KMTC/QP-07/COL

KENYA MEDICAL TRAINING COLLEGE

MAKINDU CAMPUS

YEAR I SEMESTER 1

Immunology

CREDIT hours 10 hrs

FACULTY

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CONTENT

1. Definitions
2. Immunological concepts
    1. Antibody
    2. Antigen
    3. complement
3. Types of immunity
    a. Humoral
    b. Cellular
    c. Passive
    d. Active
    e. Herd immunity
4. Clinical importance
5. Principles of infection prevention and contral

Concepts and Introduction

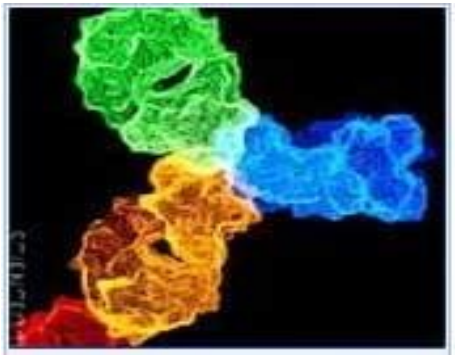
- The Latin term "**immunis**" meaning "exempt" gave rise to the English word "immunity",= mechanisms used by the body to protect against environmental agents that are foreign to the body.
- These agents may be microorganisms or their products, foods, chemicals, drugs, pollen or animal hair.

- **Definition:**
- **Immunity** The study of the physiologic mechanisms that allow the body to recognize materials as foreign or abnormal and to neutralize or eliminate those foreign materials.
- **Immunology**
  - Study of the components and function of the immune system

- **Immune system** = cells, tissues, and molecules that mediate resistance to infections
- **Immunology** = study of structure and function of the immune system
- **Immunity** = resistance of a host to pathogens and their toxic effects
- **Immune response** = collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules of the immune system

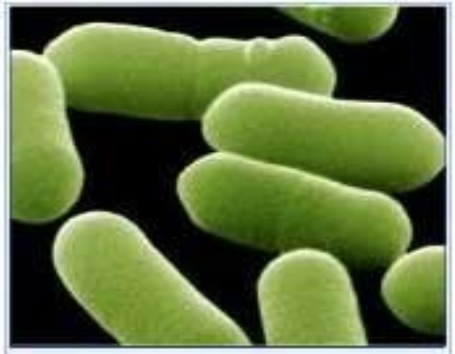
- **Endemic** when a small number of cases occur constantly among the population of a community e.g. Typhoid
- **Epidemic** The disease flares up and large number of cases develop with in a community with in a short time. E.g. Influenza
- **Pandemic** when an epidemic becomes very widespread areas in the world involving large number of people within a short period).

