Immunodeficiencies (IDs)

Faihaa hkima abou fkher
PhD in immunology
University of damascus – laboratory medecine

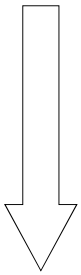
What is an Immunodeficiency?

Failing of one or more of the body's defensive mechanisms resulting in morbidity or mortality

Clinical features associated with IDs

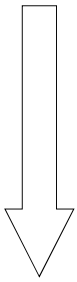
- ✓ **Chronic, recurrent infection**
- ✓ **Recurrent abscesses**
- ✓ **Unusual microbial agents**
- ✓ **Incomplete response to treatment**
- ✓ **Diarrhea (chronic)**
- ✓ **Growth failure**
- ✓ **Recurrent osteomyelitis,**
- ✓ **Telangiectasia, partial albinism**

Immunodeficiencies



Primary

(Congenital)



Secondary

(Aquired)

Secondary Immunodeficienies

- Infection (ex. AIDS)
- Renal failure, or protein losing enteropathy
- Cancers and cancer therapies (Leukaemia or lymphoma, Myeloma)
- Extremes of age
- Certain Drug Therapies
- Malnutrition

Immune Deficiency in HIV infection

- Memory CD4+ T cells are depleted from circulation
- CD4+ T cells (naive and memory)are lost from circulation.
- All CD4 cell populations are depleted from circulation and from lymphoid tissue sites.
- CD4+ T cells is used as a measure of immune competence“
- Lymphadenopathy

Immune Deficiency in HIV infection

❖ Failure of CD4+ lymphocytes to undergo cell division.

❖Diminished expression of IL-2.

❖In early HIV infection, CD8+ T-cell numbers increase. numbers of these cells do not fall until HIV disease progresses.

❖ CD8+ T cells fail to proliferate in response to activation in vitro

Immune Deficiency in HIV infection
B Lymphocytes and Antibody

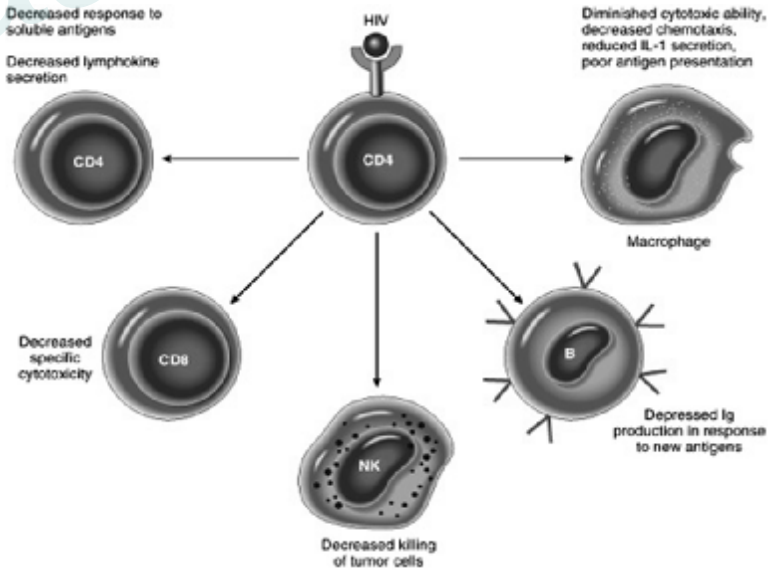
- Hyperactivation and hyporesponsiveness
- polyclonal hyperglobulinemia:a portion of which is directed against HIVAg
- bone marrow plasmacytosis
- heightened expression of activation molecules on circulating B
- Autoreactive antibodies in plasma: autoimmunelike disease
- increased risk of B-cell lymphomas in HIV-infected persons,
- diminished B-lymphocyte responsiveness to antigenic stimulation in vitro

