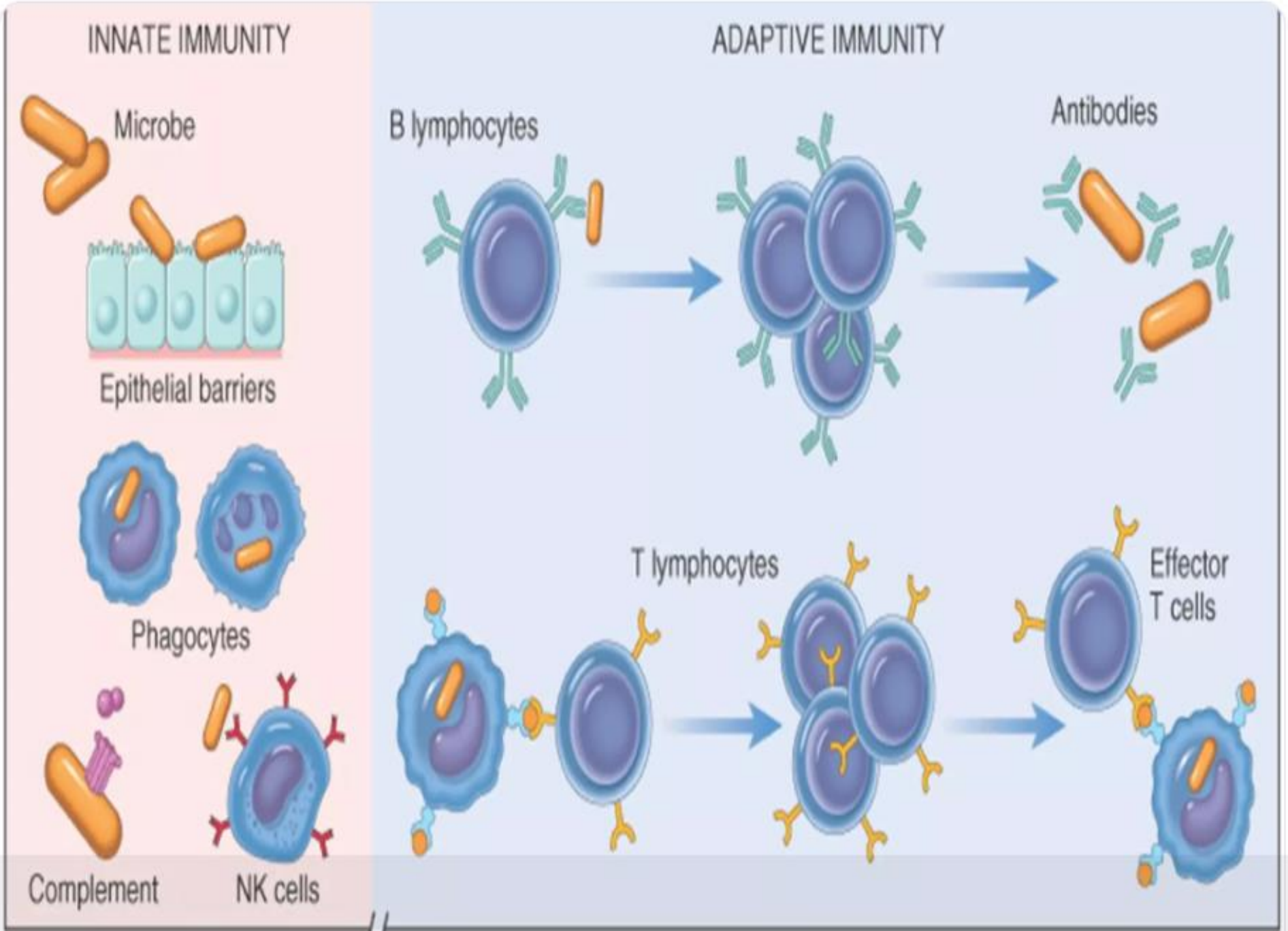
Immune-deficiency diseases

Dr. Hind Al-Sarayrah, M.D


INNATE IMMUNITY
ADAPTIVE IMMUNITY
Microbe
B lymphocytes
Antibodies
Epithelial barriers
Phagocytes
T lymphocytes
Effector
T cells
Complement
NK cells

What is immune deficiency

- A state in which the ability of immune system is compromised or entirely absent to fight against infectious diseases and cancer.
- Signs that causes suspicion for ID: Recurrent infections, infections caused by rare microorganisms, and Opportunistic infections.
- Patients with immunodeficiencies are also susceptible to certain types of cancer. Many of these cancers appear to be caused by oncogenic viruses, such as the Epstein-Barr virus.

