PRIMARY IMMUNODEFICIENCY.

Learning Objectives:

- Define immune deficiency and note its frequency and inheritance pattern
- Understand the genetic basis for immune deficiency.
- Enumerate and define the more common forms of B lymphocyte deficiency
- Enumerate and define the more common forms of T cell deficiency.

Primary verses secondary immune deficiency.

- Immune deficiency syndromes exist which affect many cells of the immune system.
- Immune deficiencies can be primary (genetic) or secondary (caused by an exogenous agent).
- Secondary immune deficiencies can result from a variety of agents.
- The single most common cause of acquired immune deficiency a part from AIDS is iatrogenic.

- **NB:** Most importantly, the underlying immune deficiency, regardless of its cause, predicts the clinical and laboratory features of the disease.
- E.g. AIDS is primarily a malfunction/depletion of CD4+ lymphocytes and hence the unique role of CD4+ lymphocytes in immune function.

Primary immune deficiency Syndromes.

- The primary immune deficiencies are genetic and as such are usually apparent within the first several years of life.
- Often, they appear after the newborn is six months of age.
- The diagnosis is always suspected in children who suffer from recurrent, protracted infections.

Types of Primary Immune deficiency Syndromes.

1. Congenital, X-linked Agammaglobulinemia (Bruton Disease)

- The disease is related to an inherent inability of the B cells to properly rearrange immunoglobulin heavy chain genes.
- Without proper gene rearrangement, it is impossible for the pre-B cell to differentiate into a mature B cell.
- The molecular basis is a defect in Bruton's tyrosine kinase (BTK).
- Symptoms appear 5-6 months after birth

- Histologically, these patients have underdeveloped germinal centers in lymphoid organs;
- They have decreased levels of circulating B cells but have normal levels of pre-B cells in the bone marrow.
- Total serum immune globulins are reduced.

- **Clinically**, the patients have a plethora of infections most commonly caused by *Streptococcus pyogenes, Staphylococcus aureus* and encapsulated organisms such as *Haemophilus influenzae* and *Streptococcoccus pneumoniae*.
- These can result in lethal pneumonias.
- Increased susceptibility to enteroviruses is also seen.
- The incidence of autoimmune disorders is increased.

2. Common Variable Immune Deficiency.

- This disease may be congenital or acquired.
- All patients have hypogammaglobulinemia. This may be all isotypes or only IgG.
- About one third of patients have a decreased circulating number of B lymphocytes.

- The B lymphocyte-rich areas of lymphoid organs are hyperplastic.
- The underlying mechanisms are different in various patients.
- Some have B-cell defects while others are affected by antibodies directed against B cells.
- A few have T-cell regulatory abnormalities.
- **Clinically**, patients are susceptible to recurrent bacterial infections similar to Bruton's Disease; however, onset is frequently in late (> 2yrs).

3. Isolated IgA deficiency.

- IgA deficiency is characterized by frequent respiratory infections, diarrhea, and hypersensitivity reactions.
- This disease is relatively frequent, affecting 1:700 individuals
- Most remain entirely asymptomatic.

- The underlying disorder is not well characterized but it appears that the maturation and terminal differentiation of IgA-secreting B cells is blocked.
- Rare patients also lack IgG2 and IgG4 as well as IgA and are more susceptible to infections.
- About one half of patients have IgE directed to IgA; these patients can have anaphylactic reactions to exogenous IgA if given experimentally or therapeutically.

4. Thymic Hypoplasia (DiGeorge Syndromes)

- This is a rare, severe immune deficiency and is a classic example of T-cell deficiency.
- It occurs when the third and fourth pharyngeal pouches fail to develop properly, leading either to absent or severely hypoplastic thymus.
- Additionally, these patients frequently lack parathyroid glands and have malformation of the great vessels of the heart.
- Presentation of this defect may be calcium abnormalities early in life, secondary to the lack of parathyroid glands.
- Abnormal facies are common.

- This disease is developmental but has a genetic basis in that 22q11 is deleted.
- If there is some thymic tissue, the patients frequently will develop normal thymic responses by the age of five years.
- The types of opportunistic infections mimic children with AIDS.
- They include fungal, viral, protozoan infections and recurrent infections with intracellular bacteria.

5. Severe Combined Immune Deficiency

- The term “combined” suggests that a portion of both the humoral (B cells) and cell-mediated (T cells) immune system is affected.
- Errors may occur primarily within one system or the other.
- Several variants exist. All are rare.
- In all cases, the thymus is hypoplastic.

- The most common form is X-linked and results from a mutation in the gamma (γ) chain of a cytokine receptor family, resulting in aberrant responses to a variety of cytokines.
- The second common variant, adenosine deaminase deficiency (ADA), affects T cells more than B cells. In this disease, there is an accumulation of adenosine and deoxyadenosine triphosphate which is toxic to lymphocytes and especially to T lymphocytes.

- The most common opportunistic pathogens seen in SCID are *Candida sp. Pneumocystis carinii*, and *cytomegalovirus* although any number of bacterial, viral, fungal, and protozoal infections can occur.
- Therapy is bone marrow transplantation.

6. Wiskott-Aldrich Syndrome.

- This X-linked disease is an X-linked recessive disorder with complex clinical features including eczema, thrombocytopenia, and recurrent infection by encapsulated bacteria.
- The immune deficiency is not known but appears to involve both B and T lymphocytes.
- IgM is usually quite deficient.
- The defect appears to be in a cytoskeletal protein called Wiskott Aldrich syndrome protein (WASP)