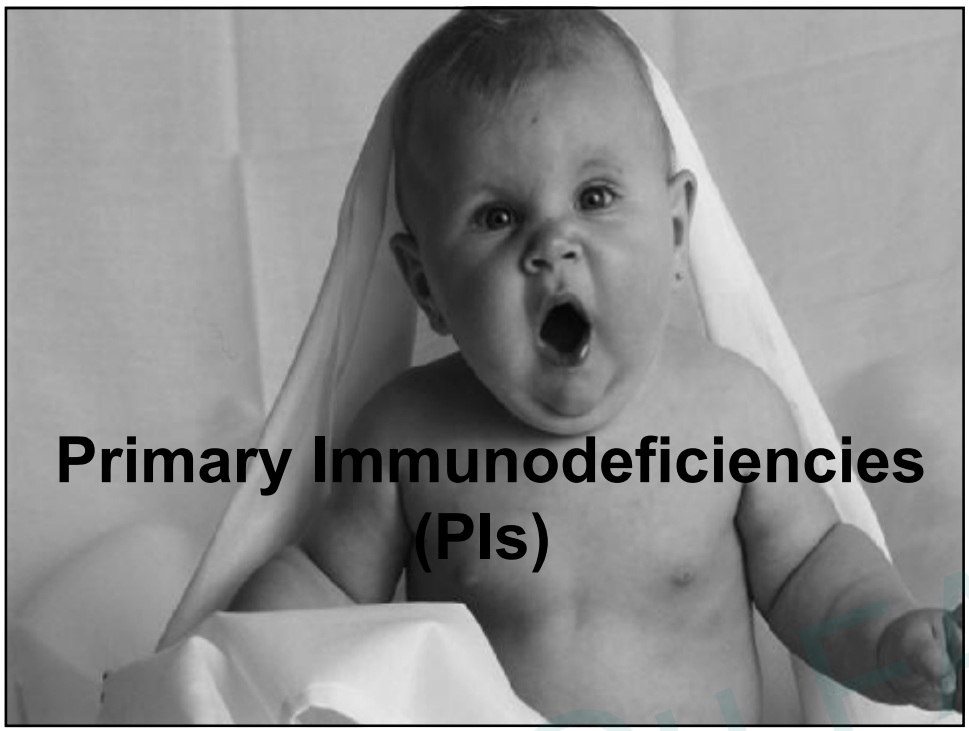
Pathogenesis of Immune Deficiency in HIV Infection

The characteristic depletion of CD4+ T lymphocytes in HIV disease appears to result from factors other than the direct cytopathic effect of HIV itself.

- ❖ Cellular destruction,
- ❖ diminished cellular production,
- ❖ cellular sequestration

Loss of CD4+T cells effects in HIV infection





Primary Immunodeficiencies (PIs)

- Innate immune responses
- Adaptive immune responses

Defects in the innate immune response

- ✓ **Phagocytic disorders**
- ✓ **Complement deficiencies**

Phagocytic disorders

- Leukocyte adhesion deficiency
- Chronic granulomatous disease
- Congenital Neutropenia
- Chediak- Higashi syndrome
- Defects in IL-12 / IFNγ pathway

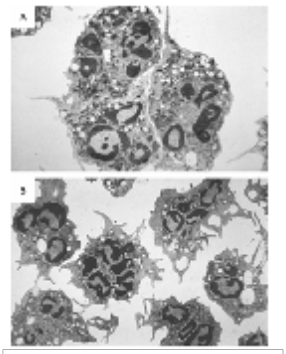
Leukocyte Adhesion Deficiency1 (LAD1)

- Recurrent infections of the mucosal surfaces (*Staph. Aureus, Aspergillus,Candida* species)
- Autosomal recessive mutations in **CD18, the common subunit of many β2 integrins**
- Neutrophils cannot leave the circulation and extravasate into sites of infection or injury
- Numbers of circulating neutrophils are almost twice those in normal individuals

Leukocyte Adhesion Deficiency (LAD1)

In vitro

Neutrophils are unable to aggregate or bind to endothelial cells.



