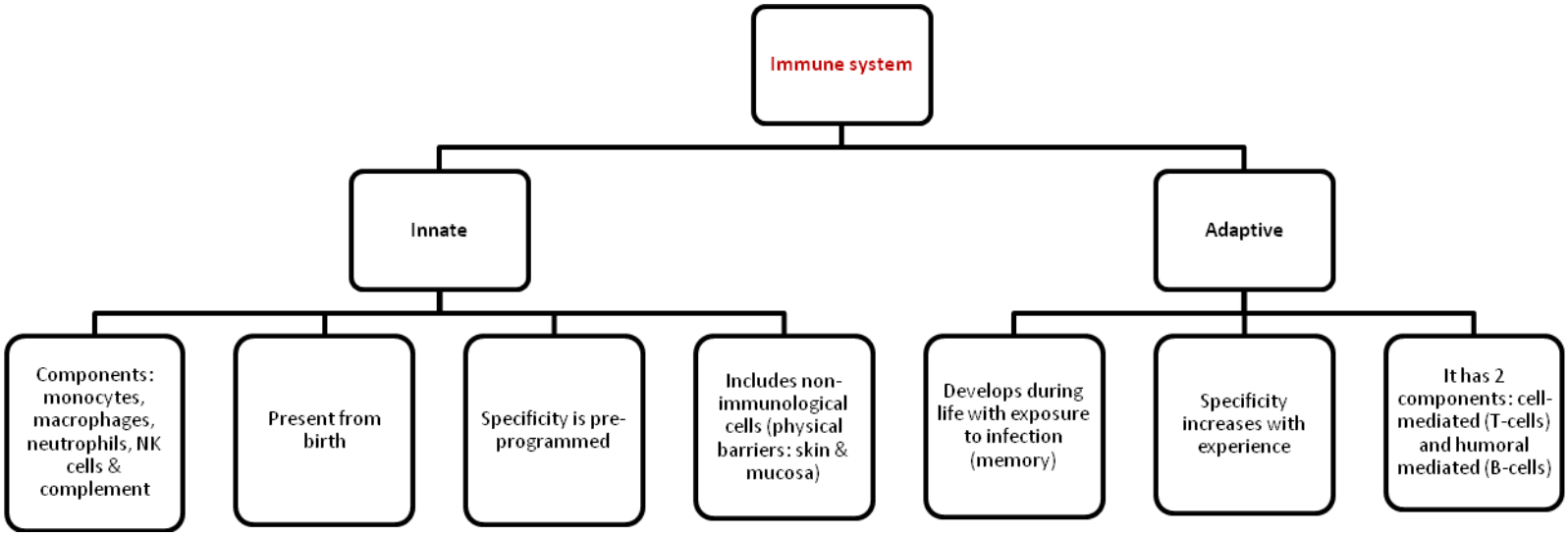
THE IMMUNE SYSTEM

- **Function**: recognizing pathogens (foreign non-self antigens) and organizing a defense response against them by facilitating destruction and elimination.



- **Lymphoid organs:**
  - **Primary:**
    - ✓ *Bone marrow*: where B-lymphocytes are produced and mature.
    - ✓ *Thymus*: T-lymphocytes which are produced in the bone marrow will migrate to thymus for proliferation and maturation.
  - **Secondary (where naïve lymphocytes will get exposed to antigens so they develop specificity):**
    - ✓ Spleen.
    - ✓ Lymph nodes.
    - ✓ MALT: Mucosal Associated Lymphoid Tissue (this was explained in anatomy notes).
- **Monocytes (CD14) & macrophages:**
  - They interact with microbes and secrete cytokines (TNF & IL-1).
  - In addition they act as antigen presenting cells (APC): they will ingest pathogens, process and present them to T-cells so these cells can recognize them and be activated.
  - Macrophages are activated by IFN-γ which is produced by TH1 cells so they can kill the microbes.
  - They use complement and antibodies to phagocytose microbes
    Note: this is known as opsonization where there will be enhancement of phagocytosis by IgG and C3b.
- **Natural Killer (NK) cells (CD15/CD56):**
  - They are produced by lymphoid progenitor cells (which also produce B & T lymphocytes) but they are considered as part of the innate immune system.
  - They kill tumor cells and virus infected cells… HOW?
    This is mediated by binding of the activation receptor which is present on the surface of NK cells to lectins which are presented on the surface of virus infected cells and tumor cells. Then, killing will be initiated by perforin and granzymes which induce cell apoptosis.
- **B-lymphocytes (CD9/CD20):**
  - They develop and mature in the bone marrow.
  - Considered as humoral-immunity because they produce antibodies when they are converted to plasma cells. These antibodies or immunoglobulins:
    - ✓ Neutralize viruses by forming immune complexes.
    - ✓ Opsonize microbes for phagocytosis (only IgG), usually with complement (C3b).
    - ✓ Target cells for cytotoxicity (ADCC: antibody-dependent cellular cytotoxicity).