Divisions of Immunology



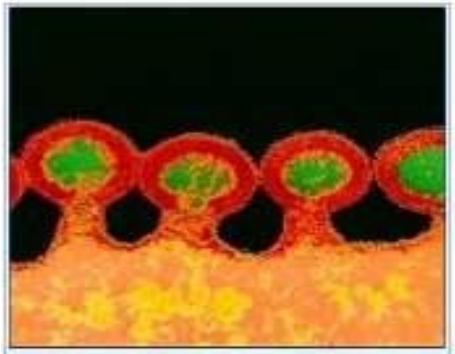
Adaptive Immunity

Innate Immunity

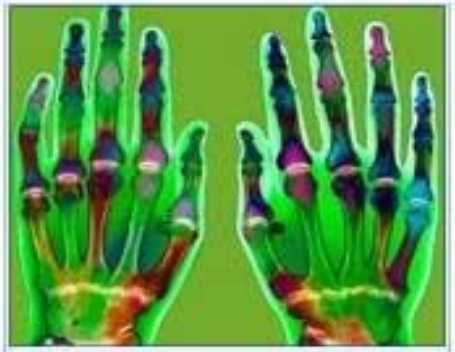


Infectious Disease

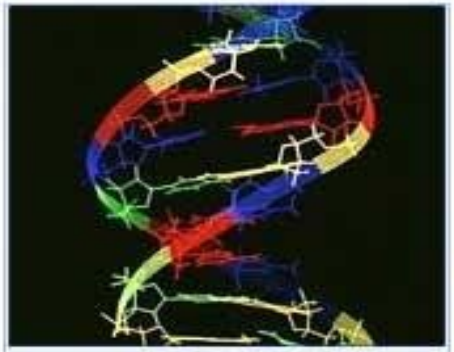
Developmental Immunology



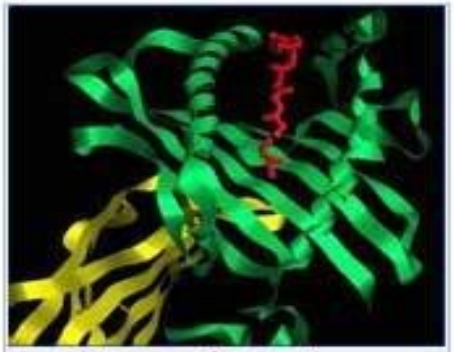
Immunodeficiency



Autoimmunity



Cancer Immunology



Transplantation Immunology

- **Immune System**
  - Molecules, cells, tissues and organs which provide non-specific and specific protection against
    - Microorganisms
    - Microbial toxins
    - Tumor cells
  - Crucial to human survival

- **Immune response**
  - Innate (non-specific)
  - Adaptive (specific)
    - Primary
    - Secondary
- **Immunity**
  - State of non-specific and specific protection
- **Acquisition of Immunity**
  - Natural
  - Artificial

SELECTIVITY and SPECIFICITY—

The immune system is highly selective and specific for each pathogen

1 pathogen=1 response

MEMORY— Once having met a pathogen, the immune system never forgets it.

If you are re-challenged with the same pathogen the memory response will recognize it immediately-- and destroy it or neutralize it.

- With such a fabulous memory we should *never* get the same disease twice! Exceptions…?

So, how do you acquire memory?

- You either suffer the infection…
- VACCINATE, VACCINATE, VACCINATE!
- ??????future
- Shampoos as vaccines
- using foods

Organs Of Immune System

- Primary Lymphoid Organs
  - Bone Marrow and Thymus
  - Maturation Site
- Secondary Lymphoid Organs
  - Spleen, lymph nodes,
  - MALT (mucosal associated lymph tissue)
  - GALT (gut associated lymph tissue)
  - Trap antigen, APC, Lymphocyte Proliferation

ORIGIN OF CELLS OF THE IMMUNE SYSTEM

- Derived from common progenitor cell in bone marrow
  - Pluripotent hematopoietic stem cell
- Progenitor Stem Cells
  - Erythroid lineage
    - Erythrocytes and Megakaryocytes
  - Myeloid lineage
    - Monocyte/macrophage, dendritic cells, PMN's, mast cells
  - Lymphoid lineage
    - Small and large lymphocytes

CELLS OF INNATE AND ADAPTIVE IMMUNITY

- Myeloid Lineage
  - Neutrophil
    - Principal phagocytic cell of innate immunity
  - Eosinophil
    - Principal defender against parasites
  - Basophil
    - Functions similar to eosinophils and mast cells
  - Referred to as
    - Polymorphonuclear leukocytes (PMN's)
      - Nuclei are multilobed (2 to 5)
    - Granulocytes
      - Cytoplasmic granules

- Myeloid lineage
  - Monocytes
    - Leukocytes with bean shaped or brain-like convoluted nuclei
    - Circulate in blood with half life of 8 hours
    - Precursors of tissue macrophages
  - Macrophages
    - Mononuclear phagocytic cells in tissue
    - Derive from blood monocytes
    - Participate in innate and adaptive immunity

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- Dendritic cells
  - Cells with dendriform (star shaped) morphology
  - Interdigitating reticular cells (synonym)
  - Capture and present antigens to T lymphocytes
- Mast cells
  - Located in mucous membrane and connective tissue throughout body
  - Major effector cell in allergy
  - Modulation of initial immune response

- Lymphoid Lineage
  - Large lymphocytes (large granular lymphocytes)
    - Natural killer (NK) cells (CD16, CD56)
    - Innate immunity to viruses and other intracellular pathogens
    - Participate in antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Small lymphocytes
    - B cells (CD19)
    - T cells (CD3, CD4 or CD8)
    - Adaptive immunity
  - Lymphocytes refers to small lymphocytes

THE CLUSTER OF DIFFERENTIATION (CD)

- CD markers on leukocytes

Granulocyte	CD45+, CD15+
Monocyte	CD45+, CD14+
T lymphocyte	CD45+, CD3+
T helper lymphocyte	CD45+, CD3+, CD4+
T cytotoxic lymphocyte	CD45+, CD3+, CD8+
B lymphocyte	CD45+, CD19+
Natural killer cell	CD45+, CD16+, CD56+, CD3-