The 10 warning signs of immune deficiency

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

The 4 Arms of Immune System & Their command

Humoral (B cell)

1-Encapsulated organisms (S.pneumo; H. flu)

2-Giardia

Cellular (T cell)

1-Viruses

2Fungi(candida,aspergillus)

3-Protozoa (Pneumocystis carinii, toxoplasma)

4-Bacteria (mycobacterium)

Phagocytic

1-Fungi (aspergillus)

2-Bacteria (low low-virulence organisms

Complement

1-Bacteria (encapsulated organisms

Types of ID

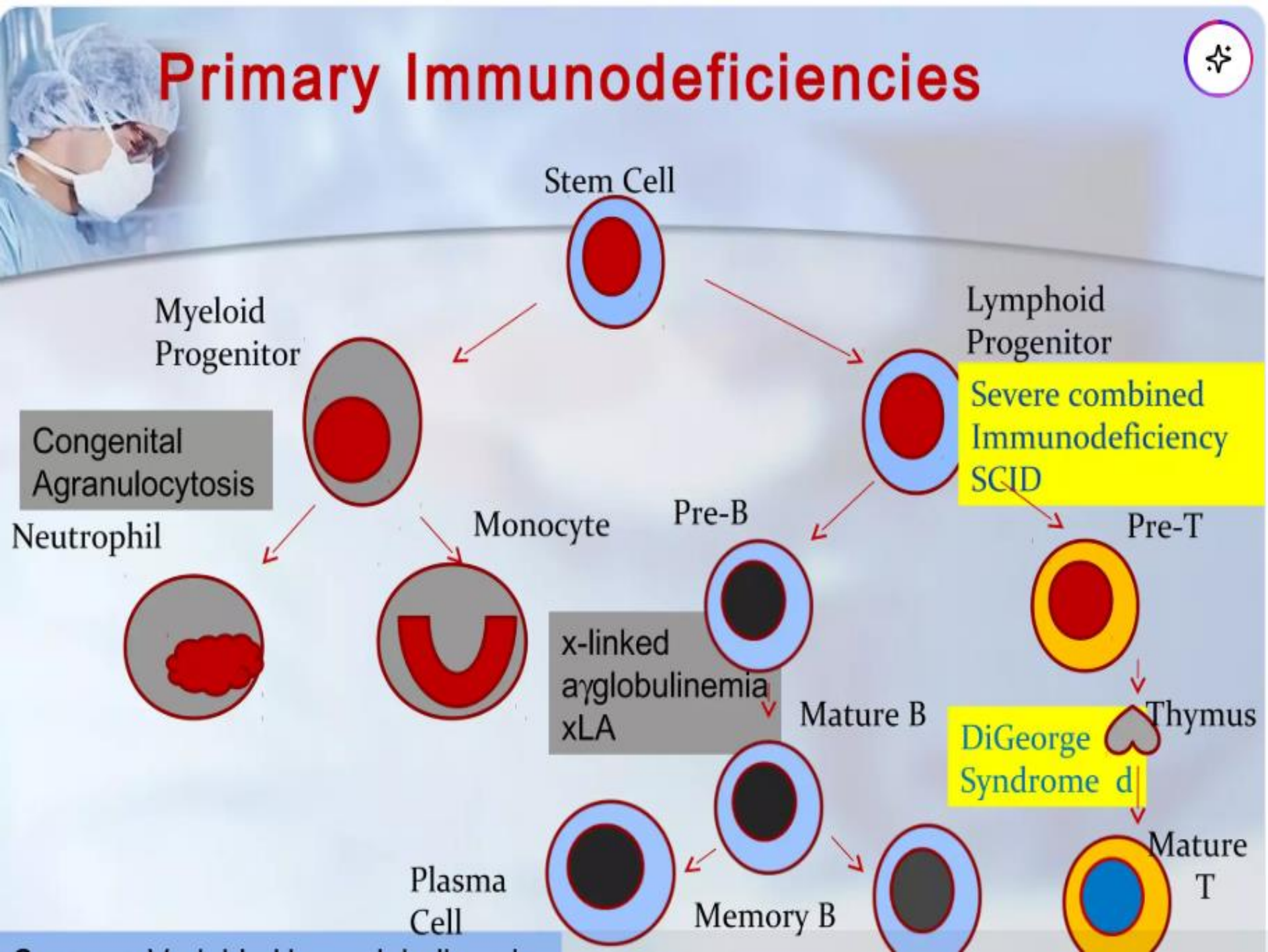
1. Congenital or primary *Immunodeficiency (PID):*

