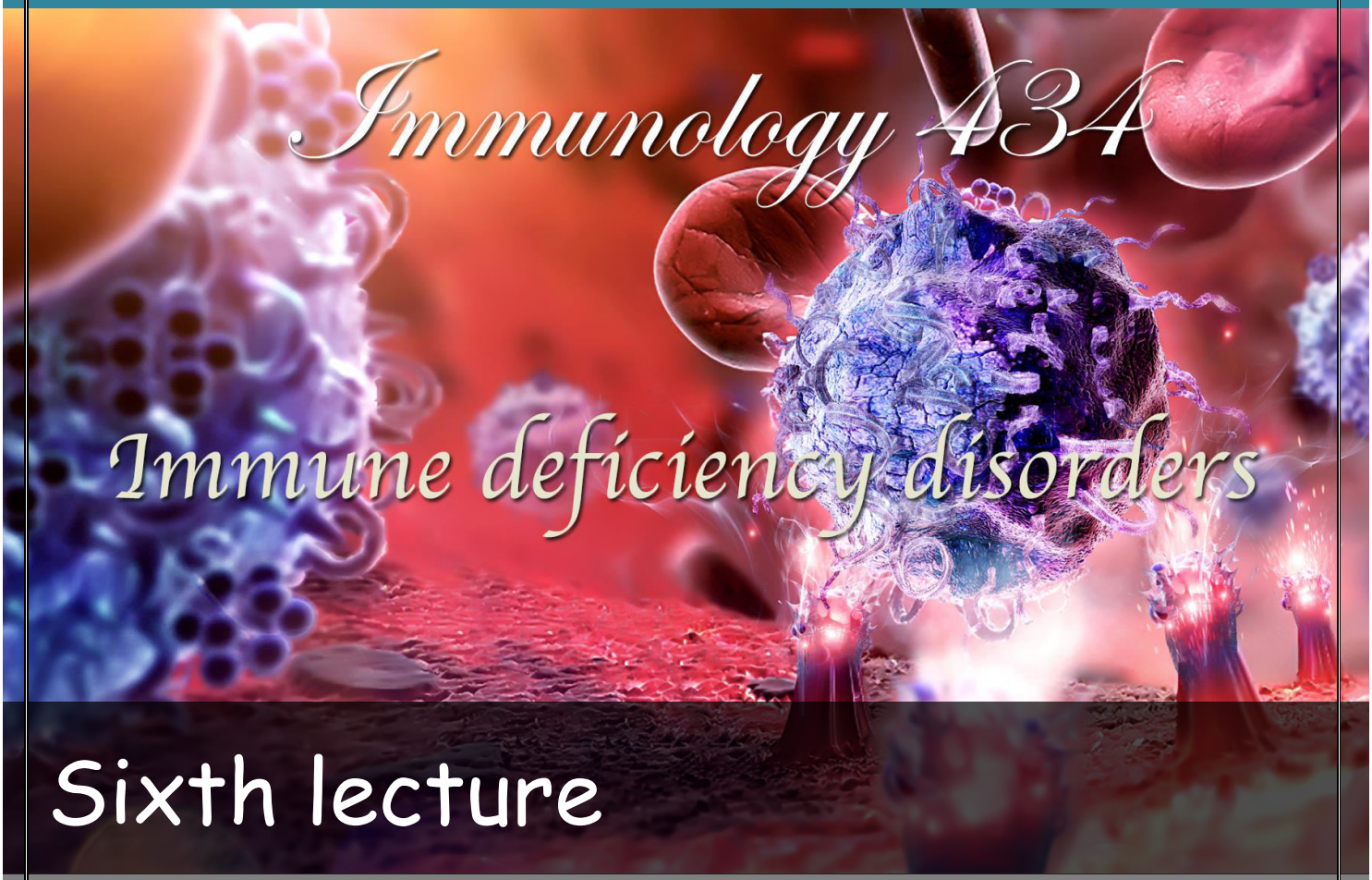

Immunology 434

Immune deficiency disorders

Sixth lecture

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 immunodeficiency disorders

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❖ Table of Contents

Colors of text:

