disease but that still have some of their chemical antigens.
  - typhoid, whooping cough, diphtheria, tetanus toxoid
- Infection with attenuated organisms…
  - Smallpox, yellow fever, polio, measles, herpes zoster, other viral diseases
- Passive immunity…the person’s own body doesn't generate antibodies, we give him already made immunoglobulins to protect him
  - Infusing antibody or activated T cells from an immune individual (antibodies last 2-3 weeks)

Allergy and hypersensitivity

- **T cell mediated (delayed)…**is caused by activated T cells and not by antibodies.
  - **poison ivy, nickel allergies**
  - **usually cutaneous; can occur in lungs with airborne antigens**

- **IgE mediated (immediate)…**is characterized by the presence of large quantities of IgE antibodies in the blood When an allergen enters the body, an allergen-antigen reaction takes place and a subsequent allergic reaction occurs. Some complications eventually leading to diseases such as urticaria on skin or asthma in respiratory system
  - **typical allergies**
  - **a single mast cell / basophil can bind 500,000 IgE molecules**

Mast cell / basophil degranulation

- **Histamine**
- **Proteases**
- **Leukotrienes**
- **Eosinophil and neutrophil chemotactic factors**
- **Heparin**
- **Platelet activating factor**

Allergic manifestations

- **Anaphylaxis**
  - **systemic, potentially fatal**
  - **widespread vasodilatation**
  - **↑↑ capillary permeability, volume loss**
  - **leukotrienes → bronchospasm and wheezing**

    <u>Treatment</u>: epinephrine and antihistamines

- **Urticaria**
  - **localized vasodilatation and red flare**
  - **Increased permeability and swelling (“hives”)**

    <u>Treatment</u>: antihistamines

Allergic manifestations (cont'd)

- **Hay fever**
  - **histamine mediated**
  - **vascular dilatation in the nasal passages and sinuses (and eyes)**
  - **leakage of fluid**
  - **sneezing**

    Treatment: Anti-histamines, local corticosteroids

- **Asthma**
  - **mediated largely by leukotrienes**
  - **sustained bronchospasm**

    Treatment: β agonists, inhaled steroids, leukotriene receptor blockers; treat upper airway component

UNIT VI
Chapter 36:

Blood Types; Transfusion; Tissue and Organ Transplantation

Ebaa M Alzayadneh, PhD Associate Professor of Physiology

Early transfusions

. **WHY TO STUDY THE BASIC PRINCIPLES OF BLOOD TRANSFUSION?**

* Long time ago when the science was not as revealed as now , Physicians used to transfuse blood without the knowledge of the immune system and antigens. So they noticed that blood transfusion may cause severe reactions that may be lethal. However, sometimes it's life saving.

* After knowing the science behind that, they discovered that all our cells, including the RBCs, have several antigens that can elicit an immune response if they were foreign to the acceptor of the transfused blood and this transfusion can lead to the severe and lethal reactions that cause death .

- **Red cell agglutination and lysis ,** Without the knowledge of blood groups, red blood cells from the donor would sometimes clump (agglutinate) and break down (lyse) in the recipient's body, leading to dangerous reactions
- **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** like those in the ABO and Rh systems, were eventually identified ,along with **many rare ones**

The ABO System

- **Red blood cell surface antigens: glycolipids or glycoproteins**
- **Present on all cells in the body, not just blood cells**
- **Agglutinogens: surface antigens (A,B)**
  - **Genes: A, B, O (maternal, paternal alleles)**
    - **Genotypes: OO, OA, OB, AA, BB, AB (6 probabilities)**

      The blood types of those genotypes respectively: O , A , B , A , B , AB

      The only way to get (O blood type) is to have 2 alleles of O in your genotype
- **Agglutinins (immunoglobulins): anti-A, anti-B**
- **Occurance :** (the prevalence of blood groups among the population)

O: 47%
A: 41%
B: 9%
AB: 3%

- We have two main antigens related to the ABO system , **A** antigen and **B** antigen .
- We have **three** genes responsible for the inheritance of these antigens , **A B O genes .**
- These antigens are not only present on the RBCs , but on the surface of **all** cells.
- most of the blood transfusions do not cause severe reactions unless there is a **mismatch** in the blood types , that's why we should learn about the ABO system.
- Gene **A** will lead to the production of antigen **A** and Gene **B** will lead to the production of antigen **B**
- gene **O** is like a non-functional gene that does not produce neither **A** or **B** antigens.
- Each individual has 2 alleles , one from each parent , these 2 alleles are responsible for the genotype which can be one of six probabilities of genotypes, depending on the parents genotypes.