- These disorders are caused by a genetic abnormality.
- Mild to severe.
- Most PIDs are diagnosed in childhood. The rest are not diagnosed until adolescence or early adulthood

- **Types of primary ID:**

1. B cell (antibody) deficiencies
2. T cell deficiencies
3. Combined B and T cells deficiencies
4. phagocytes deficiencies
5. Complement system deficiencies

Primary Immunodeficiencies



Treatment of PID

- Managing infections: treatment and prevention
- Immunoglobulin therapy.
- Interferon-gamma therapy.
- Growth factors for immune cells
- Bone marrow transplantation.

2. Acquired or secondary:

- More common than primary ID.
- Develop as a consequence of:

1. Malnutrition and extremes of age.
2. Disseminated cancer.
3. Treatment with immunosuppressive drugs, chemotherapy and radiotherapy.
4. Infection: such as Human Immunodeficiency Virus (HIV) and chronic TB.
5. Severe burn
6. Chronic diseases: such as diabetes

❖ Disseminated cancer:

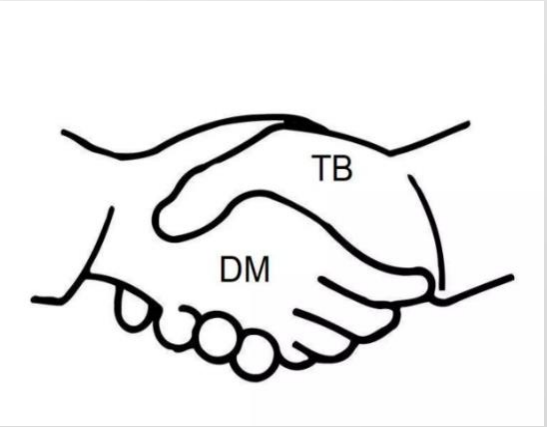
- Cancer cells produce mediators that reduce the proliferative responses of T or B cells or both, and macrophages. Bone Marrow metastases also reduce production of immune cells. Also radio and chemotherapy contribute to the ID.

❖ Extremes of age:

- **Prematurity**: infants rely on maternally transferred IgG antibodies for immune protection during the first 6 months after birth.
- Breastfeeding provides extra gut protection, especially through IgA-rich colostrum in the first days.
- **Elderly**: there is a decrease in the production and function of T cells and B cells.

❖ **Diabetes**:

- Macrophage and Neutrophil Function Reduction (These cells are responsible for engulfing and destroying pathogens).
- Elevated glucose levels can alter the function of immune cells, including T cells and B cells, impairing their ability to recognize and respond to pathogens.
- Increased Susceptibility to Specific Infections: Fungal (candida). Bacteria (Mycobacterium TB)



AIDS (Acquired Immune Deficiency Syndrome)

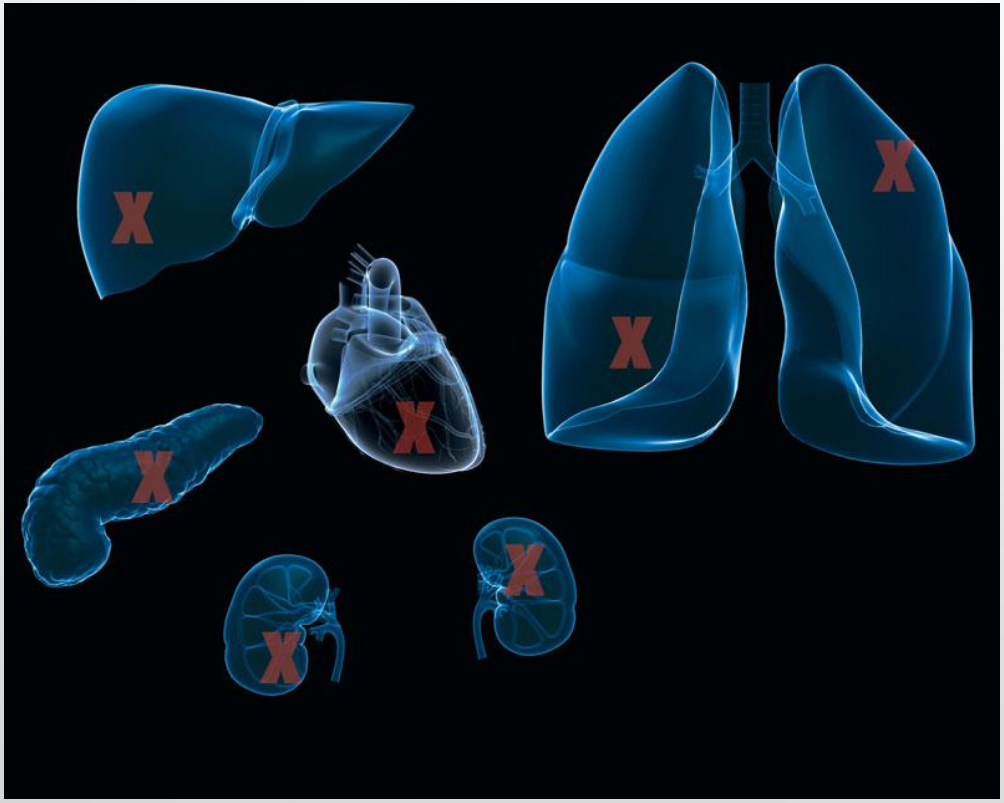
- HIV is a retrovirus that primarily infects CD4+ T cells , macrophages and dendritic cells.
- It destroys CD4+ T cells
- Once the number of $CD4^+$ T cells per microliter of blood drops below 200, cellular immunity is lost and AIDS start.
- In the absence of therapy, the median time of progression from HIV infection to AIDS is nine to ten years, and the median survival time after developing AIDS is only 1.5 year.

