

Immunodeficiency disorders

Immunology Unit

Department of Pathology

College of Medicine

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 Immunodeficiencies (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 immunodeficiency disorders

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



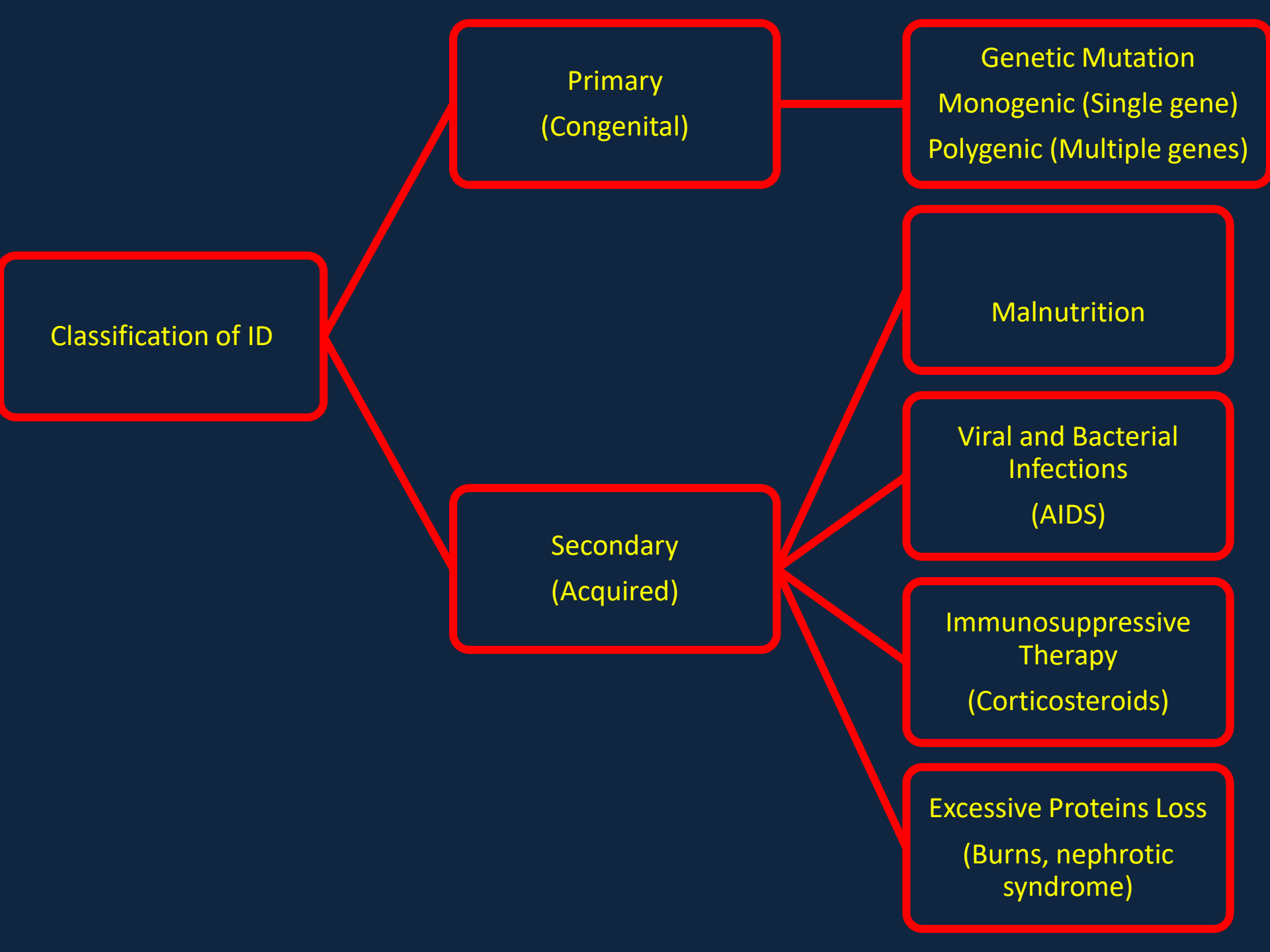
Immunodeficiency is considered to be present when infections are:

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graph TD; A[Immunodeficiency is considered to be present when infections are:] --- B[Frequent and severe]; A --- C[Caused by opportunistic microbes]; A --- D[Resistant to antimicrobial therapy];
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Frequent and severe

Caused by opportunistic microbes

Resistant to antimicrobial therapy



Classification of ID

Primary
(Congenital)

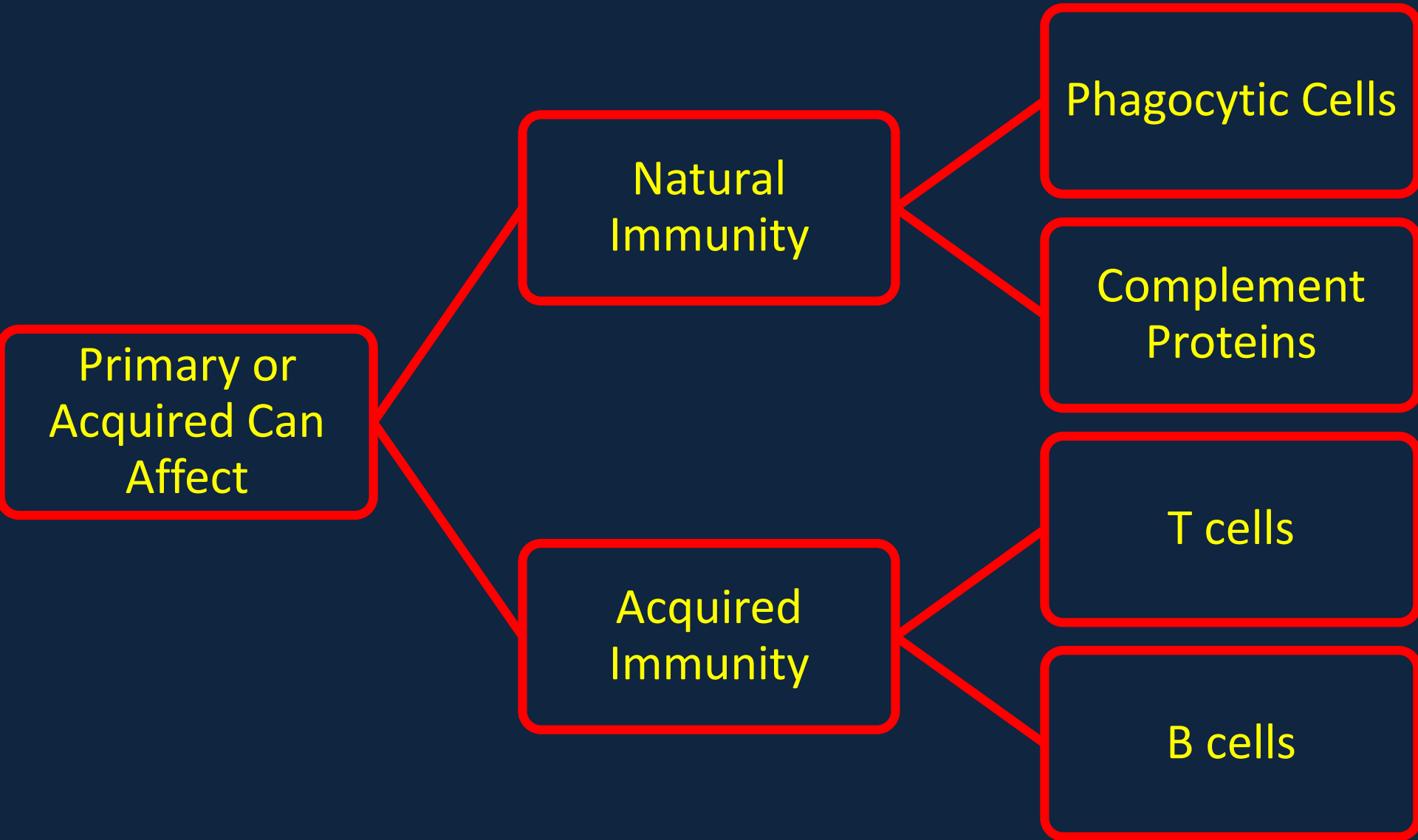
Genetic Mutation
Monogenic (Single gene)
Polygenic (Multiple genes)