Extra explanation: grey Girls notes: purple

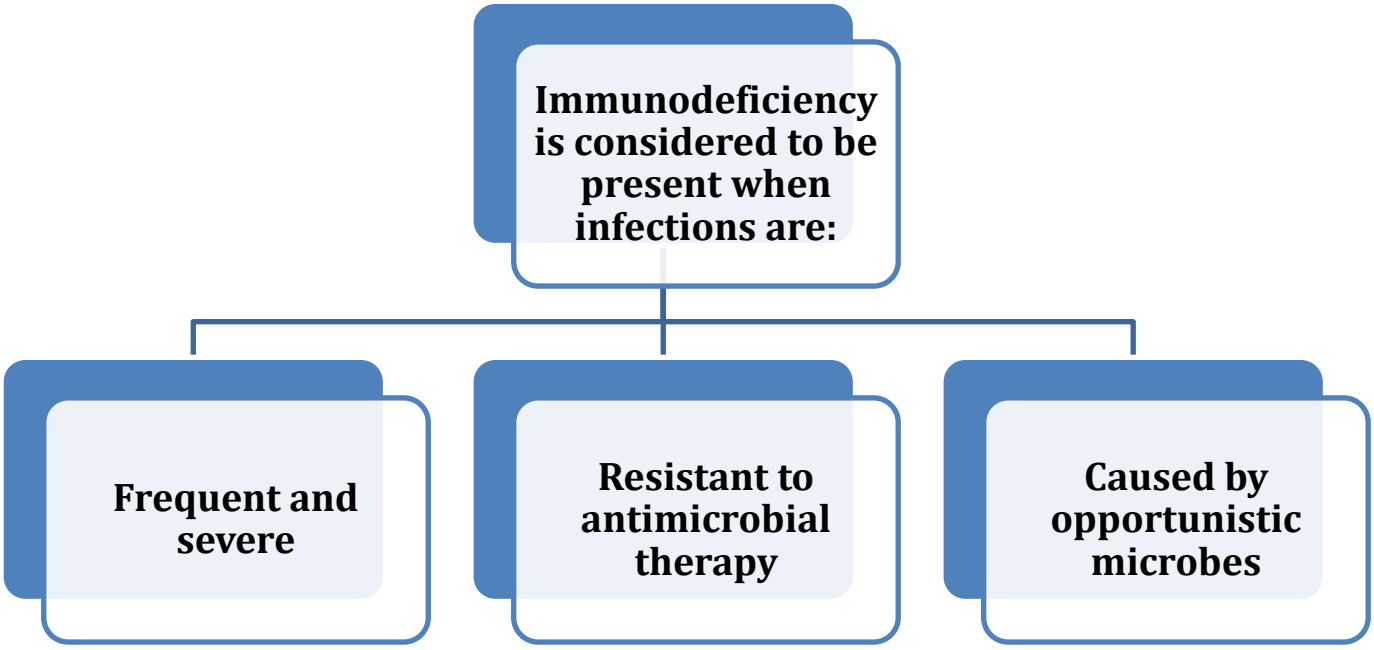
: Important

❖ Definition:

(1st objective)

- **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 immune-compromised.



(2nd objective)

Classification of ID

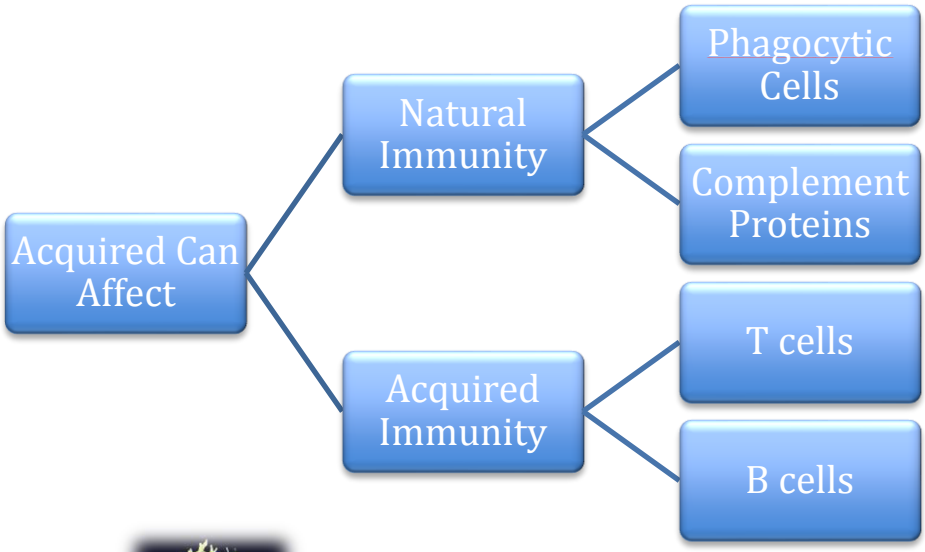
Primary (Congenital)