- **Complement**:
  - They function alone or with antibodies to:
    - ✓ Kill microbes and lyse cells (C5b).
    - ✓ Opsonize microbes for phagocytosis (C3b).
  - Chemotaxis of monocytes and neutrophils (C5a).
  - Contributes to inflammation after tissue damage.

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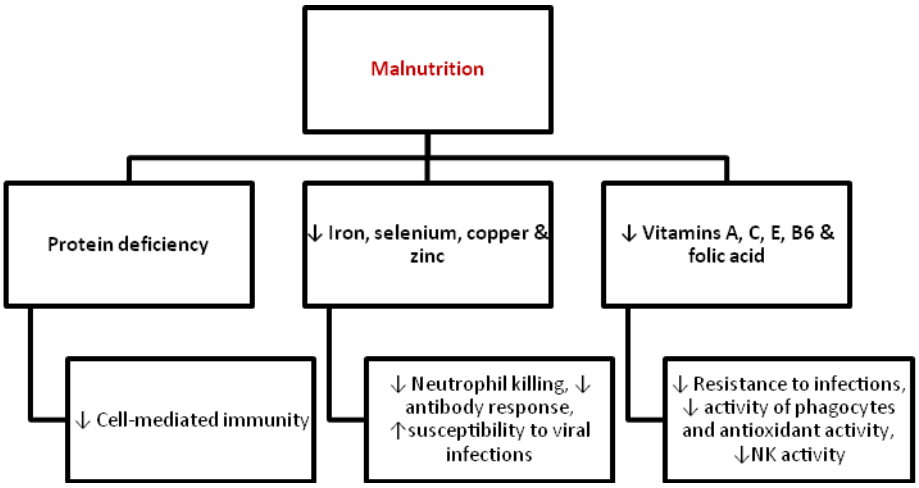
AQUIRED IMMUNODEFICIENCIES



- **Other causes include**: AIDS, measles, liver failure, neutropenia, hyposplenism & steroids.

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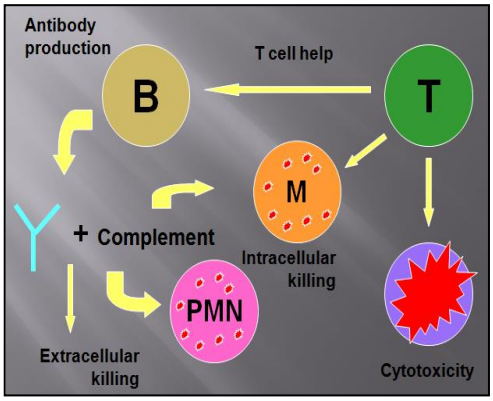
PRIMARY IMMUNODEFICIENCY DISEASES

- **Definition**: conditions characterized by intrinsic deficits (عجز داخلي في الجسم) within the immune system and are caused by inherited or de novo genetic defects.
- **Primary immunodeficiency disease are mostly:**
  - Antibody deficiencies (65%).
  - And combined cellular and antibody deficiencies (15%).
- **Symptoms of immunodeficiency include (look to the 10 warning signs of immunodeficiency in the figure):**
  - **Infections**:
    - ✓ Which tend to be frequent, severe with unusual organisms that are difficult to treat.
    - ✓ And thus these infection will cause failure to thrive (failure of an infant to gain weight or grow normally).
  - **Autoimmune diseases:**
    - ✓ These occur when the immune system of the body cannot distinguish self from non-self and therefore it starts attacking the own antigens of the body.
  - **Immune dysregulation:**
    - ✓ ↑ risk of malignancy.

- **Diagnosis**:
  - This is done by medical history (patterns of infection), physical examination, laboratory testing and referral to an immunologist.
- **Immune effector mechanisms (figure):**
  - starting at the upper right hand corner, T cells help B cells in the process of antibody production. Antibodies and complement work together to kill extracellular pathogens and complement attracts PMNs and aids in opsonization/phagocytosis and intracellular killing by macrophages. T cells also activate macrophages and mediate cytotoxicity. NK cells are not shown, but also mediate cytotoxicity.