In vivo

Serious periodontitis and tooth decay are common

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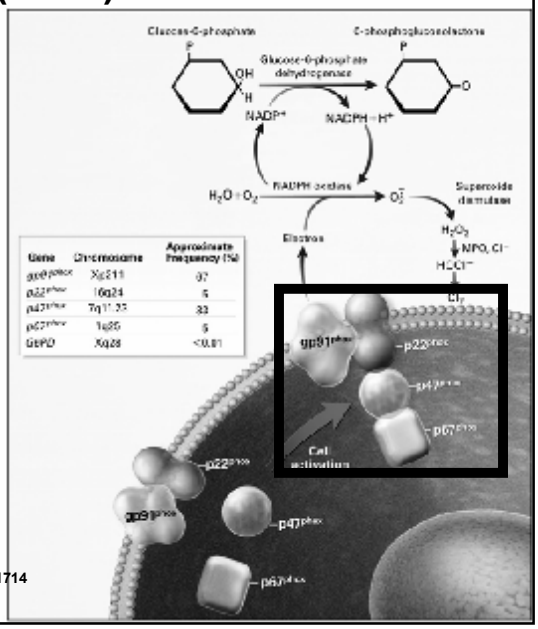
Chronic Granulomatous Disease (CGD)

X-linked CGD is the most common and most severe form (70%)
(gp91phox gene mutation)



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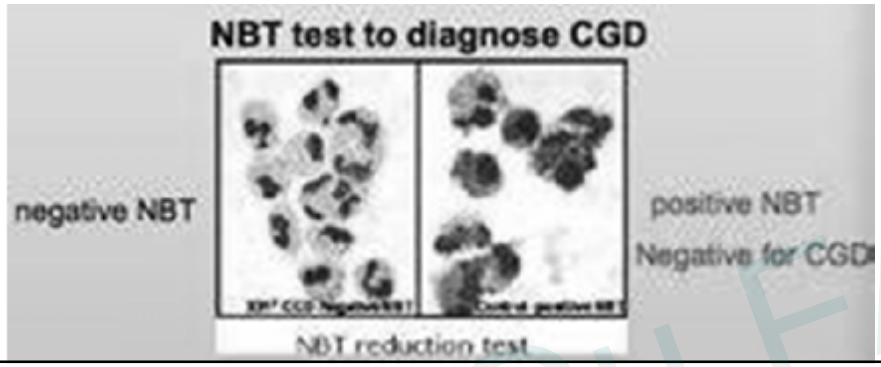
Nitroblue tetrazolium test

❖ is a blood test

❖ measures the ability of the immune system to convert the colorless nitroblue tetrazolium (NBT) to a deep blue.

❖ is performed as a screen for (CGD).

❖ an individual has CGD, the white cells in their blood will not turn blue when exposed to the NBT.



Phagocytic disorders

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Congenital Neutropenia

- **Severe congenital neutropenia**
- **Cyclic neutropenia**

- Regular, periodic oscillation in the number of peripheral neutrophils.
- Neutropenia every 21 days.
- May develop fever, stomatitis, pharyngitis, pneumonia, occasionally sepsis and death.
- May spontaneously abate.
- Cycles become less noticeable with age.

Phagocytic disorders

- Leukocyte adhesion deficiency
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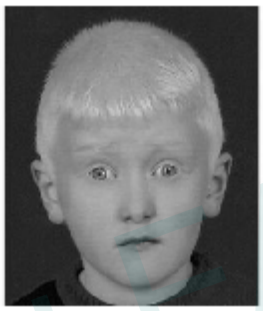
Chédiak-Higashi syndrome (CHS)