Phase of disease	Clinical feature
Acute HIV disease	Fever, headaches, sore throat with pharyngitis, generalized lymphadenopathy, rashes
Clinical latency period	Declining *blood* $CD4^+$ T cell amount
AIDS	**Opportunistic infections** Protozoa (*Pneumocystis carinii, Cryptosporidium*) Bacteria (*Toxoplasma, Mycobacterium avium, Nocardia, Salmonella*) Fungi (*Candida, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*) Viruses (cytomegalovirus, herpes simplex, varicella-zoster) **Tumors** Lymphomas (including EBV-associated B cell lymphomas) Kaposi's sarcoma Cervical carcinoma **Encephalopathy** **Wasting syndrome**

Transmission of HIV

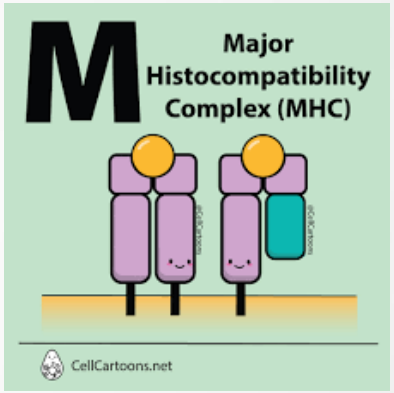
- Sexual transmission
- Blood products
- Mother to fetus

Transplant Rejection



- Rejection occurs when the recipient's immune system identifies the graft as foreign and attacks it.

✓ Major antigens that cause rejection:



- 1. MHC (Major Histocompatibility Complex) type.
- 2. Blood group.

✓ Site of transplant play a role:

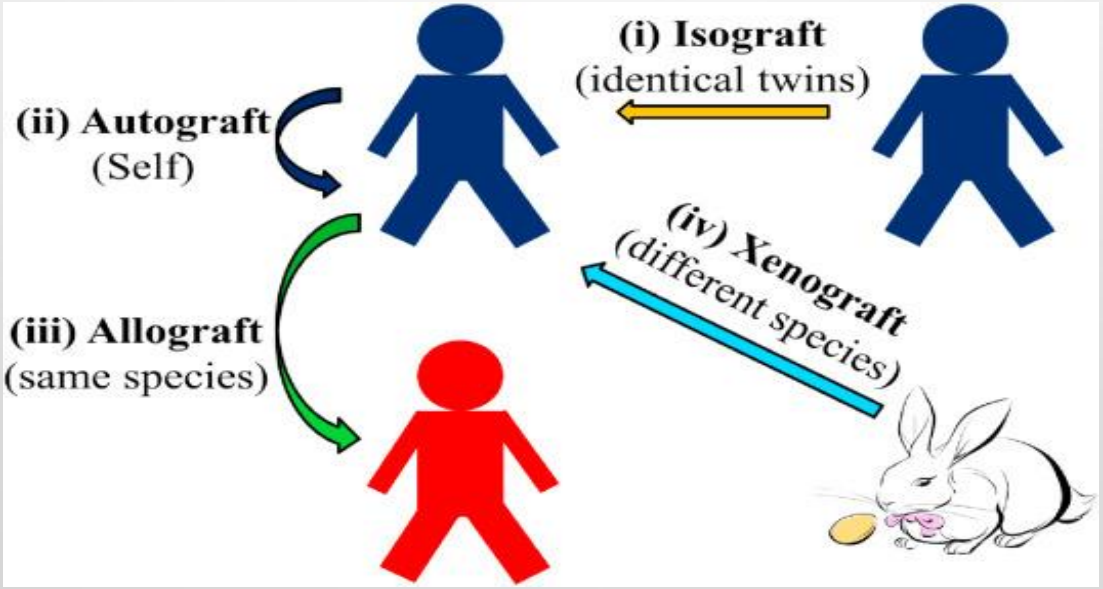
- Eye and the brain, are immunologically privileged (ie, they have minimal or no immune system cells and can tolerate even mismatched grafts).
- Skin grafts are not initially vascularized and so do not manifest rejection until the blood supply develops.
- The heart, kidneys, and liver are highly vascular organs and lead to a vigorous cell mediated response in the host.

