Immunodeficiency disorders

Immunology Unit
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KSU

Reference
Kuby Immunology 7th Edition 2013
Chapter 18 Pages 593-624

Objectives

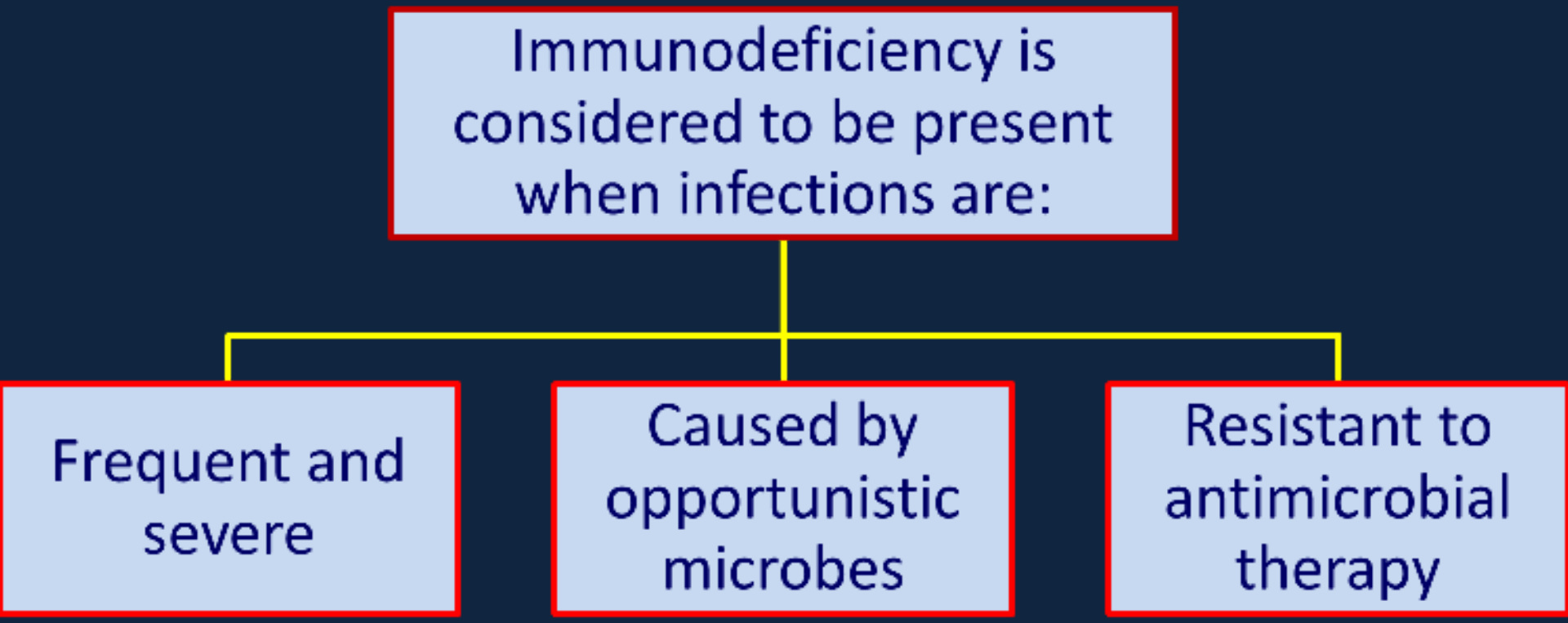
- Identify that Immunodeficiency is due to a defect in the immune function.
- Describe the classification of Immunodeficiency.
- Explain the presentations of different types of Immuno-deficiencies (e.g. recurrent infections).
- Understand the varieties of immune system deficiencies involving defects in :
  - T cells, B cells, phagocytes and complement.
- Know the laboratory investigations for