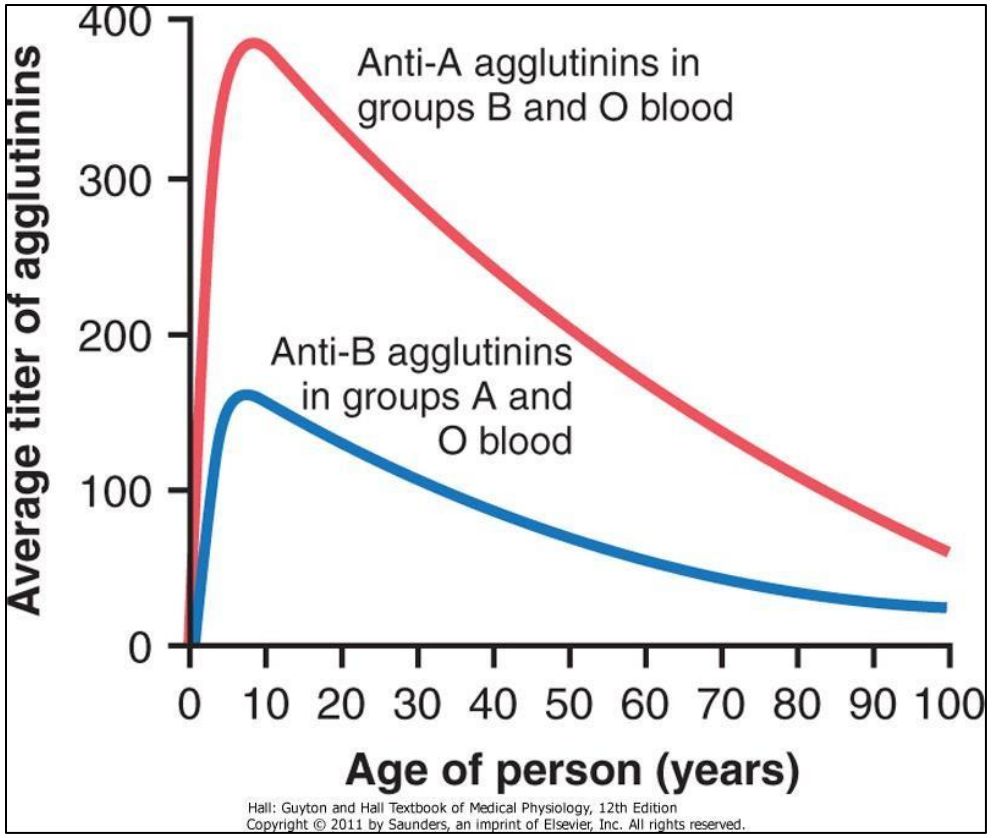
- Once you are born you will develop immunity against antigens that you don't have and this occurs **without** being exposed to other blood groups. For example:
- if your blood type is **B** this means that you have **B** antigens so you will develop immunity against antigen **A** which is foreign to you.
- if your blood type is **A** this means that you have **A** antigens so you will develop immunity against antigen **B** which is foreign to you.
- if your blood type is **O** then you will develop immunity against antigen **A** and Antigen **B** which are foreign to you.
- If your blood type is **AB** you have both antigens, so you won't develop antibodies against any of them.
-
- Typically, antibody titers are elevated following prior exposure rather than from an initial response. This raises the question: **how do we develop antibodies against foreign blood type antigens without being exposed to transfused blood**? As shown in the figure, the antibody titer is high, and here is the question .
- One theory that addresses this question suggests that before a baby is born, antigens on red blood cells (RBCs) have not yet fully developed. As these antigens begin to form and the blood type becomes established, the immune system develops tolerance to its own antigens. This self-tolerance prevents the immune system from attacking the body's own cells. However, **foreign antigens are introduced to the immune system either by bacteria or ingested food, and then immunity will be developed against them.**

- The term **Agglutinogens** means **antigens**.
- The term **Agglutinins** means **antibodies**.
- Because the antigen-antibody reaction will cause agglutination in the blood.

Agglutinins

- The titer peaks at the age of 10 then it declines with age.

