10) Secondary Immunodeficiencies

I. Overview of Secondary (Acquired) Immunodeficiencies

Secondary immunodeficiencies are **not genetic**; they are **acquired during life** due to external factors. They increase susceptibility to infections by reducing immune cell production, survival, or function.

Major Causes and Mechanisms

- **HIV Infection:** Leads to the **depletion of CD4+ helper T cells**.
- **Cancer Treatments:** Irradiation and chemotherapy cause **decreased bone marrow precursors** for all leukocytes.
- **Immunosuppressive Drugs:** Used for graft rejection or inflammatory diseases; they **blunt immune responses by design**.
- **Cancers involving Bone Marrow:** (e.g., leukemias, metastases) Reduce the site of leukocyte development.
- **Protein-Calorie Malnutrition:** Causes **metabolic derangements** that inhibit lymphocyte maturation and function. It is a common cause worldwide in settings of poverty.
- **Loss of Spleen:** Results in **decreased phagocytosis** of microbes.

II. HIV Structure and Entry

HIV is a **retrovirus** that primarily infects **CD4+ T lymphocytes**, leading to their progressive destruction.

- **Viral Components:** Contains two RNA strands, a protein core (p24 capsid), and a lipid envelope. Key enzymes include **reverse transcriptase, integrase, and protease**.
- **Mechanism of Entry:** The viral glycoprotein **gp120 binds to CD4** and chemokine receptors (**CCR5 or CXCR4**) on the host cell.
- **Targets:** While CD4+ T cells are the major target, macrophages and dendritic cells can also be infected or serve as reservoirs.

III. The HIV Life Cycle

1. **Binding and Fusion:** gp120 binds to receptors; the viral membrane fuses with the host cell.
2. **Reverse Transcription: Reverse transcriptase** creates a DNA copy of the viral RNA.
3. **Integration: Integrase** inserts the viral DNA into the host genome, forming a **provirus**.
4. **Activation:** When the T cell is activated by cytokines/infection, the provirus is transcribed.
5. **Assembly and Budding:** Viral proteins are processed by **proteases**, and new virions bud from the cell membrane.

IV. Pathogenesis and Clinical Course

The progression to AIDS (Acquired Immunodeficiency Syndrome) occurs over many years.

- **Clinical Latency:** A period with few symptoms where the virus spreads to lymphoid tissues, and CD4+ T cells steadily decline.
- **CD4+ T Cell Depletion:** Primarily caused by the **cytopathic effect** of viral replication.
- **AIDS Diagnosis:** Occurs when the blood **CD4+ count falls below 200 cells/mm³** (Normal is ~1500).
- **Opportunistic Infections:** Patients become susceptible to intracellular microbes (e.g., *Pneumocystis jirovecii*, CMV) normally controlled by T cells.
- **Malignancies:** Prone to **EBV-associated B cell lymphomas** and **Kaposi sarcoma**.

V. Treatment and Resistance

- **ART (Combination Antiretroviral Therapy):** Targets reverse transcriptase, protease, and integrase. It reduces opportunistic infections but **cannot eradicate the virus** due to latent reservoirs and high mutation rates.
- **Genetic Resistance:** Rare individuals lacking functional **CCR5** (32-bp deletion) are resistant to HIV.
- **Elite Controllers:** Patients who control the infection without therapy, often associated with specific HLA alleles like **HLA-B57 and HLA-B27**.

Summary Table: Causes of Secondary Immunodeficiency

Cause	Mechanism of Immunodeficiency
HIV Infection	Depletion of CD4+ helper T cells
Chemotherapy / Irradiation	Decreased bone marrow precursors for all leukocytes
Immunosuppressive Drugs	Depletion or functional impairment of lymphocytes
Bone Marrow Cancers	Reduced site of leukocyte development
Protein-Calorie Malnutrition	Metabolic derangements inhibit lymphocyte maturation/function
Splenectomy (Loss of Spleen)	Decreased phagocytosis of microbes