- **Defects of humoral immunity (antibody deficiency):**
  - **Pattern of infections:**
    - ✓ *Bacteria*: pneumococcus, meningococcus, Pseudomonas, H.flu, Noraxella, S.aureus, Campylobacter, Mycoplasma & Ureaplasma.
    - ✓ *Viruses*: enteroviruses and rotavirus.
    - ✓ *Protozoa*: Giardia & Cryptospordium.
  - **Diagnostic tools for antibody deficiency:**

Deficiency	Screening Tests	"Advanced Tests"
Antibody	Quantitative serum immunoglobulins (IgG, A, M, E)	IgG subclasses (only helpful in some cases)
	Antibody response to vaccinations (tetanus, diphtheria, pneumococcus)	Antibody response to vaccinations post boosting
	Isohemagglutinin titer (IgM)	B cell enumeration CD19, CD20
		Bacteriophage (neoantigen)

→ This is done by flow cytometry which will reveal the absence of CD19 or CD20 (no dots will appear on the graph)

  - **Diseases of antibody deficiencies:**
    - ✓ *Agammaglobulinemia*: which can be X-linked or AR and characterized by universally low immunoglobulins (IgM, IgG and IgA).
    - ✓ *Hyper-IgM syndrome*: this is X-linked and caused by deficiency of CD40L on activated T-cells. Signs and symptoms include: high serum titers of IgM without other isotypes.
    - ✓ *Common variable immunodeficiency*: the reason behind it is unknown. Signs and symptoms include: onset in late teens, immunoglobulin levels will decrease with time and there will be increased autoimmunity.
    - ✓ *Selective IgA-deficiency*: signs and symptoms include repeated sino-pulmonary & gastrointestinal infections + increased atopy.
    - ✓ *Transient hypogammaglobulinemia of infancy (it resolves by 16-30 months)*: the reason behind this condition is delayed onset of normal IgG synthesis. Signs and symptoms include: susceptibility to pyogenic bacteria.

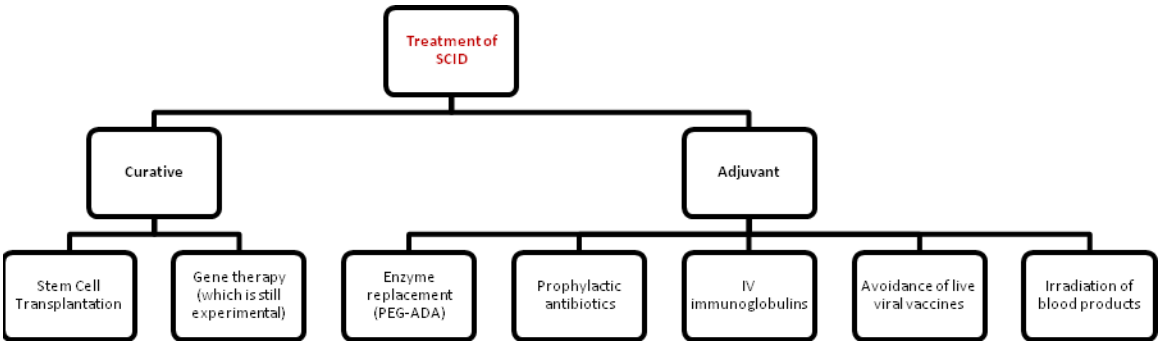
    Note: the treatment of these diseases is by immunoglobulins and antibiotics prophylaxis

- **Cellular immunodeficiency:**
  - **Defects in IL-12/IFN-γ axis:**
    - ✓ *Pattern of infections:*
      * Mycobacteria, Salmonella, Candida, Pneumocystis & Herpes viruses.
  - **Combined immunodeficiency:**
    - ✓ *Pattern of infections: same as for humoral and cellular deficiencies plus:*
      * Bacteria: Listeria.
      * Viruses: measles, influenza, parainfluenza & RSV.
      * Fungi: Cryptococcus & histoplasma.
      * Protozoa: toxoplasma
  - **Diagnostic tools for T-cell deficiency:**