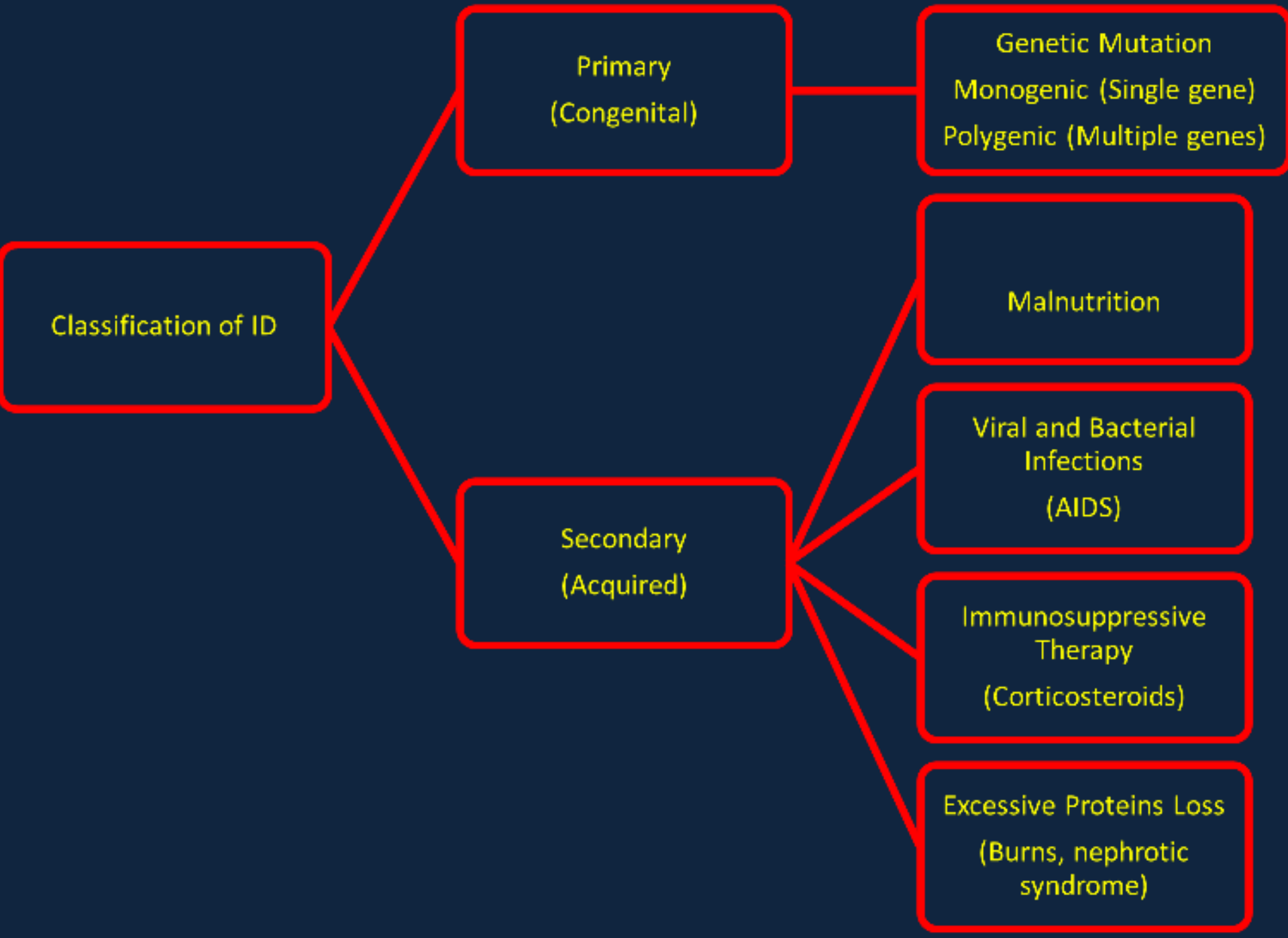
Definition

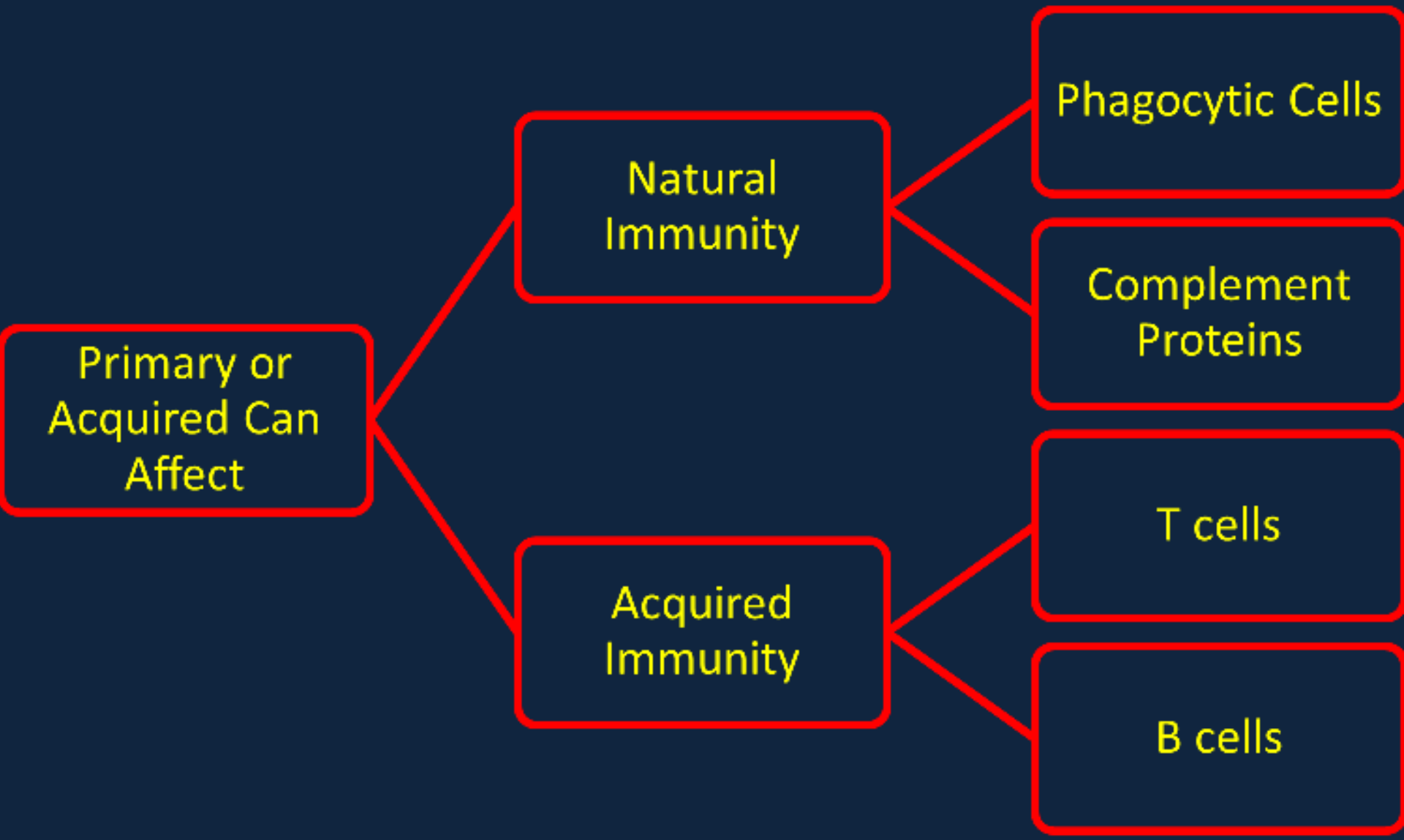
- A state in which the ability of the immune system to fight infectious disease is compromised or entirely absent