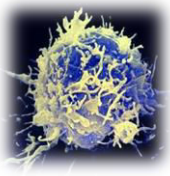
- Genetic Mutation
  - Monogenic (Single gene)
  - Polygenic (Multiple genes)

Secondary (Acquired)

- Malnutrition
- Viral and Bacterial Infections (AIDS)
- Immunosuppressive Therapy (Corticosteroids)
- Excessive Proteins Loss (Burns, nephrotic syndrome)

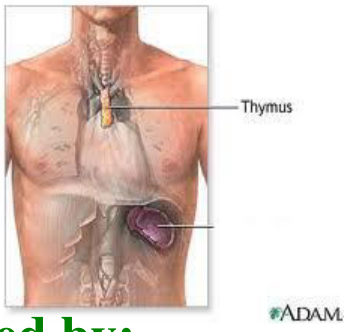
- corticosteroids are anti-inflammatory drug that stops production of interferon's
- Severe diets might cause acquired immune deficiency.





(3rd & 4th objectives)

❖T-cell defects



➢ DiGeorge Syndrome (Congenital Thymic Aplasia):

A congenital defect that is marked by:

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

Features of DiGeorge syndrome

- **Children may present with tetany**
- **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 the normal immunity to most viral and fungal infections.

Diverse spectrum ranging from:

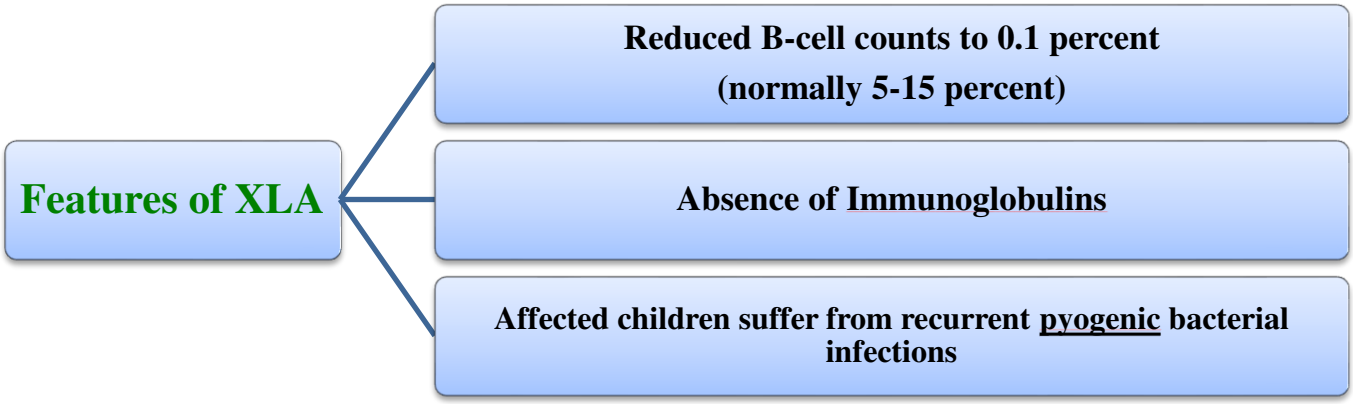
- **Complete absence of B-cells**
- **Complete absence of plasma cells**
- **Low or absent immunoglobulins**
- **Selective absence of certain immunoglobulins**

-X-linked disease:

Females: carriers (normal)
Males: manifest the disease

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

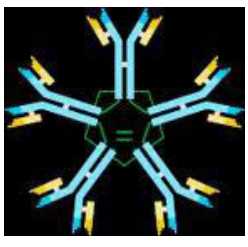
The most common type, 80 to 90 percent
Defect in Bruton Tyrosine Kinase (BTK)
The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow



➢ 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:

- **Markedly elevated IgM**
- **Low IgG, IgA & IgE**

The enzyme in making antibodies IgA,IgE.IgG is the same and IgM is different

❖ Management of immunoglobulin deficiencies:

Periodic IntraVenous ImmunoGlobulin (IVIG) reduces infectious complications.

❖ Severe Combined Immunodeficiency (SCID) (Congenital disease):

➢ Causes of SCID:

Enzyme deficiencies:

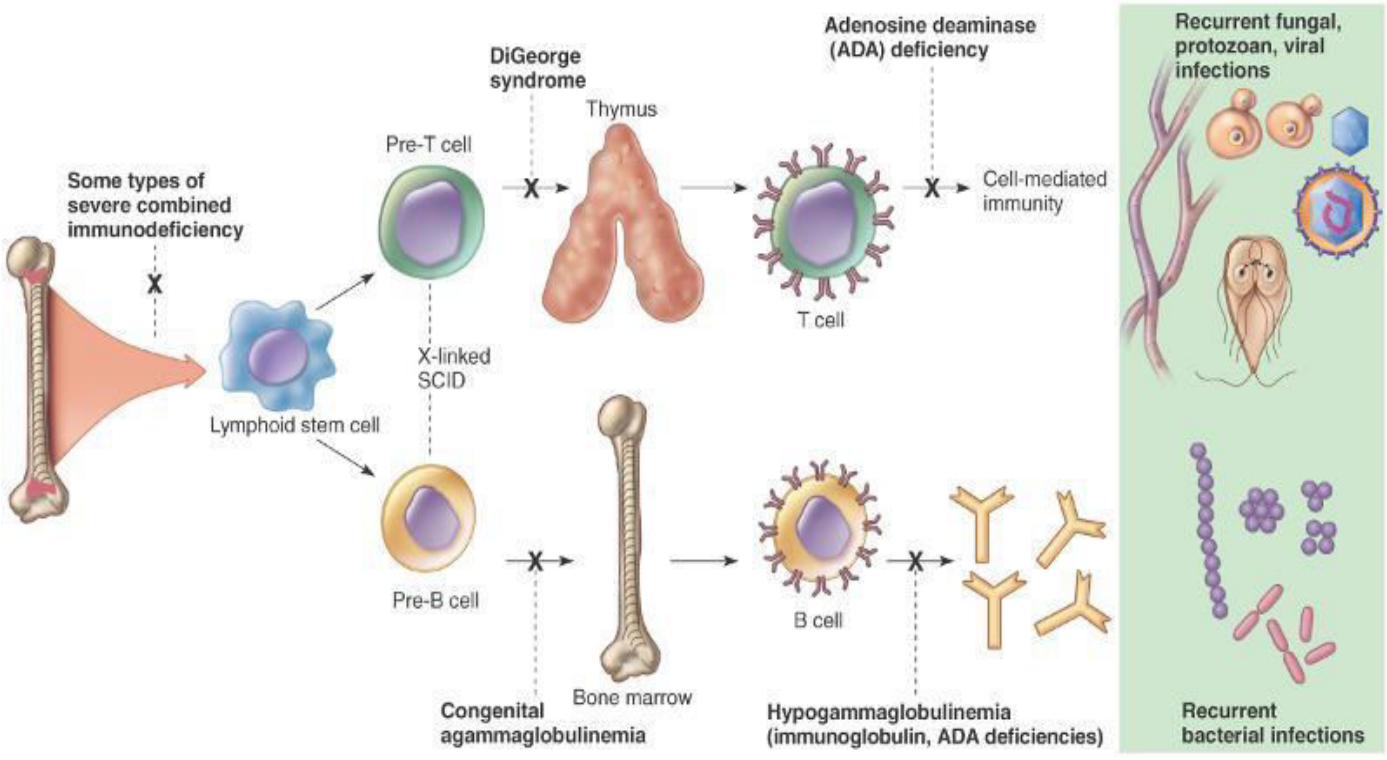
1. **ADA (adenosine deaminase) deficiency.**
2. **PNP (purine phosphorylase) deficiency.**