Malnutrition

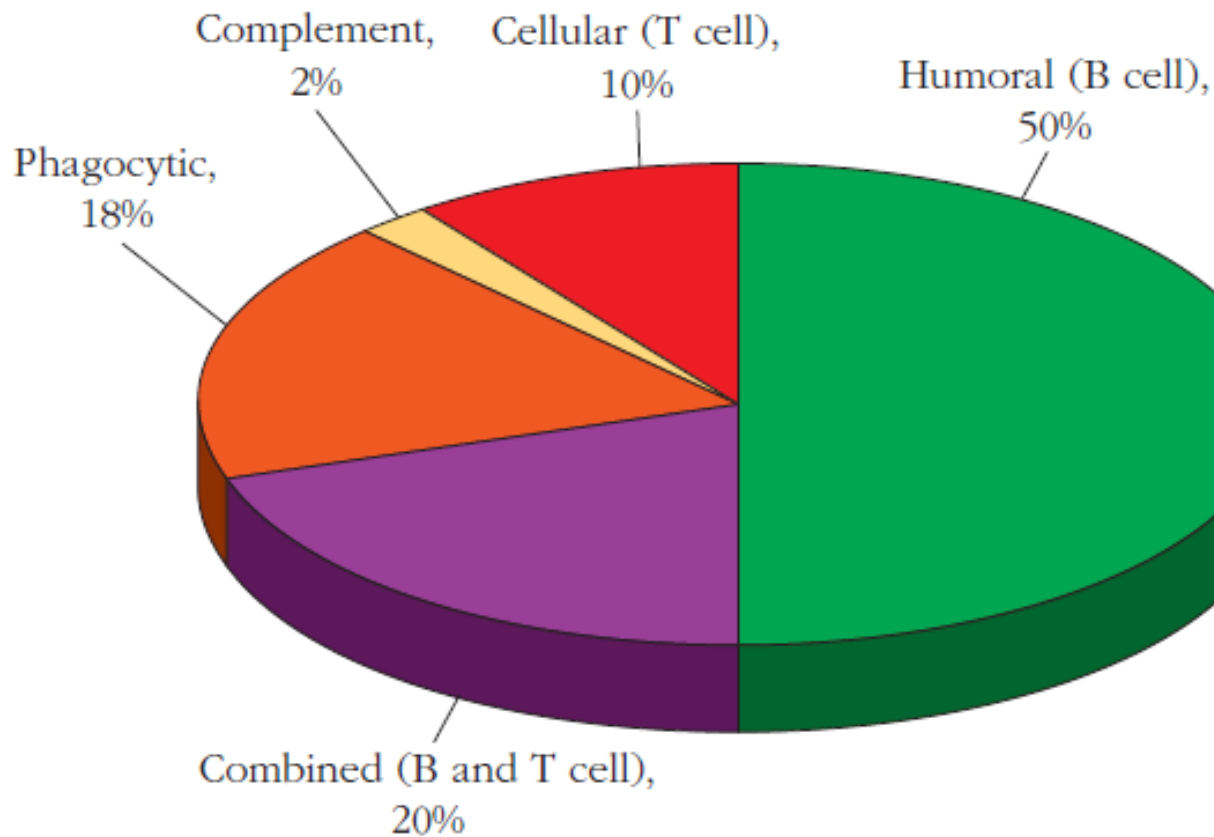
Viral and Bacterial
Infections
(AIDS)

Immunosuppressive
Therapy
(Corticosteroids)

Excessive Proteins Loss
(Burns, nephrotic
syndrome)