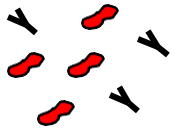
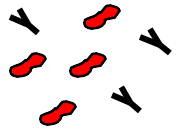
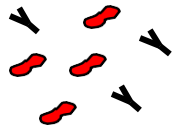
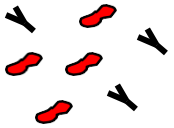
- **Antibodies** against antigens that are not present in the blood of the recipient **, mostly IgM and IgG**
- **Begin developing age 2-8 months, peak ~age 10 years**
- **Response to A and B antigens in food , bacteria; initial exposures are environmental**



Blood Groups

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	------

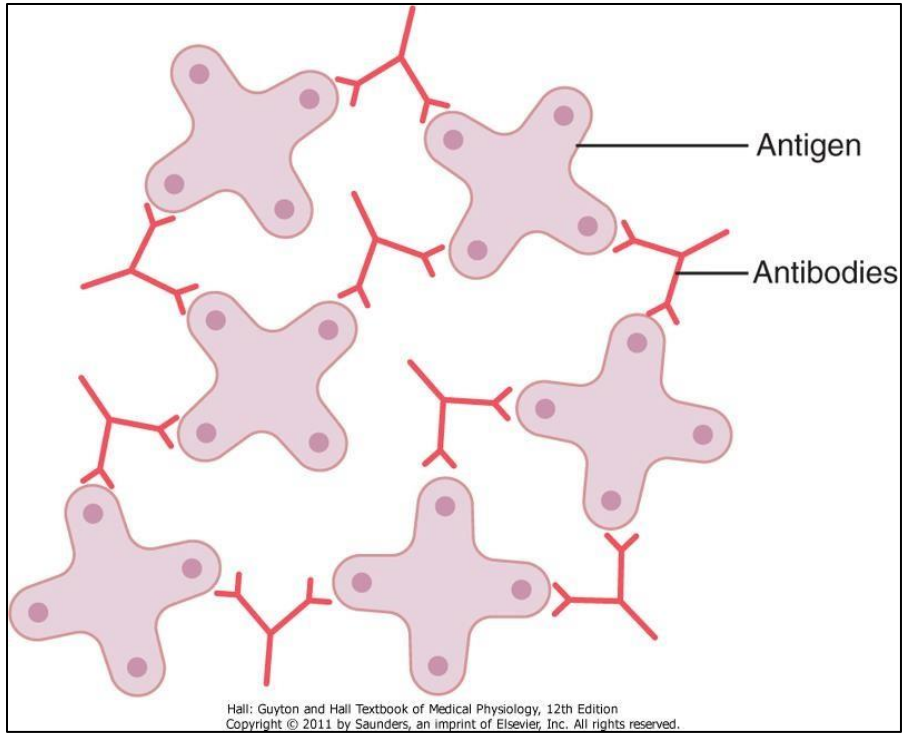
Blood Typing

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

- How to do blood typing?
- Traditionally, they would have a bottle containing **antibody A serum and another with antibody B serum**. They would mix the blood sample with each bottle , and if at reaction occurred in one of them, it indicated the presence of the corresponding antigen.
- For example, if a reaction occurs in the Anti A serum bottle , this means that antigen A is present in the blood, so the blood type may be A or AB depending on the rxn result in the other bottle .

Transfusion reactions

- **Red cells agglutinate**
- **Plug small vessels**
- **Physical distortion, phagocytic attack >> hemolysis**
- **In some cases, immediate, complement dependent hemolysis, depending on Ig type.. IgM “ hemolysin “ .**



- Immediate, complement-dependent hemolysis refers to a type of hemolysis (the destruction of red blood cells) that occurs rapidly after the binding of antibodies to antigens on the surface of red blood cells. This process typically involves IgM antibodies, which are highly effective at activating the complement system—a group of proteins in the blood that assist in the immune response. If the level of IgM is high, there will be very fast hemolysis

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 (European ancestry), 100% Africans) and particularly antigenic**
- **C and E can also cause transfusion reactions, generally milder**

- each individual will have only one C, one D, one E, either capital or small and anyone that have the **capital D, Then he is RH positive.**
- If a person is Rh positive, there is no concern about receiving blood transfusions, regardless of whether the donor blood is positive or negative. However, if the person is Rh negative, it's crucial to avoid transfusing Rh positive blood. If an **Rh negative individual receives Rh positive blood for the first time, it typically won't cause an immediate reaction, but it can lead to complications in future transfusions.**
- This doesn't mean that other ones cannot elicit an immune reaction, they can if you have antibodies against them but the rxn maybe minor and not noticeable. However the most serious reaction is developed from D antigen

Anti-Rh Transfusion Reactions

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

  -First time, delayed mild transfusion reaction, but you will be sensitized against it .

  -sensitization to further Rh+ transfusion

  - **agglutinins peak after 2- 4 months, to get the severe rxn, you need to be exposed 2-3 times .**

- **50% of Rh- are sensitized by 1st exposure**
  - **20% after a second exposure**
  - **30% are non-responders , They will not develop immune reaction even after the second exposure.**
- **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

- The Rh system of immunity differs from the ABO blood group system, where **antibodies are already present and can trigger an immune reaction upon first exposure. In contrast, a person with Rh-negative blood typically does not have a significant reaction during initial exposure to Rh-positive blood. Instead, antibodies may develop over several months,** after subsequent exposures, such as during a second or third exposure to Rh-positive blood.

