11) Primary Immunodeficiencies

I. Overview of Immunodeficiencies

- **Definition**: Immunodeficiency results from a failure or absence of elements of the immune system, including lymphocytes, phagocytes, and the complement system.
- **Primary (Congenital)**: These are genetic defects that result in increased susceptibility to infection, frequently manifested in infancy and childhood.
- **Secondary**: These occur when the immune system is compromised due to environmental factors and are far more common than primary immunodeficiencies.
- **Clinical Presentation**: Patients typically have a history of recurrent infections, infections caused by rare microorganisms, and opportunistic infections. They are also susceptible to certain cancers, often caused by oncogenic viruses like Epstein-Barr.

II. Innate Immunity Defects

1. Phagocyte Disorders

- **Chronic Granulomatous Disease (CGD)**:
  - **Mechanism**: Caused by mutations in components of the **phagocyte oxidase (phox)** enzyme complex.
  - **Effect**: Results in defective production of superoxide anion, leading to a failure to kill phagocytosed microbes, especially those producing **catalase**.
  - **Result**: Because infections are not controlled, they stimulate chronic cell-mediated responses, resulting in the formation of **granulomas**.
- **Leukocyte Adhesion Deficiency (LAD)**:
  - **Mechanism**: Autosomal recessive disorders caused by defects in leukocyte and endothelial adhesion molecules.
  - **LAD 1**: The molecular basis is absent or deficient expression of **\beta_{2} integrins**.
  - **LAD 2**: Results from an absence of **sialyl Lewis X**, the carbohydrate ligand required for binding to E-selectin and P-selectin.
  - **Clinical Signs**: Characterized by failure of neutrophil recruitment to sites of infection, severe **periodontitis**, and an **inability to make pus**.
- **Chédiak-Higashi Syndrome**:
  - **Mechanism**: Caused by mutations in the gene encoding the lysosomal trafficking regulator protein **LYST**.
  - **Effect**: Results in **defective phagosome-lysosome fusion** in neutrophils and macrophages.
  - **Manifestations**: Reduced resistance to infection, **albinism** (defective melanosomes), nerve defects, and bleeding disorders.

2. Complement Deficiencies

- **C2 Deficiency**: This is the **most common** human complement deficiency.
- **C3 Deficiency**: Associated with frequent serious **pyogenic bacterial infections** that may be fatal, due to its central role in opsonization.
- **Terminal Component Defects (C5-C9)**: The only consistent clinical problem is a propensity for disseminated infections by **Neisseria bacteria**.

III. Adaptive Immunity Defects

1. Severe Combined Immunodeficiencies (SCID)

- **Definition**: Congenital immunodeficiencies that affect both humoral and cell-mediated immunity, specifically those where most peripheral **T cells are missing or defective**.
- **Mechanism (X-linked)**: About 50% of SCIDs are X-linked, often involving **cytokine receptor common \gamma chain mutations**.
- **DiGeorge Syndrome**:
  - **Mechanism**: A congenital malformation (22q11 deletion) causing defective development of the **thymus** and parathyroid glands.
  - **Clinical Features (CATCH-22)**: Cardiac abnormalities, Abnormal facies, **Thymic hypoplasia** (T cell deficiency), Cleft palate, and **Hypocalcemia**.
- **"Nude" Mouse System**:
  - **Mechanism**: A mutation causes a failure of differentiation of epithelial cells required for the development of the **thymus and hair follicles**.
  - **Effect**: Consequently, these mice lack **T cells and hair**.

2. Antibody Deficiencies (B Cell Development and Activation)

- **X-linked Agammaglobulinemia (Bruton's)**:
  - **Mechanism**: A prototype of failure of B cell maturation caused by a **Btk mutation**.
  - **Findings**: Absence of B cells in peripheral blood, **no germinal centers** in lymph nodes, and no plasma cells in tissues.
- **Common Variable Immunodeficiency (CVID)**:
  - **Definition**: A group of heterogeneous disorders defined by **reduced levels of serum Ig**, impaired antibody responses to infection or vaccines, and increased incidence of infections.
- **X-linked Hyper-IgM Syndrome**:
  - **Mechanism**: Mutations in the gene encoding the T cell effector molecule **CD40 ligand (CD154)**.
  - **Effect**: Defects in isotype switching, somatic mutation, and germinal center formation.

3. Defect in T Lymphocyte Activation and Function

- **Wiskott-Aldrich Syndrome**:
  - **Definition**: An X-linked disease characterized by **eczema**, **thrombocytopenia** (reduced blood platelets), and susceptibility to bacterial infection.

IV. Assessment and Conclusion

- **Investigation**: Includes assessment of immunoglobulins, **B and T-lymphocyte counts**, lymphocyte stimulation assays, and phagocytic activity.
- **Red Flags**: Suspect primary immunodeficiency if there are unexplained recurrent infections, infections with opportunistic pathogens, or **failure to thrive**.
- **Conclusion**: Physicians must rule out **secondary immunodeficiencies** (e.g., HIV, malnutrition, use of immunosuppressive drugs) as they are far more common than primary genetic defects.

V. High-Yield Revision Summary

Disease Category	Specific Disease	Key Mechanism / Gene	Major Clinical Finding
Phagocyte	CGD	**phox** mutation	**Granulomas**; catalase+ infections
Phagocyte	LAD 1	**\beta_{2} integrin** defect	**No pus**; severe periodontitis
Phagocyte	Chédiak-Higashi	**LYST** mutation	**Albinism**; pyogenic infections
Complement	Terminal (C5-C9)	Terminal components	**Neisseria** infections
SCID	DiGeorge	**22q11 deletion**	**Thymic hypoplasia**; hypocalcemia
Antibody	X-linked Agamma.	**Btk** mutation	**Absent B cells**; no germinal centers
Antibody	Hyper-IgM	**CD40L** mutation	No isotype switching; high IgM
T Cell Function	Wiskott-Aldrich	X-linked	**Eczema**; thrombocytopenia