- **Toxic metabolites accumulate in T and B cells.**
- **Incompatible with life and affected infants usually die within the first 2 y unless they are rescued with BMT. (BMT means bone marrow transplantation)**

➢ Features of SCID:

- **Develop recurrent infections early in life.**
- **Prolonged diarrhea due to rotavirus or bacterial infection of GIT.**
- **Pneumonia, usually due to the protozoan,**
- **Pneumocystis carinii. (**pneumocystis carinii infection is an important sign of immune deficiency**)**
- **The common yeast organism Candida albicans (mouth or skin).**
- **If they are vaccinated with live organisms, such as poliovirus or (BCG), they die of progressive infection from these ordinarily benign organisms**

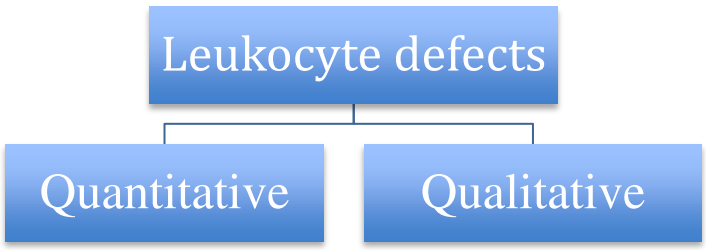
Increased susceptibility to: viral, fungal, bacterial and protozoal infections (starting at 3 months of age)

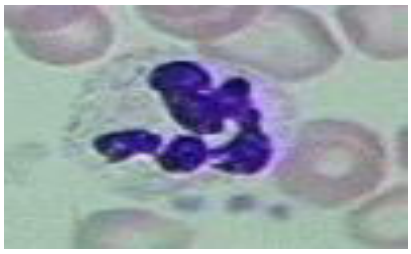


➢ Management of SCID:

1. Infusion of purified enzymes.
2. Gene therapy.

❖ Leukocyte defects

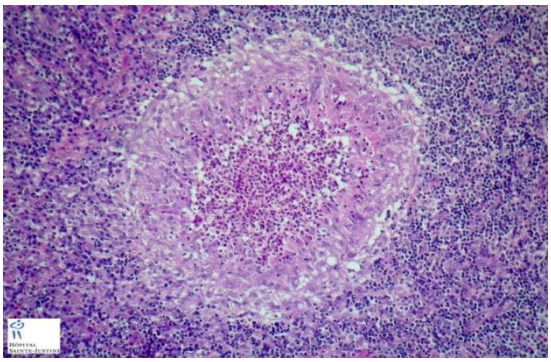




➢ Quantitative Defects

➢ Congenital agranulocytosis:

Defect in the gene inducing G-CSF (granulocyte colony stimulating factor)
Features: Pneumonia, otitis media and abscesses
Q) A child having bacterial (extracellular antigen) and fungal (intracellular antigen) Infections after the pathologic test its showed granulomas?
A) Diagnosis Chronic granulomatous disease (CGD)
Symptoms:
From one year the child would have a verity of infections and mostly hospitalized
Also it would severe malnutrition which is a secondary immune deficiency.
And might develop tumors.



➢ Qualitative Defects (Congenital disease)

A. Defect in chemotaxis
Leukocyte adhesion deficiency (LAD)
B. Defect in intracellular Killing
Chronic granulomatous disease:
Defect: in the oxidative complex responsible for producing superoxide radicals