Distribution of Primary immunodeficiencies

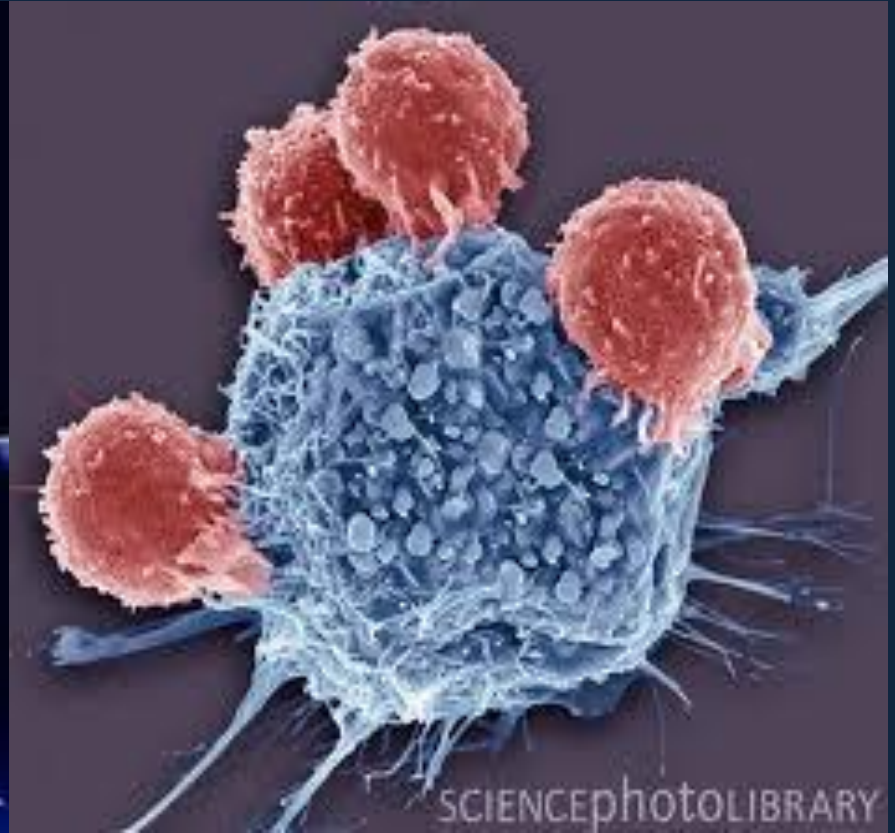
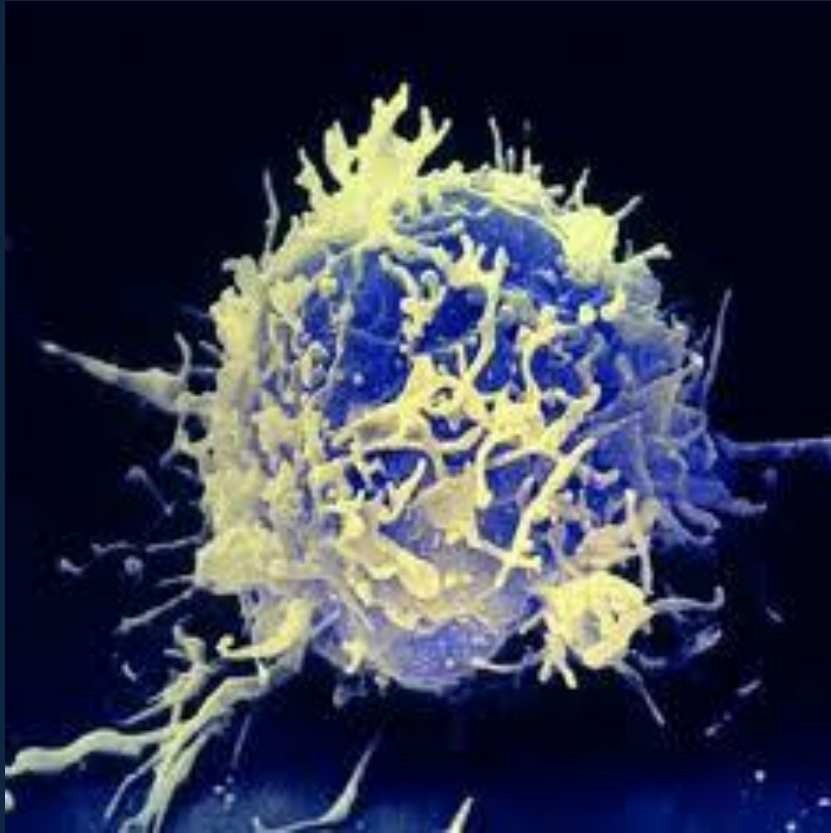