Hemolytic Disease of the Newborn (Erythroblastosis fetalis)

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

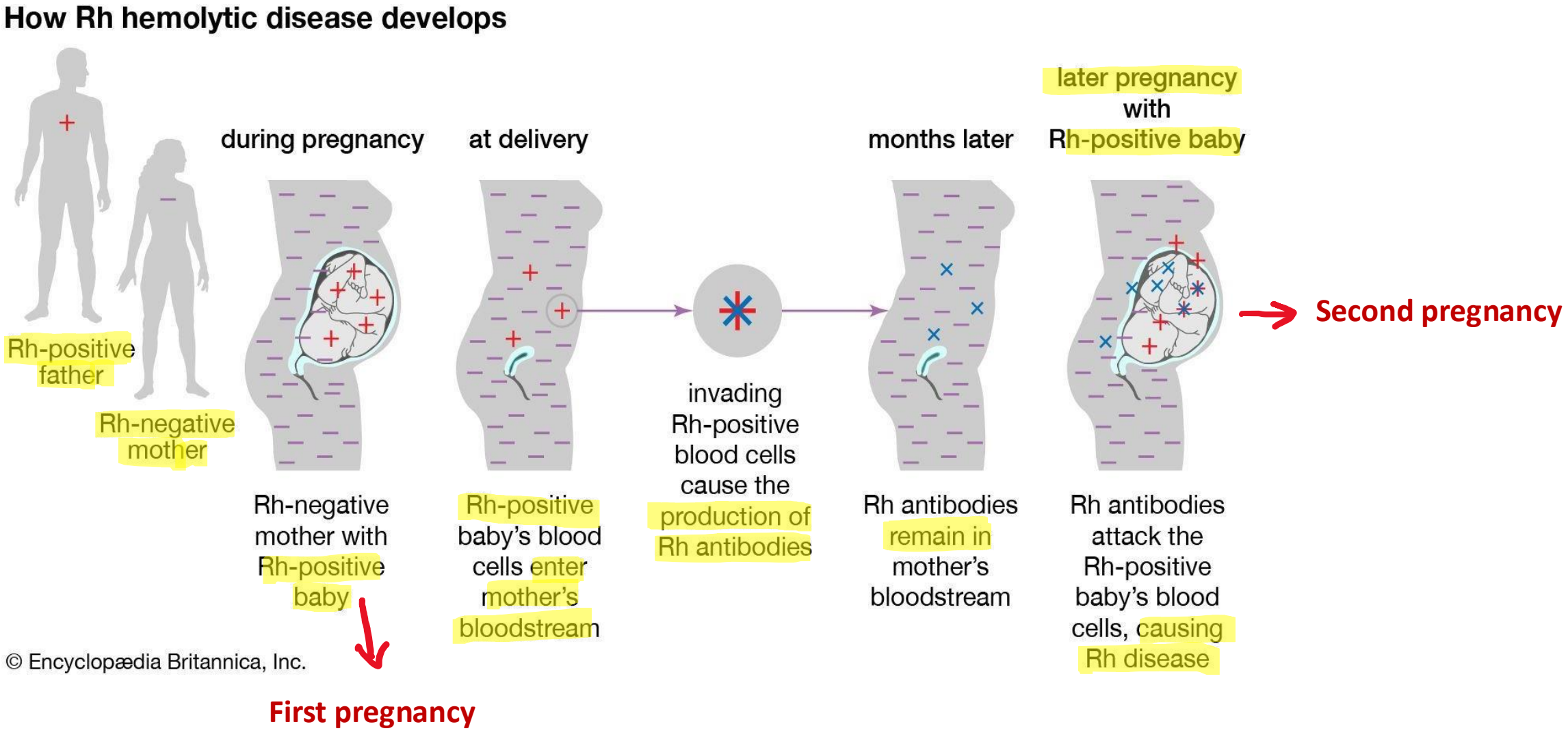
  - **Unusual:**
    - **Most anti-A is IgM, does not cross placenta**
    - **ABO antigens not well developed in fetus**

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

  - **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)**

- When we have **Rh-positive father and an Rh-negative mother** there is a probability that the babyis Rh-positive , there typically won't be any problems in the **first pregnancy** because the mother has not been exposed to Rh-positive blood before and therefore **does not have antibodies against it.** However, during childbirth, the **baby's Rh-positive blood can mix with the mother's blood. As a result, the mother may become sensitized and develop antibodies against Rh-positive blood.** In a subsequent pregnancy with another Rh-positive baby, these antibodies **can cross the placenta and attack the baby's red blood cells, potentially leading to complications. This condition is known as Rh incompatibility** and can result in hemolytic disease of the newborn. Hemoglobin accumulates in the tissues during a condition known as erythroblastosis fetalis, which is characterized by mental retardation, severe anemia, and jaundice.