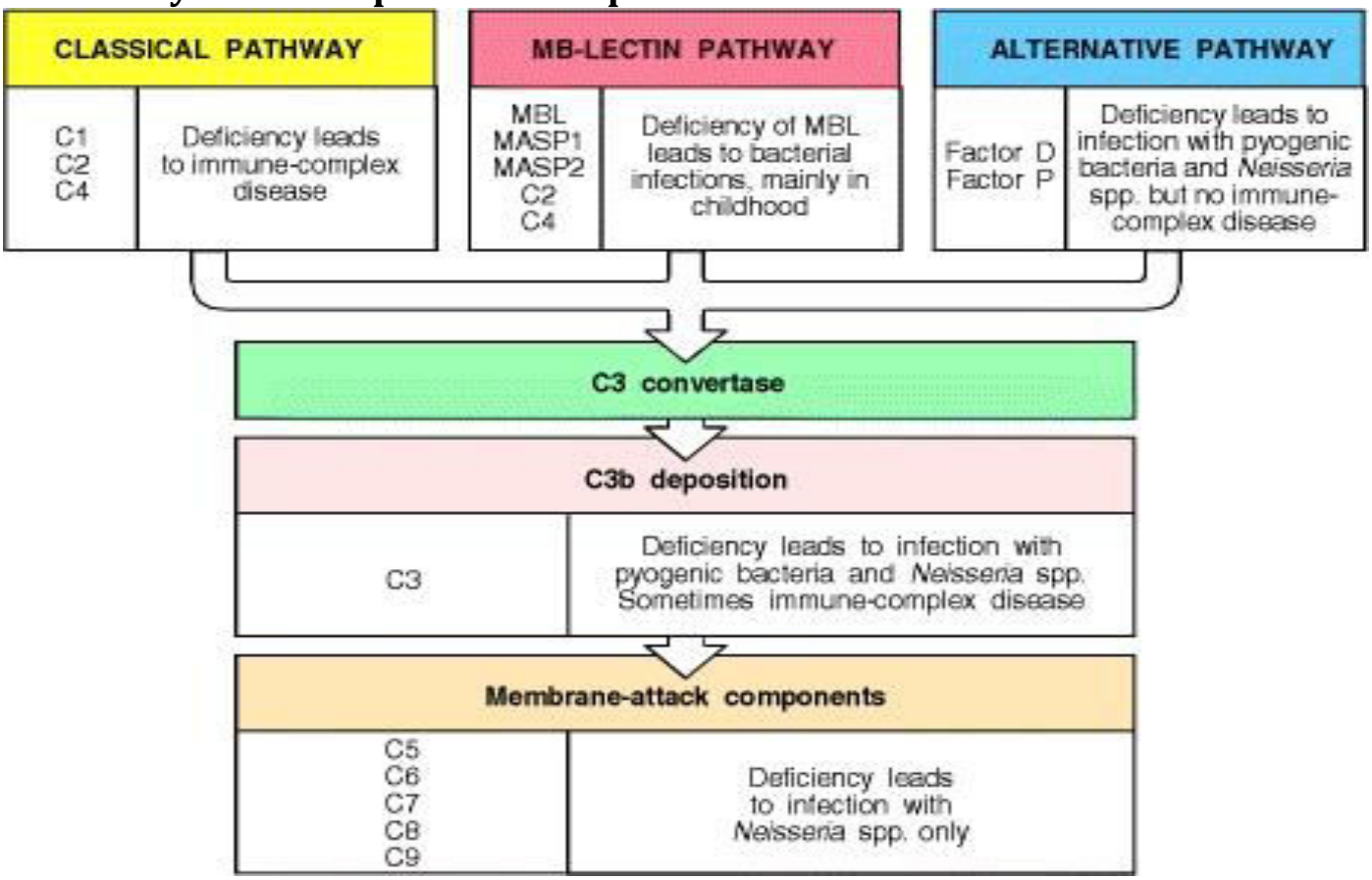
Chronic granulomatous disease (CGD) (Congenital disease)

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



When there is a deficiency complement components that actiate or forms MAC (membrane attack complex) there is a very high possibility of getting neisseria which causes meningitis.

➢ Laboratory diagnosis of ID

(5th objective)

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**

❖Review:

(1st objective)

It is a defect in the immune system, which may be entirely absent sometimes. (3rd page)
Immunocompromised person: a person with a defect immune system. (3rd page)
A clinician should consider an immunodeficiency disease when the infections are:

1- Severe and frequent.
2- Caused by opportunistic microbes (Usually don't cause infection)
3- Resistant to therapy.