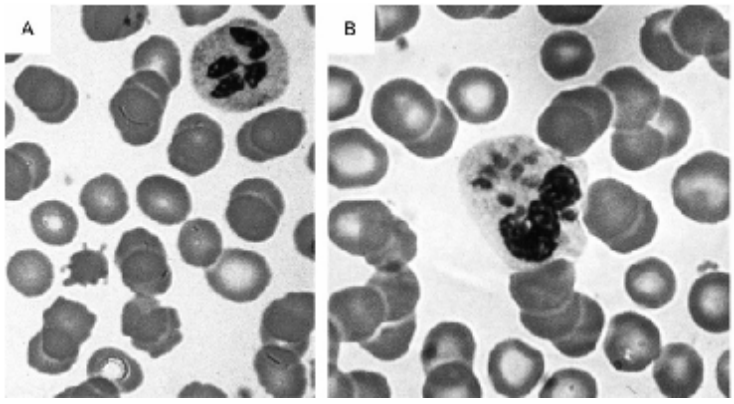
- Autosomal recessive mutation
- Inability of the giant granules to release their lytic contents
- Clinical symptoms include hematopoietic and neurological manifestations.



recurrent pyogenic infections
peripheral neuropathy,
partial oculocutaneous albinism,
slight mental retardation,
platelet dysfunction,
severe periodontitis,

Diagnosis of Phagocytic Defect on the Basis of Light-Microscopical Findings

Normal **CHS**



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Phagocytic disorders

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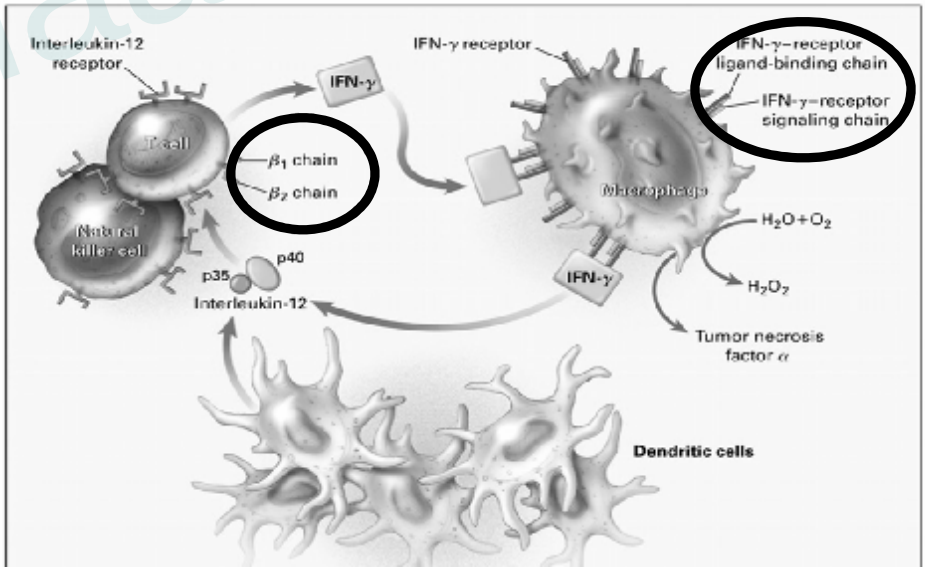
Defects in IL-12 / IFNγ pathway



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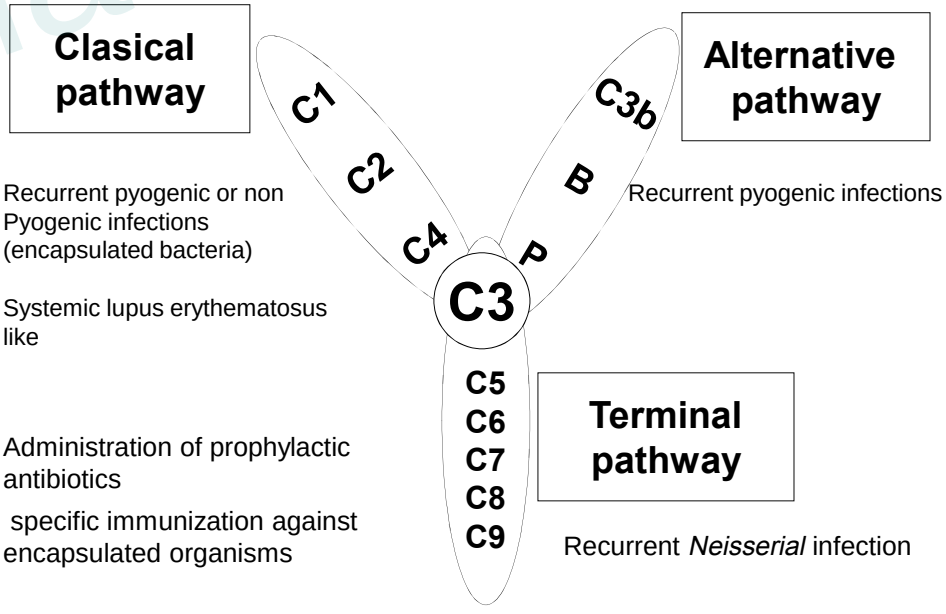
Defects in the innate immune response