A person who has an immunodeficiency is said to be immuno-compromised

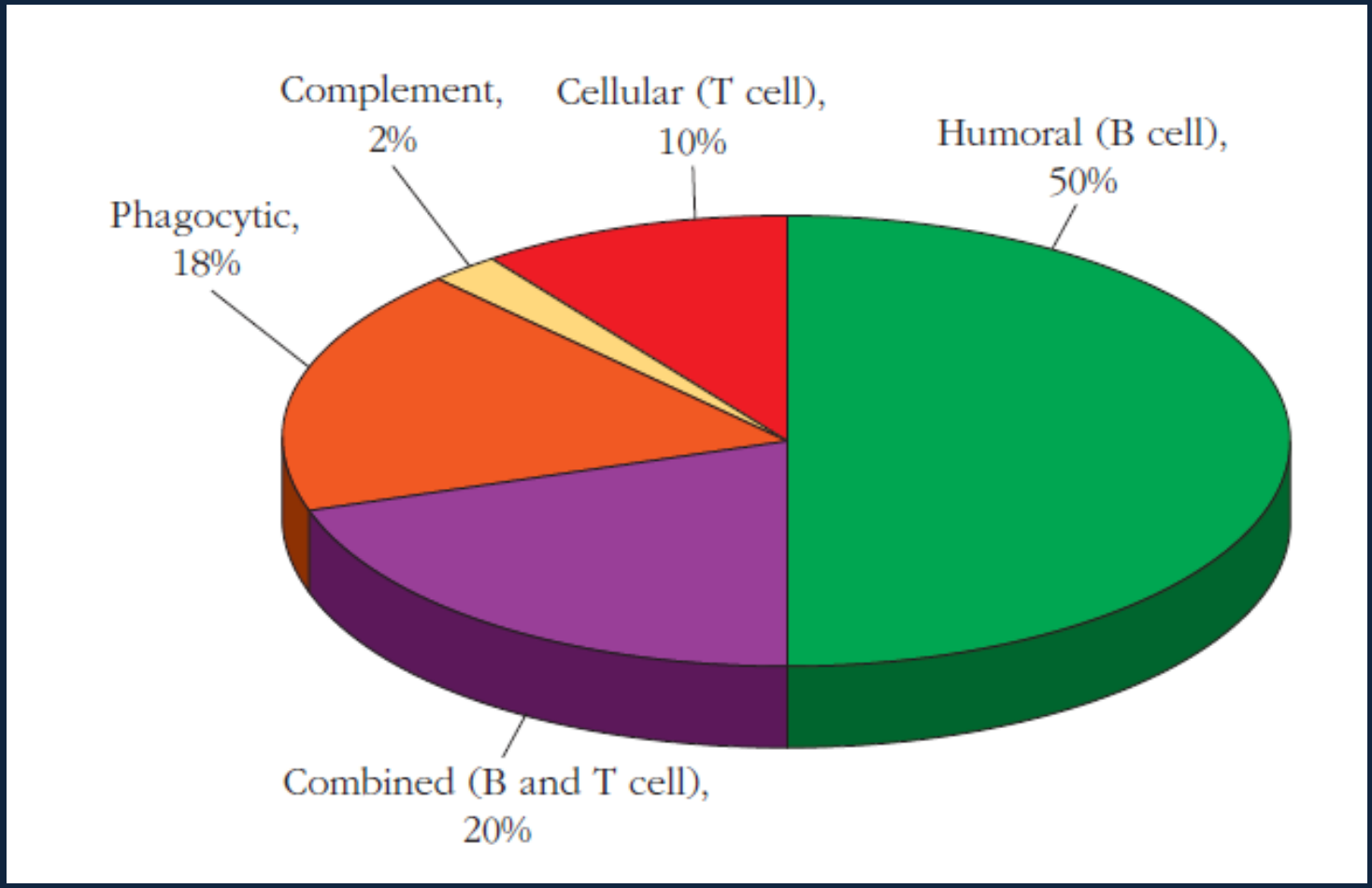

A boy with congenital ID lived in a bubble for 12 years before he died


Immunodeficiency is considered to be present when infections are:
Frequent and severe
Caused by opportunistic microbes
Resistant to antimicrobial therapy