Deficiency	Screening Tests	"Advanced Tests"
Cellular (T cell or combined)	Absolute lymphocyte count	T cell enumeration CD3, CD4, CD8 NK cell enumeration CD16/56
	Delayed Type Hypersensitivity Skin Testing	Lymphocyte proliferation to mitogens: PHA, PWM, ConA Lymphocyte proliferation to antigens: Tetanus, Candida
	HIV Antibody or PCR	

→
- CD3, present on all T cells
- CD3/CD4, helper T cells
- CD3/CD8, cytotoxic T cells
- CD19, B cells
- CD16/CD56, NK cells

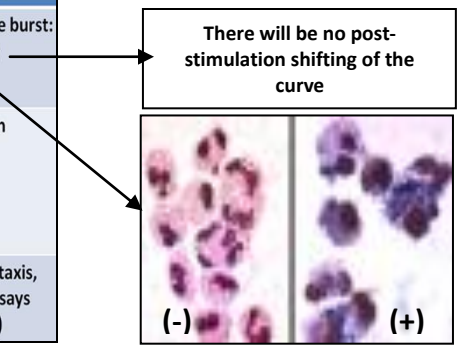
- **Diseases of T-cell deficiency:**
  - ✓ *Severe Combined Immunodeficiency (SCID):*
    * It is inherited as X-linked (most common) or AR.
    *Caused by: defects in γ-chain (which is required for the synthesis of IL-2, IL-4, IL-7, IL-9 and IL-15) or adenosine deaminase deficiency (which will result in toxic metabolic products in the cells) or rag1 & rag2 gene nonsense mutations (which will result in total absence of B & T lymphocytes).
    * Clinical features: chronic diarrhea; skin, mouth, and throat leasions; fungal infections; low levels of circulating lymphocytes; and cells are unresponsive to mitogens.
    * Treatment:



  - ✓ *Wiskott-Aldrich syndrome*: which is X-linked and caused by a defect in cytoskeletal glycoprotein, signs and symptoms include: thrombocytopenia, immunodeficiency and eczema. In addition, IgA and IgE are high.
  - ✓ *Ataxia telangiectasia*: cause by a defect in kinase involved in the cell cycle. Signs and symptoms include: ataxia (التَرنُّح في المشي), telangiectasia (capillary distortions in the eye) and deficiency of IgA and IgE production.
  - ✓ *DiGeorge syndrome*: caused by thymic aplasia. Signs and symptoms include: facial abnormalities, hypoparathyroidism, cardiac malformations and depression of T-cell numbers and their responses.

- **Phagocyte defects (chronic granulomatous disease):**
  - **Pattern of infections:**
    - ✓ *Bacteria*: catalase (+) which include:
      * S.aureus, Serratia, Nocardia & Klebsiella.
    - ✓ *Fungi:* Candida, Aspergillus, Paecilomyces.
  - **Diagnostic tools for neutrophil defects:**

Deficiency	Screening Tests	"Advanced Tests"
Neutrophil/Phagocyte	Absolute neutrophil count Cell morphology	Evaluation of oxidative burst: DHR (flow cytometry) NBT (microscopy)
		Evaluation of adhesion molecules (CD18, CD11) IFNg R on monocytes
		Phagocytic, chemotaxis, bacterial killing assays (research labs)



  - **Disease of phagocyte defects:**
    - ✓ *Chronic Granulomatous Disease (CGD)*: which can be inherited as X-linked or AR and caused by deficiency of NADPH oxidase resulting in the failure of generating superoxide anion and other oxygen radicals which function in killing the microbe. Patients will have recurrent infections with catalase (+) bacteria and fungi.
    - ✓ *Chediak-Higashi syndrome*: in which there is granule structural defect. There will be recurrent infections with bacteria, absent NK activity & partial albinism.

- ✓ *Leukocyte adhesion deficiency*: which is caused by absence of CD18. There will be recurrent and chronic infections, fail to form pus and omphalitis.

- **Complement deficiency:**
  - **Pattern of infections:**
    - ✓ Encapsulated organisms (Neisseria & pyogenic infections).
    - ✓ Autoimmune disease is frequent.
  - **Diagnostic tools for complement deficiency:**

Deficiency	Screening Tests	"Advanced Tests"
Complement	CH50 AH50 C3, C4 MBL level	Individual component testing MBL genotype

- Complement pathway defects
- Early components: C1q, C2, C4, C3 = recurrent encapsulated bacterial infections
- Terminal components, C5-C9: recurrent meningococcal infections