- ✓ **Phagocytic disorders**
- ✓ **Complement deficiencies**

Complement deficiencies



Recurrent pyogenic or non Pyogenic infections (encapsulated bacteria)

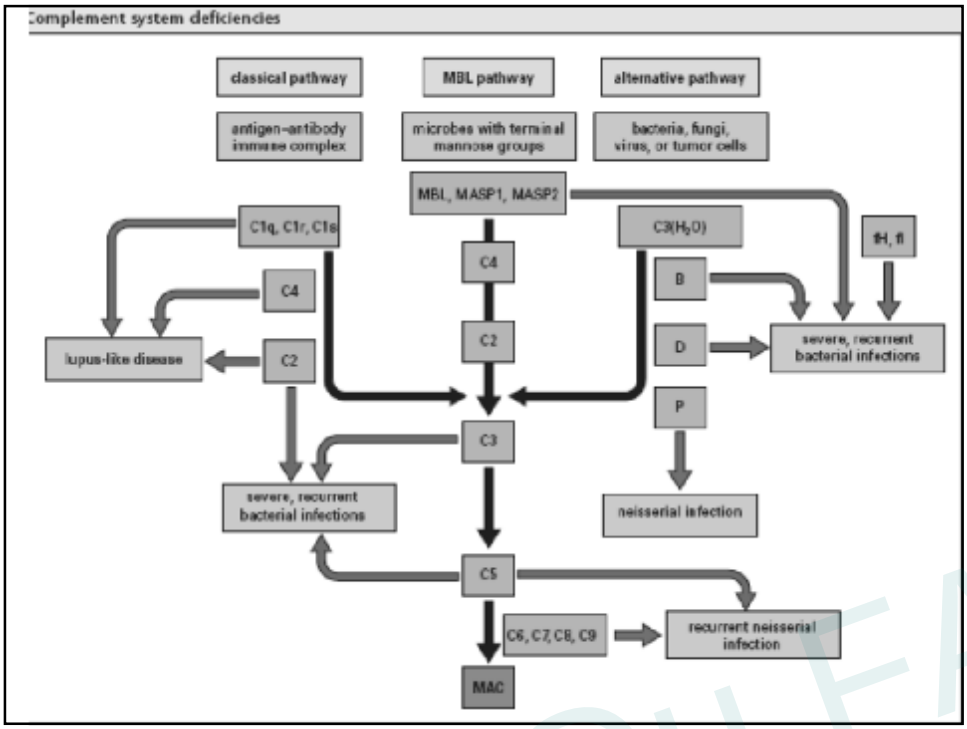
Systemic lupus erythematosus like

Administration of prophylactic antibiotics

specific immunization against encapsulated organisms

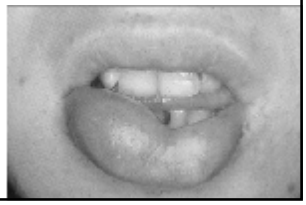
Recurrent pyogenic infections

Recurrent *Neisserial* infection



C1-inhibitor deficiency: hereditary angioedema

- Autosomal dominant disease.
- U**nregulated activation of the kinin and C systems in the affected area, inducing vascular leakiness**
- purified C1inh concentrate
- C1inh synthesis: steroids
- Minimizing consumption of C1inh using protease inhibitors.