Classification of ID
Primary
(Congenital)
Genetic Mutation
Monogenic (Single gene)
Polygenic (Multiple genes)
Secondary
(Acquired)
Malnutrition
Viral and Bacterial Infections
(AIDS)
Immunosuppressive Therapy
(Corticosteroids)
Excessive Proteins Loss
(Burns, nephrotic syndrome)


Primary or Acquired Can Affect
Natural Immunity
Acquired Immunity
Phagocytic Cells
Complement Proteins
T cells
B cells

Distribution of Primary immunodeficiencies

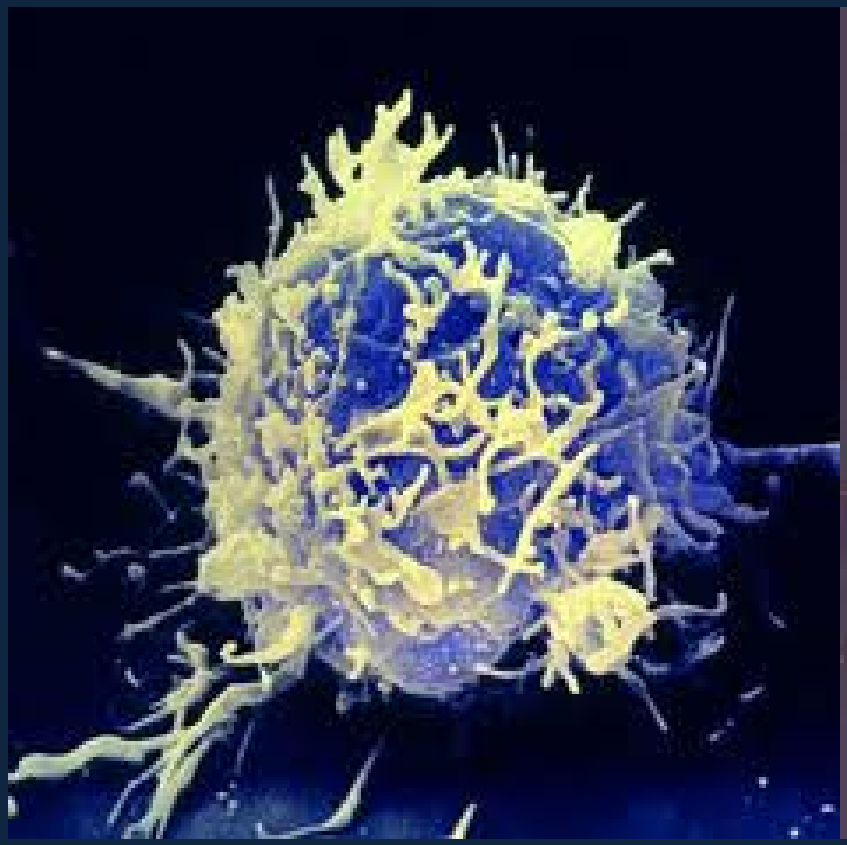


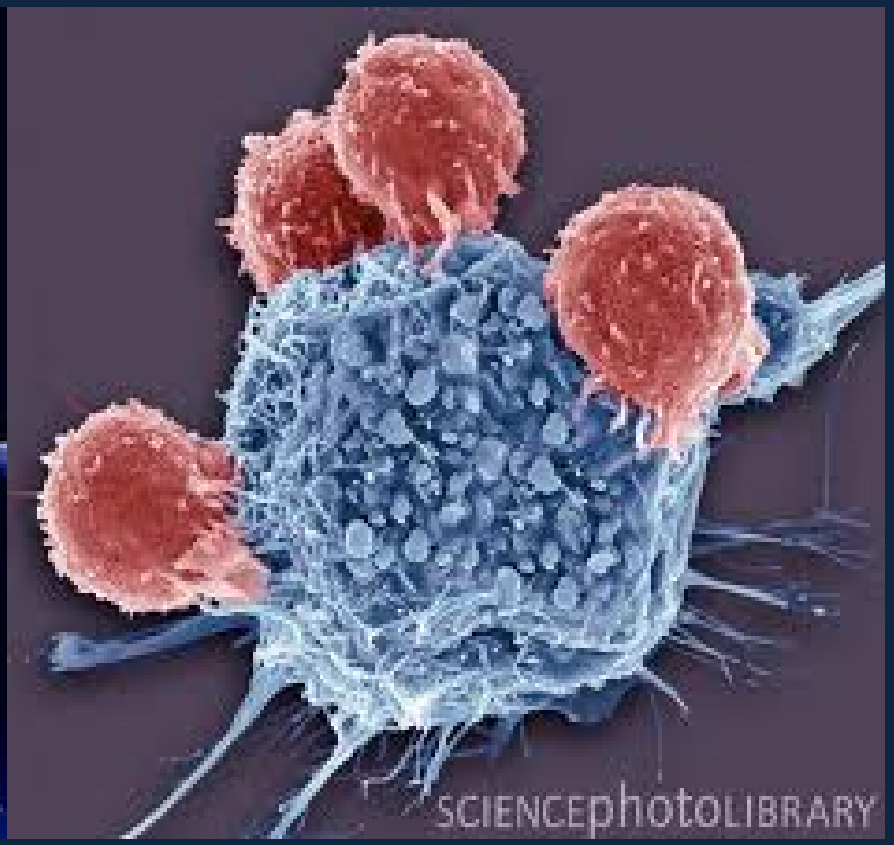
Pattern of infections and symptoms associated with primary immunodeficiencies

Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystis carinii*, viruses) Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)	
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	
Regulatory T cells	N/A	Autoimmune disease

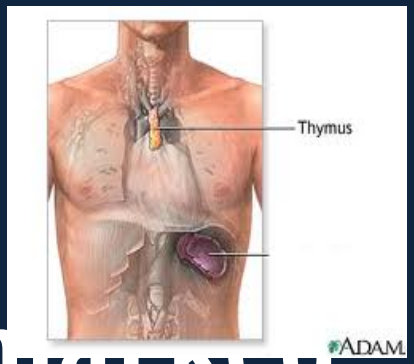
Source: Adapted from H. M. Lederman, 2000, The clinical presentation of primary immunodeficiency diseases, Clinical Focus on Primary Immune Deficiencies. *Towson, MD: Immune Deficiency Foundation* **2**(1):1.

T-cell defects





DiGeorge Syndrome (Congenital Thymic Aplasia)



A congenital defect that is marked by:

- Absence or underdevelopment of the Thymus gland (hypoplasia)
- Hypoparathyroidism
- Facial abnormalities
- Cardiovascular abnormalities

Features of DiGeorge syndrome

Children may present with tetany

In the complete form:

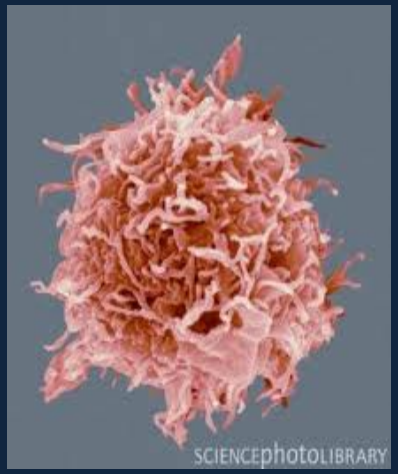
- Extreme susceptibility to viral protozoal, and fungal infections

- Profound depression of T-cell numbers

- Absence of T-cell responses

Management of DiGeorge syndrome

Fetal thymus tissue graft
(14 weeks old)



B-cell defects

(Gammaglobulinaemias)

Patients with B-cell defects are subiect to:

Recurrent bacterial infections

but

Display normal immunity to most viral and fungal infections

Why ???

Diverse spectrum ranging from:

- Complete absence of B-cells
- Complete absence of plasma cells
- Low or absent immunoglobulins
- Selective absence of certain immunoglobulins
- Genetic Transmission
    - Autosomal recessive
        - X-linked disease:
            Females : carriers (normal)

X-linked agammaglobulinaemia (XLA) or Bruton's hypogammaglobulinaemia (Congenital disease)

- The most common type, 80 to 90 percent
- Defect in Bruton Tyrosine Kinase (BTK)
- The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow

Features of XLA

- Reduced B-cell counts to 0.1 percent
  (normally 5-15 percent)

- Absence of Immunoglobulins

- Affected children suffer from recurrent pyogenic bacterial infections

Selective immunoglobulin deficiency (Congenital disease)

IgA deficiency (1:700)

Most are asymptomatic: but may have increased incidence of respiratory tract infections (R.T.I)