- The number and variety of MHC antigens tell us that probably no two humans (except for identical twins) exist on earth with perfectly compatible tissues and, so successful transplantation of grafts requires some degree of immunosuppression to avoid graft rejection.

- Bone-marrow transplants effectively bring their own immune system with them, often rejecting the new host, instead of the other way around, in a reaction known as **graft-versus-host disease**.

Types of graft

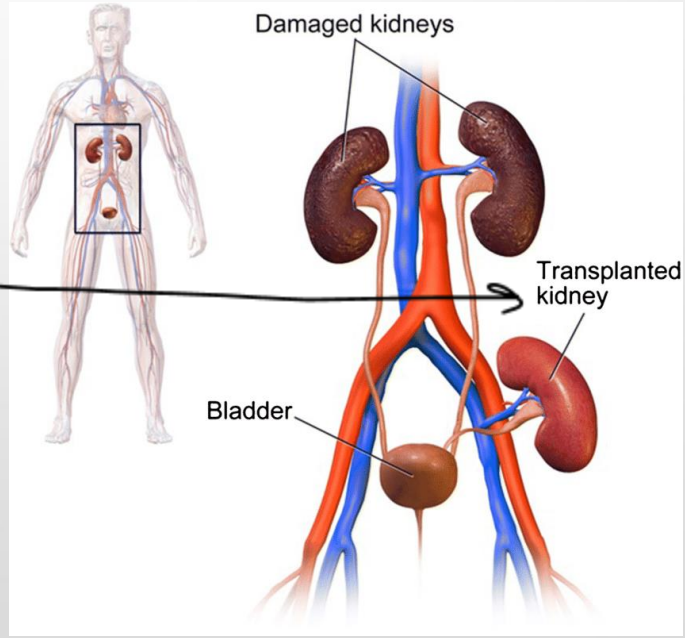
- **Autograft:** is self-tissue transferred from one body site to another in the same individual.
- **Isograft:** is tissue transferred between genetically identical individuals.
- **Allograft:** is tissue transferred between genetically different members of the same species.
- **Xenograft:** is tissue transferred between different species



Types of transplantation

- **Orthotopic:** graft placed into the same anatomic site.
- **Heterotopic:** graft placed in different site.
- **Transfusion:** for blood