(2nd objective)

Classification of immunodeficiency : (3rd page)

1- **Primary: congenital**
   Caused by *Genetic mutation* → **Single gene affected (Monogenic)**
   → **Multiple Genes affected (Polygenic)**
2- **Secondary: Acquired from :**

-Malnutrition.
-Viral and bacterial infections (AIDS)
-Immunosuppressive therapy (Example: Corticosteriods) (Sometimes, doctors need to lower the immunity of a patient in order to allow organ transplantation or to kill tumors by chemotherapy. They do so by using immunosuppressive drugs).
-Excessive protein loss. (Example: Nephrotic Syndrom and Burns.) (Nephtotic Syndrom is a case in which different disorders damage the kidneys, leading to the excessive loss of proteins).

Both Primary and acquired immunodeficiencies affect all types of immunity: (4th page)

Natural (innate) immunity	Acquired (Adaptive) immunity
Phagocytic Cells. Complement Proteins.	B and T Lymphocytes

(3rd & 4th objectives)

Disorders:

T-Cell defects: (4th page)

- **Di George Syndrome (Congenital Thymic Aplasia)**

A congenital defect having the following features:

Absence or underdevelopment of Thymus gland (Hypoplasia of Thymus) (Cellular mediated immunity depends on T-Cells, and since there is no Thymus, no T-Cells can mature leading to → Cellular Mediated immunity deficiency)
-Hypoparathyroidism is also seen in Di George Syndrome. (A condition resulting in low levels of Parathyroid Hormone or PTH, which plays a major role in maintain Calcium levels).
-Cardiovascular abnormality.

-In children, Tetany (a condition that is due to low blood calcium) **is present with Di George Syndrome. (10th slide)**
-Extreme susceptibility to viral, protozoal, and fungal infections. (Cellular mediated immunity deals with intracellular organisms, while bacteria usually stay in the extracellular matrix)
The result is a decreased number of T-Cells and absence of their functions.
Treatment: Transplantation of Thymus tissue in infants (Fetal thymus tissue Graft) (11th slide)

B-Cell defect. (5th page)

A. **Gammaglobulinaemias.**

Patients with B-Cell defects are subjects to bacterial infections but show normal immunity to viruses and fungi. (**Why?** Because B-Cells are responsible for producing antibodies for bacteria, while viruses and fungi are usually dealt with by T-Cells).

Features: -Complete absence of B-Cells leading to absence of plasma cells leading to absence of antibodies (Immunoglobulins).

-They are X-linked diseases, meaning that they are carried by the X chromosome. Females are carries, while males manifest (show) **the disease.**

- **X-Linked Agammaglobulinaemia (XLA): also called Bruton's Hypogammaglobulinaemia.** (5th page)

-A congenital disease.
-Most common type of B-Cell defects (80% - 90% of B-Cell defects are of this type)
-Caused due to a deficiency in an enzyme called Bruton Tyrosine Kinase (BTK), which is found in the bone marrow and is responsible for the maturation of pre B-Cells to fully grown B-Cells.

Features of XLA: (16th slide)
-Reduced B-Cell counts to 0.1% (Normally 5% - 15%)
-Absence of immunoglobulins (As a result of deficiency in B-Cells)
-Affected children suffer from frequent bacterial infections.

- **Selective Immunoglobulin Deficiency: A congenital disease.** (Deficiency in some Immunoglobulins) (5th page)

IgA deficiency. (Happens in 1:700 people)

-Most are asymptomatic (doesn't show symptoms).
-May have increased incidence of respiratory tract infections (RTI). (IgA is responsible for protection of mucosal surfaces of Respiratory Tract and GIT, so its deficiency will lead to infections in these areas)

X-Linked IgM syndrome: A congenital disease. (5th page)
Features:
-High levels of IgM.
-Low levels of IgG, IgA, IgE

-It is considered as an immunodeficiency because the most important immunoglobulins (IgG, IgA, IgM) are in low amounts.

Treatment of immunoglobulins deficiency (Gammaglobulinaemias): (6th page)
-Periodic intravenous immunoglobulins.