Some have recurrent R.T.I and gastrointestinal tract symptoms

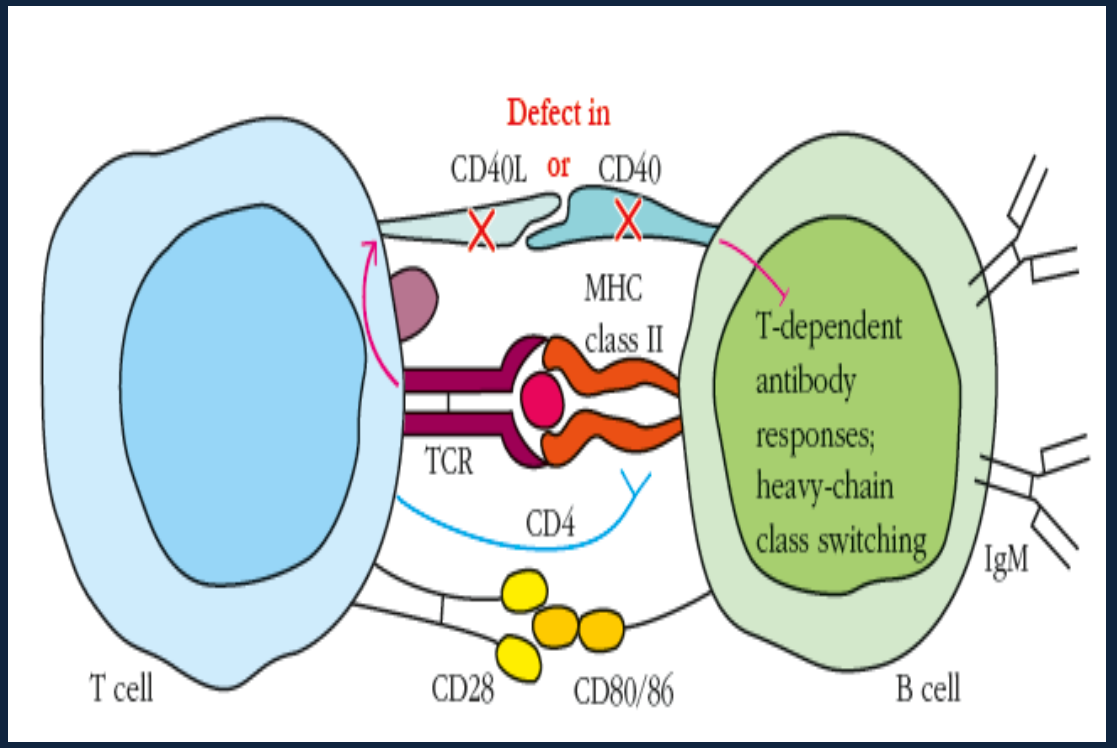
X- linked Hyper-IgM Syndrome (Congenital disease)

Characterized by:

- Defective CD40L/ CD40 interaction B cell class switching fails

- Variable IgM levels most frequently high

- Low IgG, IgA & IgE



Common Variable Immunodeficiency Disorders

- Disorders of unknown etiology

- Characterized by:
- Presentation in childhood or later in life
- Recurrent respiratory tract infections due to immunodeficiency
- Reduction in the levels of one or more antibody isotype with normal B cell numbers
- Impaired B-cell responses to antigen

Management of immunoglobulin deficiencies:

*Periodic intravenous immunoglobulin (IVIG) reduces infectious complications

Severe Combined Immunodeficiency (SCID) (Congenital disease)

Causes of SCID:

Enzyme deficiencies:

1. ADA (adenosine deaminase) deficiency

- Catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively
  which interferes with DNA synthesis.

2. PNP (purine phosphorylase) deficiency

- Toxic metabolites accumulate in T and B cells

SCID

- **Reticular Dysgenesis (RD)**

- Initial hematopoietic cell development is blocked by defects in the adenylate kinase 2 gene (AK2)
- Apoptosis of myeloid and lymphoid precursors
- Severe reductions in circulating leukocytes
- Impairment of both innate and adaptive immunity
- Susceptibility to infection by all types of microorganisms
- Without aggressive treatment children die in early infancy