Complement Deficiencies and Disease Classical Pathway

Pathway Component	Disease	Mechanism
C1INH	Hereditary Angioedema	Overproduction of C2 kinin
C1, C2, C4	Predisposition to SLE	Opsonization of immune complexes help keep them soluble, deficiency results in increased precipitation in tissues and inflammation

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Complement deficiencies and disease Lectin Pathway

Pathway Component	Disease	Mechanism
MBL	Susceptibility to bacterial infections in infants or immunosuppressed	Inability to initiate lectin pathway

Complement deficiencies and disease Alternative Pathway

Pathway/Component	Disease	Mechanism
Factors B or D	**Susceptibility to pyogenic (pus-forming) bacterial infections**	**Lack of sufficient opsonization of bacteria**
C3	**Susceptibility to bacterial infections**	**Lack of opsonization and inability to utilize the membrane attack pathway**
C5, C6, C7 C8, or C9	**Susceptibility to Gram-negative infections**	**Inability to attack the outer membrane of Gram-negative bacteria**

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Complement Deficiencies and Disease Alternative Pathway

Pathway Component	Disease	Mechanism
Properdin (X-linked)	Susceptibility meningococcal meningitis	Lack of opsonization of bacteria
Factors H or I	C3 deficiency and susceptibility to bacterial infections	Uncontrolled activation of C3 via alternative pathway resulting in depletion of C3

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Defects in adaptive immune responses

- B cell-specific immunodeficiencies
- T cell-specific immunodeficiencies
- Combined immunodeficiencies

B-PIs

•70% of all PIs

• relatively easy to diagnose and treat.

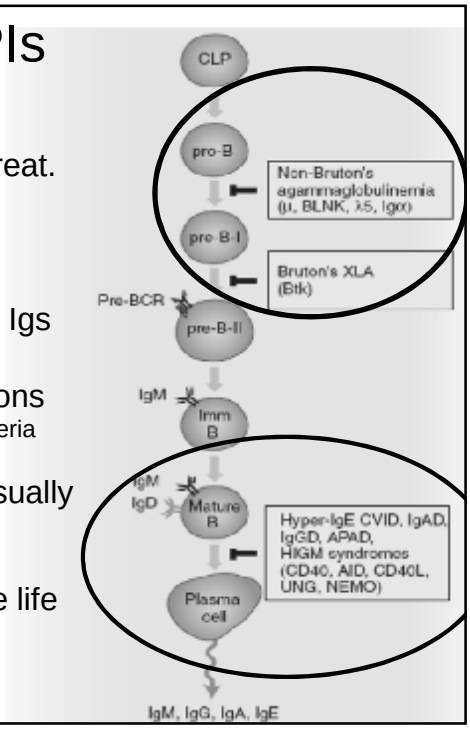
• free of infection until age 7–9 m

• Low levels of one or more serum Igs

• increased susceptibility to infections
enteroviruses, parasites, encapsulated bacteria

•The stunted growth often is not usually seen in patients with B-PIs.

•IV-IG replacement therapy for the life of the patient.



B-PIs

1. Selective IgA deficiency
2. Common Variable Immunodeficiency
3. X- linked agammaglobulinemia (Bruton's XLA)
4. IgG Subclasses deficiency

Selective IgA Deficiency

- Selective IgA deficiency is the most common ID disorder (1:700)
- IgA1 and IgA2 Abs subclasses are missing
- Gastrointestinal and respiratory infections the most common clinical signs
- T cell function is normal
- Antibiotic is usually adequate treatment for IgA deficiency

B-PIs

1. Selective IgA deficiency
2. Common Variable Immunodeficiency
3. X- linked agammaglobulinemia **(Bruton's XLA)**
4. IgG Subclasses deficiency