Severe Combined Immunodeficiency (SCID): A congenital disease. (6th page)

-Caused by:
1) Adenosine deaminase (ADA) deficiency.
2) Purine Phosphorylase (PNP) deficiency leads to Toxic metabolites accumulation in T and B Cells.

Features: (6th page)
-Increased susceptibility to viral, fungal, bacterial, and protozoal infections. (Starting from 3 months of age)
Treatment: (6th page).
-Infusion of deficient enzymes. (PNP or ADA)
-Correcting genes responsible for the disappearance of these enzymes.
-Transplantation of bone marrow in some cases.
==========

Leukocytes Defect. (7th page)

Quantitative. **Qualitative.**

- **Quantitative Defetcs. (Deficiency in Leukocyte number): Congenital Granulocyte.**

-Happens due to a defect in the gene inducing G-CSF (granulocyte Colony Stimulating Factor)
Features:
-Formation of Abscess.
-Pneumonia.
-Otitis media.

- **Qualitative Defects. (Deficiency in Leukocyte function): Congenital. (7th page)**

-Happens in two categories:
A) Defect in Chemotaxis: Leukocytes are unable to travel to the site of infection. (Example: LAD: Leukocyte Adhesion Deficiency)
B) Defect in Intracellular Killing: Cells are unable to function and kill antigens.

- **Chronic Granuloma Disease (CGD) is an example. (26th slide)**

- **Defect in oxidative complex responsible for producing superoxide radicals.**
- **Neutrophils lacking free radicals (superoxide) are unable to kill the antigen even if it is phagocytized.**
- **Characterized by frequent life threatening bacterial and fungal infections in addition to granuloma formation.**

==========

Complement Deficiency. (8th page)

Classical Pathway		Lectin Pathway		Alternative Pathway	
Deficiency in: C1, C2 and C4	Leads to immune complex disease	MBL MASR1 MASR2 C2, C4	Barcterial infection	Factor D Factor B	Bacteria and Neisseria species infections

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(5th objective)

Laboratory Diagnosis of Immunodeficiency. (8th page)

1. **Complete Blood Count (Total and differential).**
2. **Evaluation of antibody levels and response to antigens.**
3. **T and B Cells counts by Flow Cytomatic Analysis.**
4. **Measurement of complement proteins and function using CH50 test.**
5. **Assessment of phagocytosis and respiratory burst (oxygen radicals). (Tests if the neutrophils are functions properly or not).**

❖ MCQs:

1) Which ONE of the following is an example of primary T-cell deficiency disease?

A) Chronic granulomatous disease (CGD)
B) AIDS
C) DiGeorge syndrome
D) Mycosis fungoids

2) Patients with B-Cell defects are most infected to infections from

A. Viral
B. Bacterial
C. Parasite
D. Fungus

3) Viruses, parasites and fungi are usually dealt with by:

A) B-Cells
B) T-Cells

4) Which ONE of the following is <u>not</u> true about X- linked hyper-IgM Syndrome?

A) Markedly elevated IgM
B) Low IgE
C) Markedly elevated IgG
D) Low IgA

5) Which ONE of the following is <u>not</u> true about XLA?

A) Reduced B-cell count
B) Reduced T-cell count
C) Absence of Immunoglobulins
D) Affected children suffer from recurrent pyogenic bacterial infections

6) Hypoparathyroidism is a mark for DiGeorge syndrome.

A) True
B) False

7) Which one of the following is not true about DiGeorge syndrome?

A) Extreme susceptibility to viral, bacterial, protozoal and fungal infections
B) Profound depression of T-cell numbers
C) Absence of T-cell responses
D) Children may present with tetany

8) Selective immunoglobulin deficiency is an acquired disease.

A) True
B) False

9) We can manage SCID by

A) Fetal thymus tissue graft
B) Surgery
C) Chemotherapy
D) Infusion of purified enzymes

10) In CGD the neutrophils are present in respiratory burst.

A) True
B) False

For any questions and suggestions please contact us on Immunology434@gmail.com

Answers: 1) C .2) B. 3) B. 4) C. 5) B.
6) A. 7) A. 8) B. 9) D. 10) B.