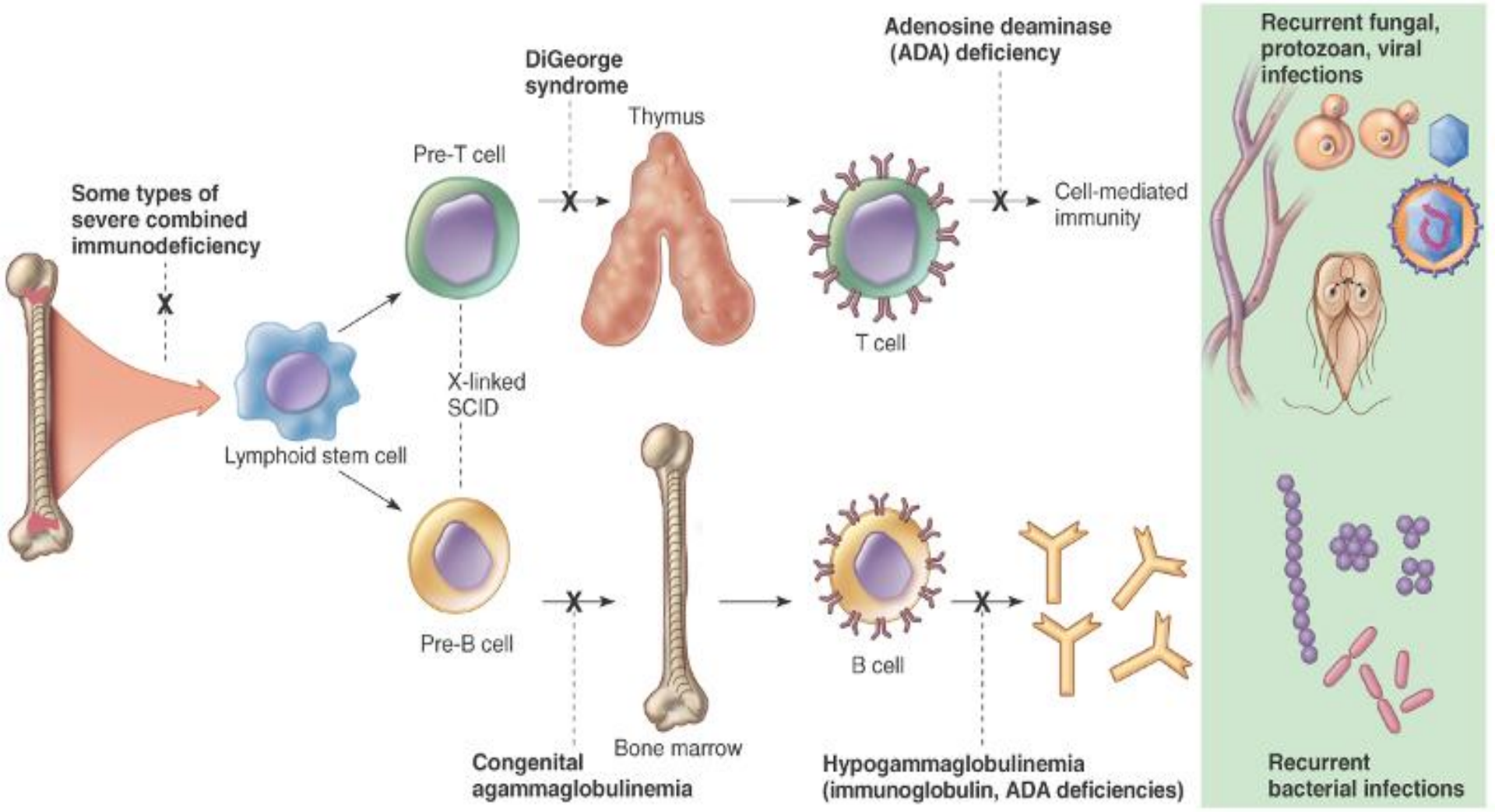
SCID

- Deficiency in cytokine signaling:

- Defects in the gene encoding for common gamma chain of the IL-2, IL-4, -7, -9,
- -15 and -21 receptors.
- This leads to widespread defects in B-, T-, and NK-cell development.

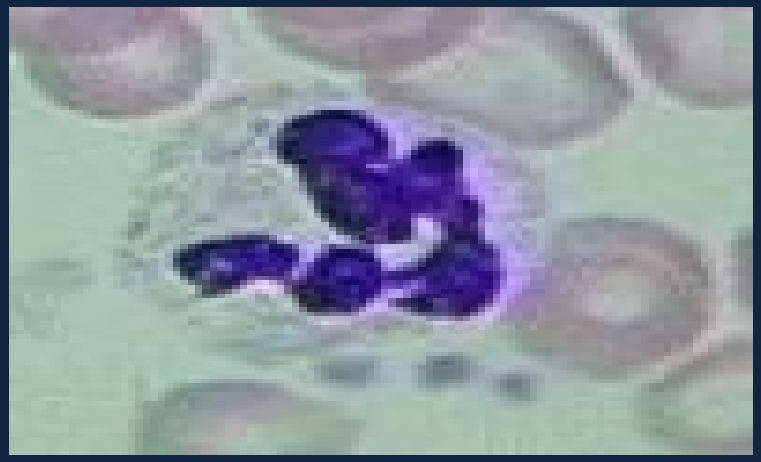
Features of SCID

- Increased susceptibility to :viral, fungal, bacterial protozoal infections (starting at 3 months of age)



Management of SCID

1. Infusion of purified enzymes
2. Gene therapy



Leukocyte defects

Quantitative

Qualitative

Quantitative Defects

Congenital agranulocytosis:

Defect in the gene inducing G-CSF (granulocyte colony stimulating factor)

Features:

Pneumonia, otitis media, abscesses

Quantative Defects (Congenital disease)

A. Defect in chemotaxis

Leukocyte adhesion deficiency (LAD)

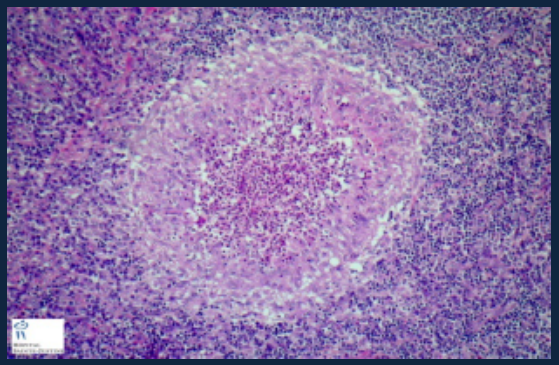
Defect: in the adhesion molecules responsible of leukocyte trafficking and migration to sites of infection