Pattern of infections and symptoms associated with primary immunodeficiencies

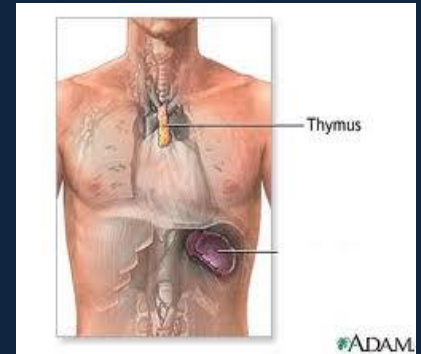
Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, <i>Pneumocystis carinii</i> , viruses) Gastrointestinal (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

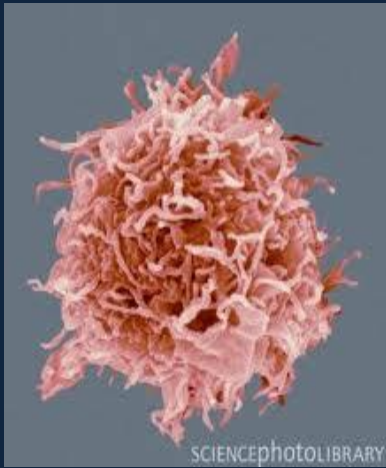
Children may present with tetany

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 subject 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**)
 - Males : **manifest** the disease

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)

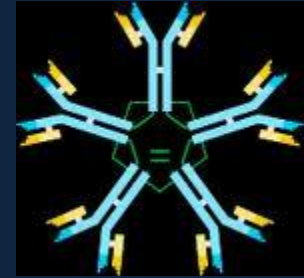
IgA deficiency (1:700)

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:



- Low IgG, IgA & IgE

- Variable IgM levels most frequently high

Management of immunoglobulin deficiencies:

*Periodic intravenous immunoglobulin (IVIG) reduces infectious complications

Severe Combined Immunodeficiency (SCID) (Congenital disease)

Causes of SCID:

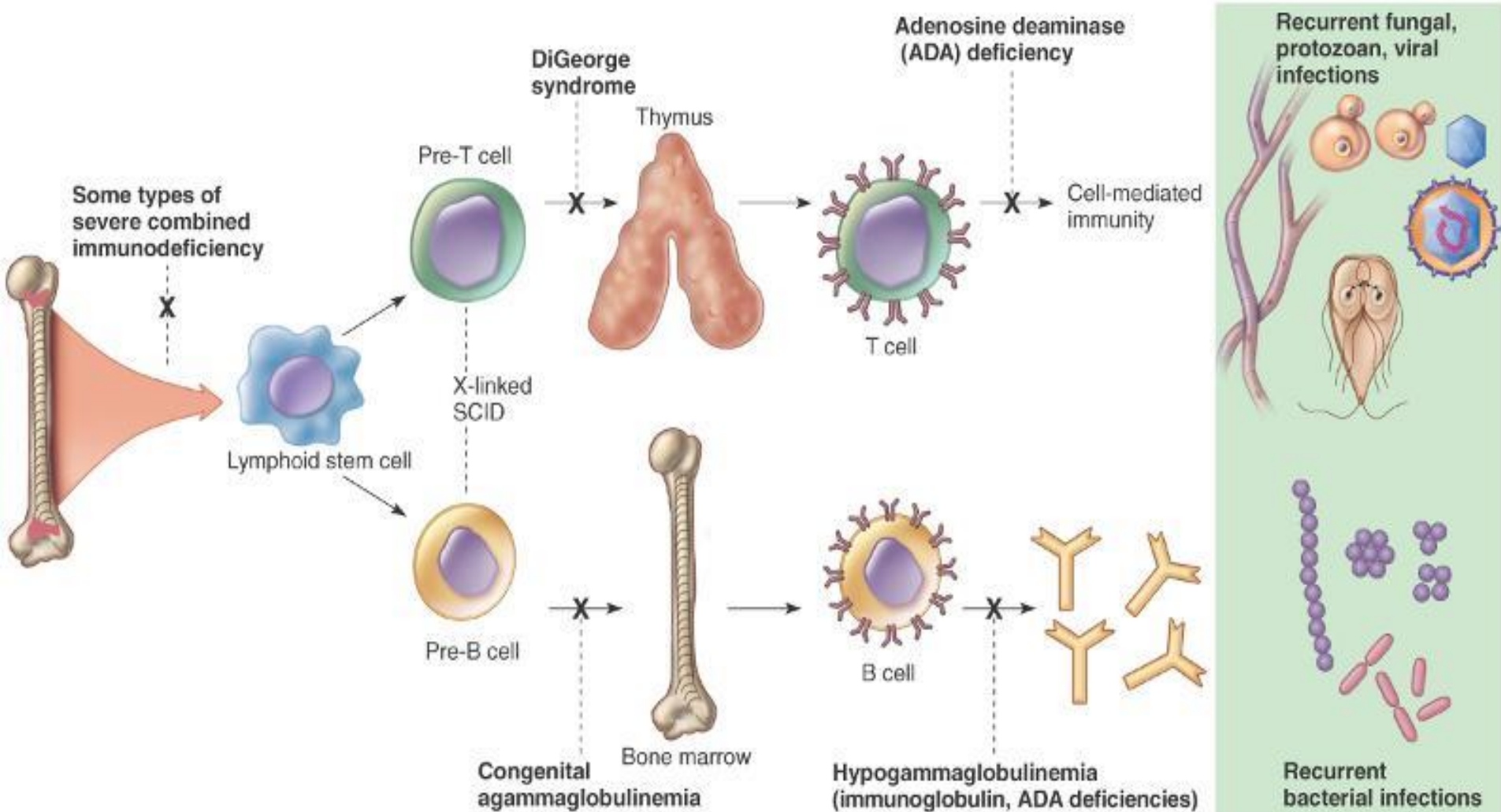
Enzyme deficiencies:

1. ADA (adenosine deaminase) deficiency
2. PNP (purine phosphorylase) deficiency
Toxic metabolites accumulate in T and B cells

Features of SCID

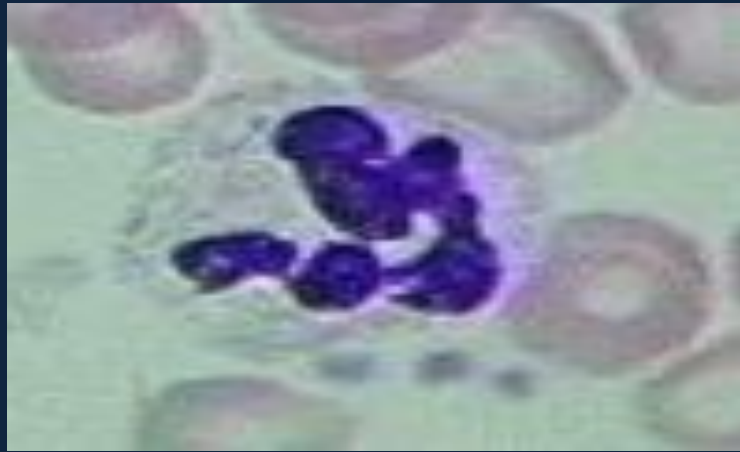
- Increased susceptibility to :viral, fungal, bacterial protozoal infections (starting at 3 months of age)

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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

Qualitative Defects (Congenital disease)

A. Defect in chemotaxis

Leukocyte adhesion deficiency (LAD)

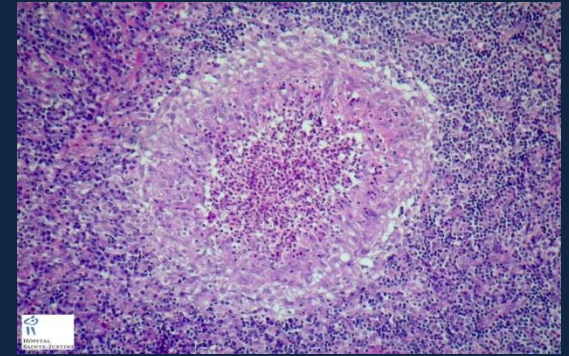
Defect: in the adhesion molecules responsible of leukocyte trafficking and migration to sites of infection

B. Defect in intracellular Killing

Chronic granulomatous disease:

Defect: in the oxidative complex responsible for producing superoxide radicals

Chronic granulomatous disease (CGD) (Congenital disease)

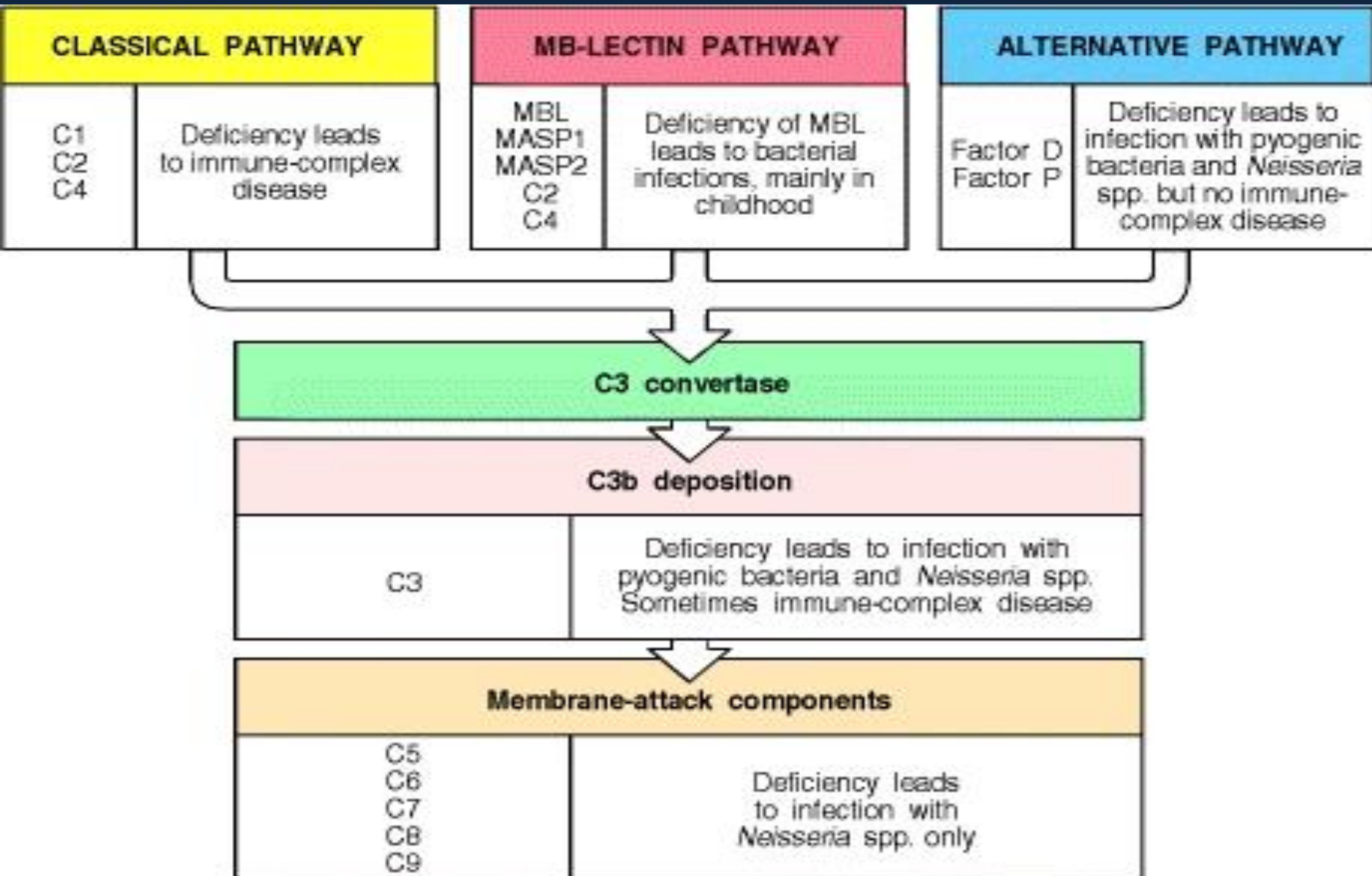


Neutrophils lack the "respiratory burst" upon phagocytosis

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

Complement Deficiency

Deficiency of all complement components have been described C1-C9



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 (CH₅₀)
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