Heterotopic transplant

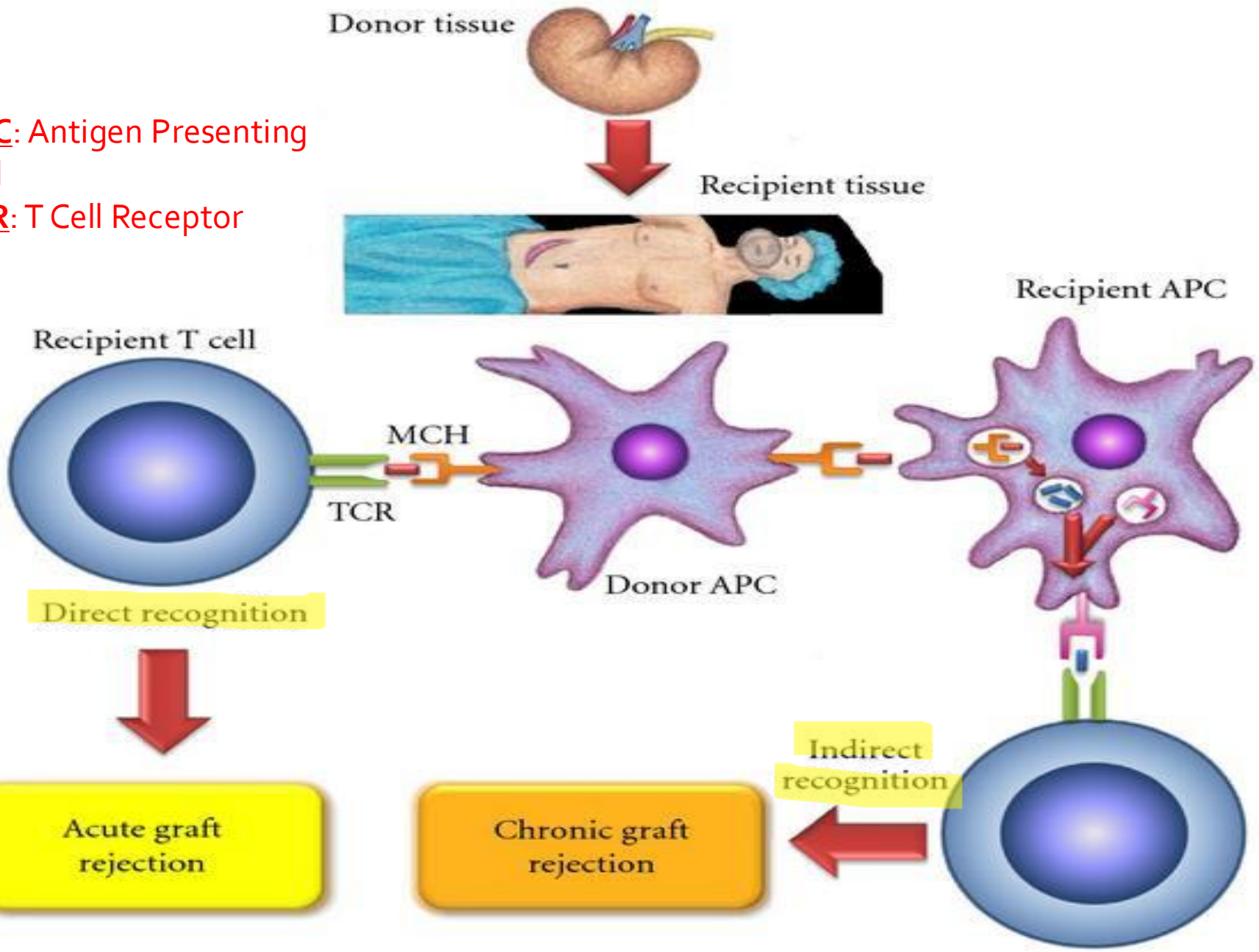


Molecular mechanisms of graft rejection

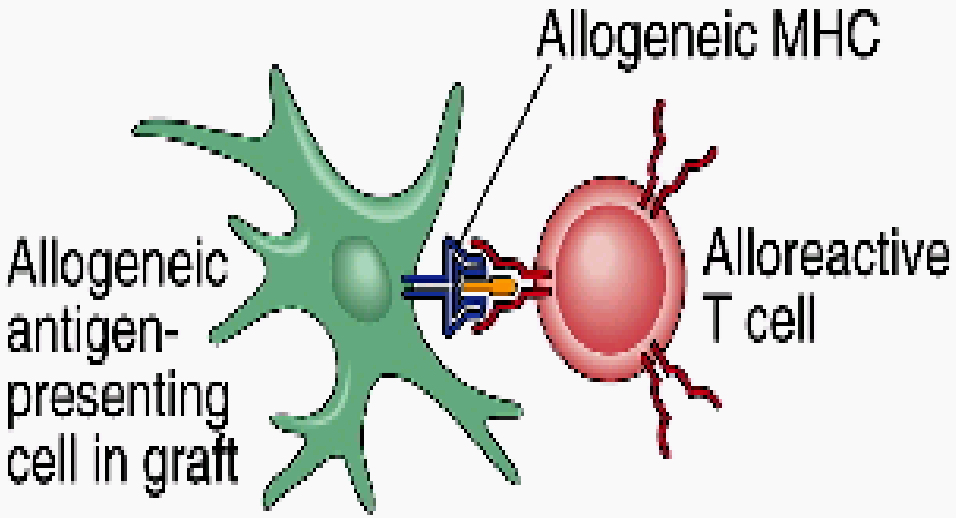
- **Direct:** T cells of a recipient graft recognize intact, unprocessed MHC molecules on the graft APC / acute rejection / and short lived.
- **Indirect:** recipient T cell recognize donor MHC processed by recipient APC and presented on recipient MHC / in chronic or late rejection / Last long.