B. Defect in intracellular Killing

Chronic granulomatous disease:

Defect: in the oxidative complex responsible for producing superoxide radicals

Chronic granulomatous disease (CGD)
(Congenital disease)

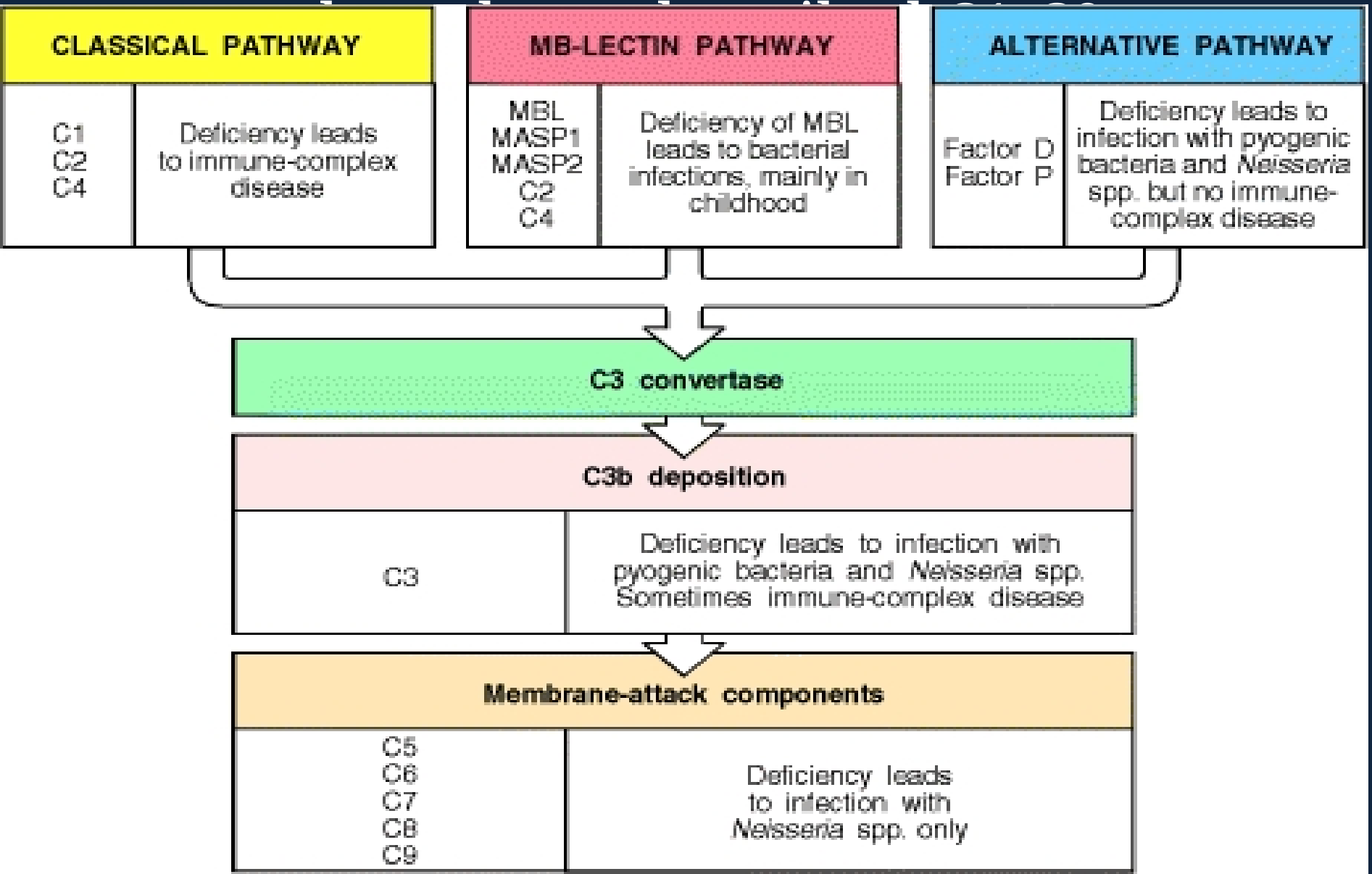


Neutrophils lack the "respiratory burst" upon phagocytosis

- Characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation

Complement Deficiency

Deficiency of all complement components



Laboratory diagnosis of ID

1. Complete blood count : total & differential
2. Evaluation of antibody levels and response to antigens
3. T and B cells counts (Flowcytometry)
4. Measurement of complement proteins and function (CH_{50})
5. Assessment of phagocytosis and respiratory burst (oxygen radicals)

Take Home Message

- Immunodeficiency may be congenital or acquired
- It can involve any component of the immune system such as cells, antibodies, complement etc.
- Most common presentation of immunodeficiency is recurrent infections that may be fatal due to delay in diagnosis and lack of appropriate therapy