Hemolytic Disease of the Newborn (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")**

- If no medical intervention occurred during the first pregnancy, certain complications may arise in future pregnancies. To prevent this, the mother is typically screened to determine if she is Rh-negative and if there is a risk of having an Rh-positive child. **If this is the case, she will receive immunoglobulin against Rh antigens just before and after delivery. This immunoglobulin will protect the baby's red blood cells (RBCs) and prevent the mother from developing immunity against them,as these given antibodies will cover the fetus RBCs (neutralizing) and prevent them from being attacked by the mama's Abs ^^** . For every subsequent pregnancy with a Rh-positive child, the mother should receive this antibody treatment to prevent her from producing any antibodies against the Rh-positive blood cells.

How to treate this condition if it has already happened ?, the procedure involves removing or replacing the baby's blood through transfusion during pregnancy and for several months after delivery, until the maternal antibodies are eliminated. This is a complex and challenging procedure."

Clinical Perspective

Hemolytic Disease of the Newborn: Treatment

- **Repetitive removal of Rh-positive blood, replacement with Rh negative (400 ml exchange over 90 minutes)**

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

- **Maternal antibodies disappear over 1-2 months so newborn's Rh-positive cells cease to be a target**

Clinical Perspective

Hemolytic Disease of the Newborn: Prevention

- **Provide exogenous anti-D antibodies to the mother in late pregnancy and just after birth**

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

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

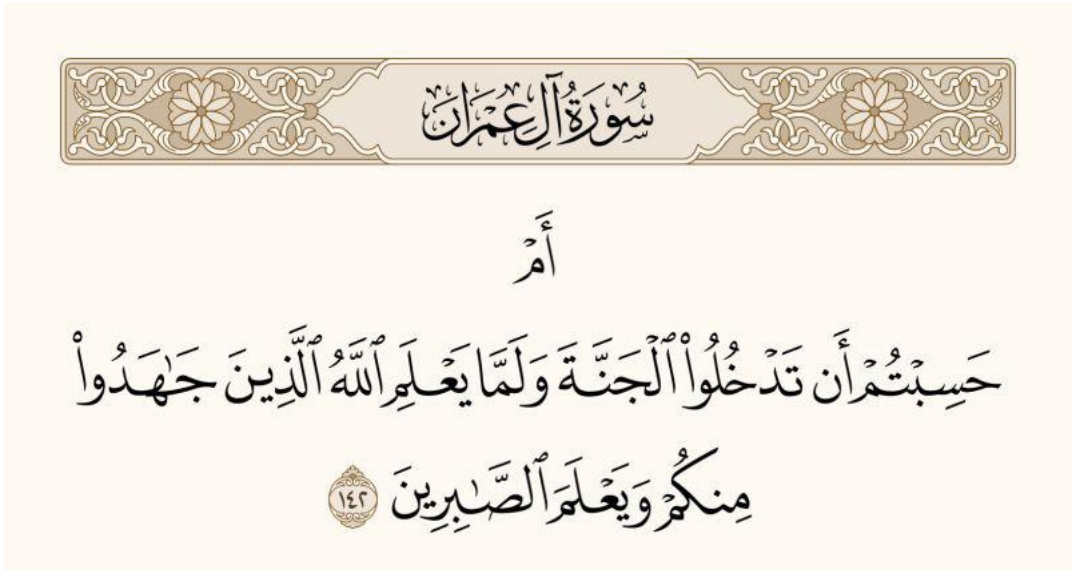
Transfusion Reactions

- 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

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



اللهمّ لا تحقّق لأعداء الدين في أرض غزّةَ غاية
ولا ترفَع لهُم فيها راية ، و اجعلهم لمن خلفَهم عبرةً و آية
اللهمّ ثبّت أقدام الصامدين المرابطين على الثّغور
زِدهُم قوّةً و عتادًا و مدادًا من عندك ..
نستغيثُ بكَ يا الله
يا من أنت على كلّ شيءٍ قادر
و فوق كلِّ متكبّرٍ ظالمٍ .. قاهِر

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	Slides (39-42) were added		Slides (39-42) were added
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!