APC: Antigen Presenting Cell

TCR: T Cell Receptor

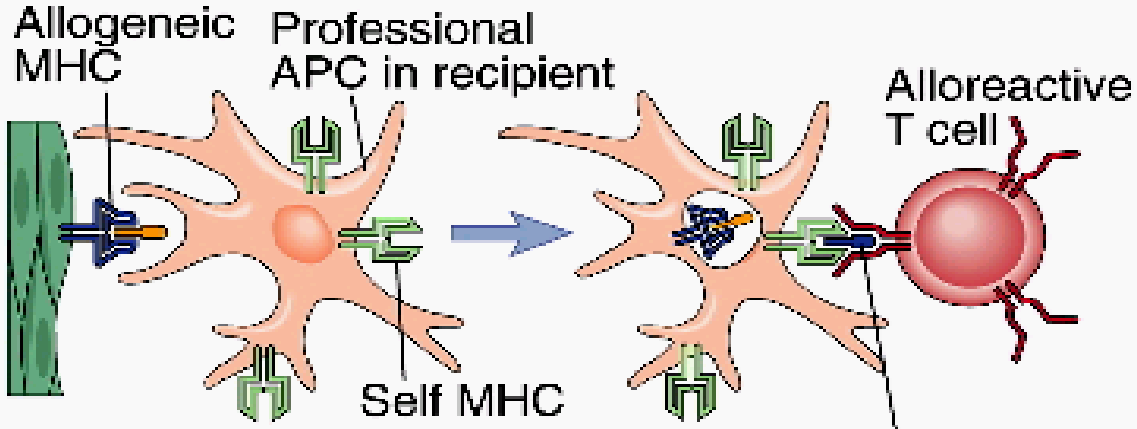


A Direct allorecognition



T cell recognizes unprocessed allogeneic MHC molecule on graft APC

B Indirect alloantigen presentation



Uptake and processing of allogeneic MHC molecules by recipient APC

Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule

Clinical stages of Allograft Rejection

Rejection type	Time to onset	Primary pathogenesis	Histological features	Clinical implication
Hyperacute	Minutes to hours (immediate)	Pre-existing host antibodies to donor blood group (ABO) leading to complement activation	Intravascular thrombosis, ischemia, and necrosis of the graft.	High fever, shock, and DIC, Graft must be immediately removed by plasmapheresis
Acute (most common)	Days to months	**T cell-mediated** immune response (CD_4+ and CD8+ T cells) against donor (MHC/HLA) molecules; can also be antibody-mediated.	inflammation, and potential injury to blood vessels (vasculitis).	symptoms are often treatable with increased immunosuppression
Chronic	Months to years (very slow and progressive)	both humoral and cellular responses, leading to long-term low-grade immunological injury.	Fibrosis of the transplanted tissue and progressive narrowing/occlusion of blood vessels (accelerated arteriosclerosis)	Often irreversible and poorly amenable to current therapies, potentially requiring re-transplantation.

Pretransfusion Compatibility Testing

- Evaluation of the donor includes
  - Testing of the donor unit for infectious diseases
  - ABO/Rh typing.
- Evaluation of the recipient includes
  - ABO/ Rh typing
  - Antibody screen.
- Crossmatch Tests: testing of the recipient serum for the presence of preformed Abs against donor HLA/MHC or ABO antigen.

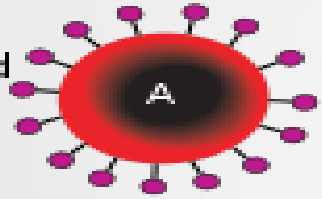
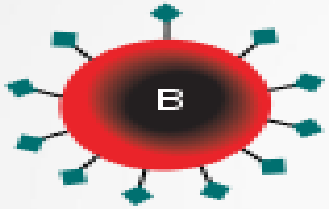
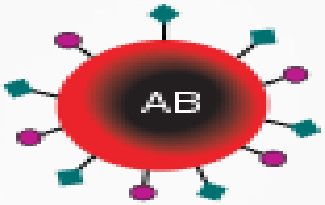
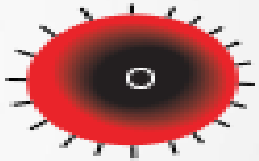
Bone Marrow Transplantation

- the transplantation of hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood.
- Used for Leukemia, Anemia and immunodeficiency.
- Recipient of a bone marrow transplant is immunologically suppressed before grafting, e. g; Leukemia patients are often treated with cyclo-phosphamide and total body irradiation to kill all cancerous cells.
- Because the donor bone marrow contains immunocompetent T cells, the graft may reject the host, causing graft versus host disease (GVHD).