CVID abnormalities

- A heterogenous group of disorders with general impairment of humoral responses.
- Circulating mature B cells are present but plasma cell differentiation and Abs production are impaired
- Decreased levels of IgA and IgG, and about 50% also lack IgM
- Onset may occur in childhood, adolescence, or adulthood
- 24% of patients die of chronic pulmonary disease or B cell lymphoma, and autoimmunity occurs in 22%

B-PIs

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2. Common Variable Immunodeficiency
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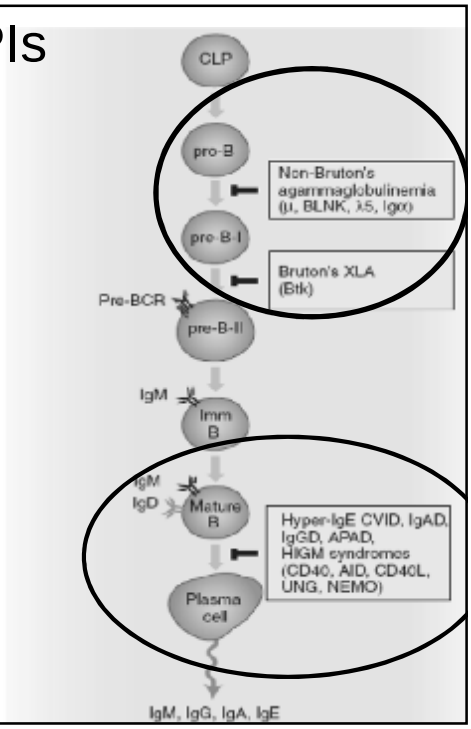
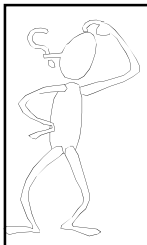
B-PIs





What is XLA?

✓Defect on the X chromosome

✓Little boys with big infections

✓Mutation in the gene of *Bruton's tyrosine kinase (Btk)*.

✓Results in an absence or severe reduction in B lymphocytes and hence **immunoglobulin of all types.**

Defects in adaptive immune responses

- B cell-specific immunodeficiencies
- T cell-specific immunodeficiencies
- Combined immunodeficiencies

T cell Immunodeficiency

1. MHC Deficiencies
2. Defect in TCR signaling,
3. Defect in Cytokine production as IL-2, IFN-γ
4. DiGeorge Syndrome

DiGeorge Syndrome

- Defective development in thymus and parathyroid that develop from third and fourth Pharyngeal pouch
- Thymic hypoplasia leading to variable immunodeficiency. Other features:
  - ✓Characteristic faces
  - ✓Deletion in 22q11 in > 80%
  - ✓Abnormal calcium homeostasis

Defects in adaptive immune responses

- B cell-specific immunodeficiencies
- T cell-specific immunodeficiencies
- Combined immunodeficiencies

Combined Immunodeficiencies:

- **Severe combined immunodeficiency (SCID)**
- **Hyper IgM syndrome**
- **ADA (Adenosine Deaminase Deficiency)**
- **Ataxia-Telangiectasia syndrome (AT)**
- **Wiskott -Aldrich syndrome (WAS)**

Severe Combined Immunodeficiency (SCID)

- The best known immunodeficiencies
- Represent about 20% of PIs.
- In all forms of SCID, cell-mediated as well as Ig immune responses are impaired.
- In some SCID cases, the B cells may have an intrinsic defect, whereas in other cases, the B cell defects are secondary to a lack of T cell help caused by non-functional or absent T cells.

  NK development and function are also impaired
- BMT/HCT treatment

Common Features of SCID

- ✓ Failure to thrive
- ✓ Onset of infections in the neonatal period
- ✓ Opportunistic infections
- ✓ Chronic or recurrent thrush
- ✓ Chronic rashes
- ✓ Chronic or recurrent diarrhea
- ✓ Paucity of lymphoid tissue