Treatment of GVHD

- Injecting donor graft with mono-clonal antibodies to inhibit T cells.
- Increase immunosuppressive drugs to the recipient.

ABO blood groups

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies present	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens present	 A antigen	 B antigen	 A and B antigens	None

- **Rh status** is inherited from our parents, separately from our blood type. If you inherit the dominant Rhesus D antigen from one or both of your parents, then you are Rh-positive (85% of us). If you do not inherit the Rhesus D antigen from either parent, then you are Rh-negative (15% of us)

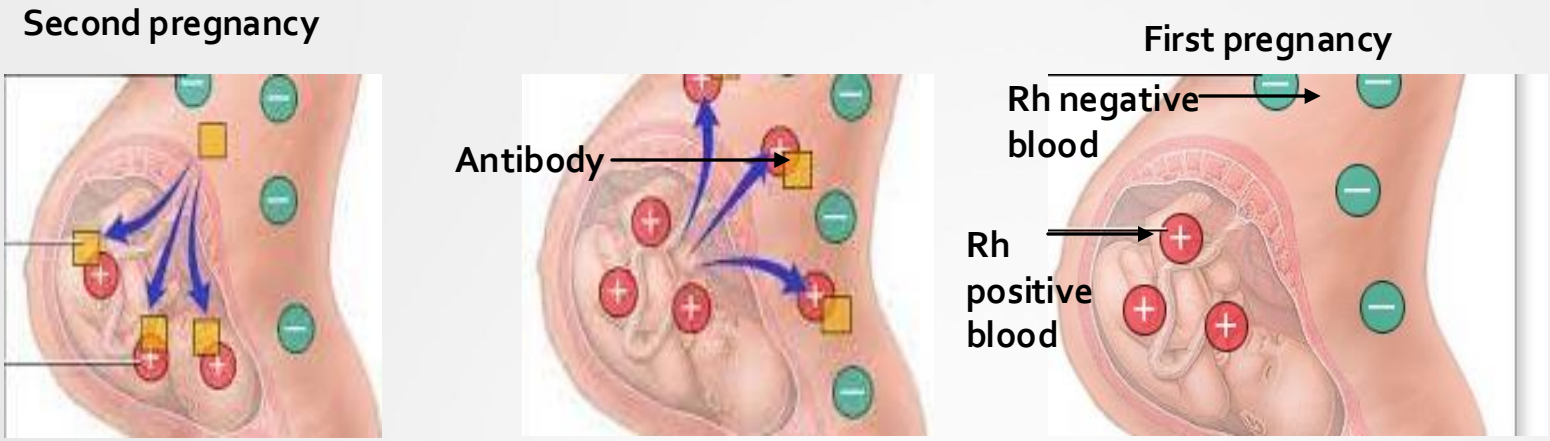
- O positive: 36% Most common
- A positive: 28%
- O negative: 14%
- A negative: 8%
- B positive: 8%
- B negative: 3%
- AB positive: 2%
- AB negative: 1% Least common

- O-negative is the universal blood type, meaning any other blood type may receive it.

Rh Antigen and Antibody

- Rh antibodies result from previous alloimmunization by ***previous pregnancy*** or ***transfusion.***

- Rh-negative mothers carrying an Rh-positive fetus can be sensitized by fetal red blood cells that enter the maternal circulation, usually during childbirth. Antibodies are generated in Rh-negative mothers. Subsequent pregnancies in which the fetus is Rh positive are at risk because the maternal anti-Rh D antibodies can cross the placenta and mediate the destruction of the fetal red blood cells. This causes anemia, dyspnea, jaundice and erythroblastosis fetalis (death).



- **How to prevent alloimmunization by Rh positive fetal blood RBCs:**
- By injection of **anti-D antibodies ,** these antibodies will attach to any Rh(D) positive red blood cells (RBCs) that have entered the Rh-negative mother's bloodstream, coating them and marking them for destruction by the spleen. This process saturates the Fc receptors on macrophages, preventing the mother's immune system from recognizing the foreign Rh(D) antigen and producing its own, potentially harmful antibodies.