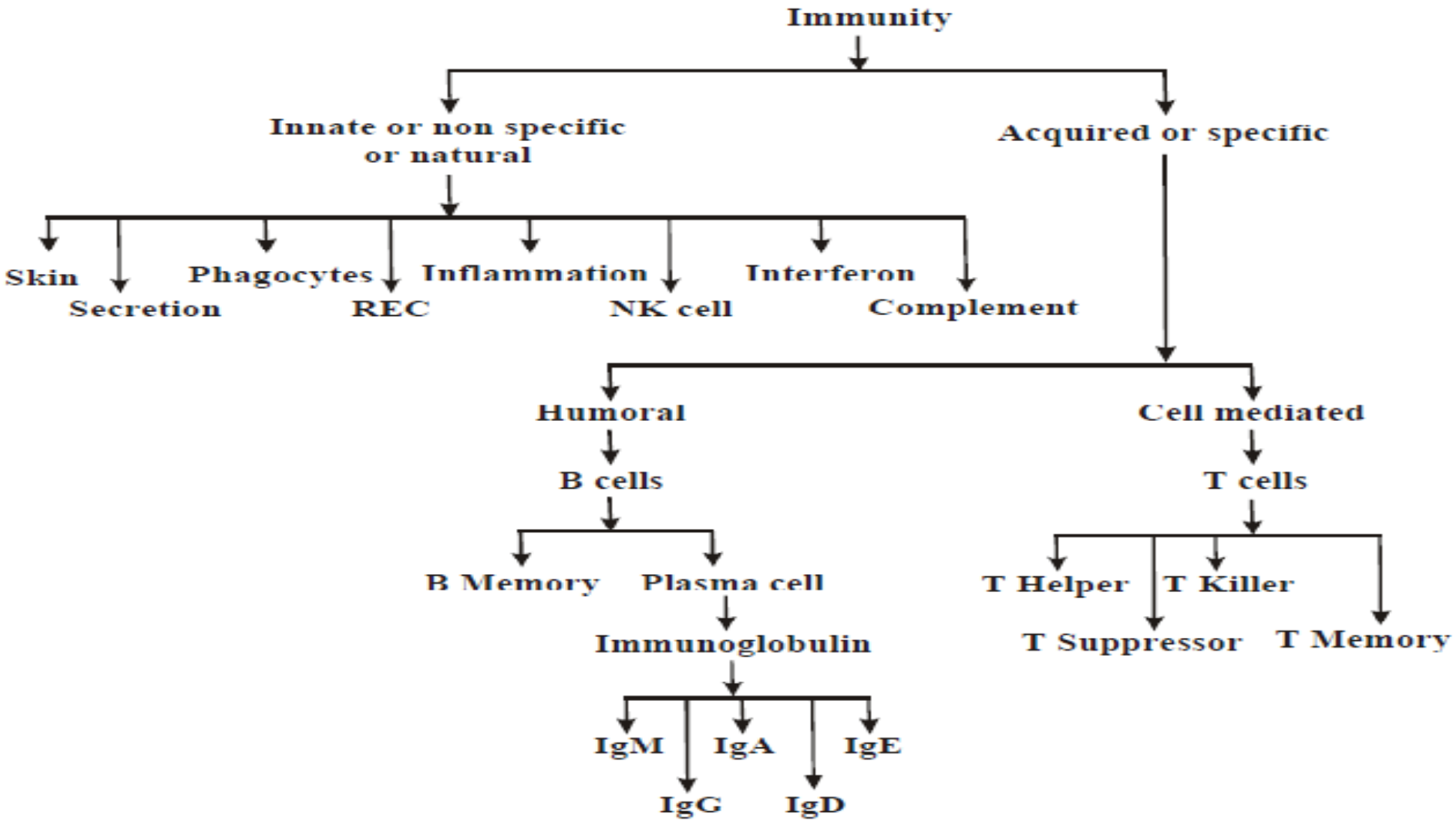
Types of immunity

- **Immunity classification**
- Depending on the nature of response towards the pathogen, Immune system is broadly classified into
  - Natural and
  - Acquired immunity.

- **Inborn or innate immunity**: It is present at birth; This is our First Line Of Defense.
- **Acquired or specific**: It is not present at birth but becomes part of our immune system as the lymphoid system develops.
- **1970: WHO defined immunity as immune response to antigen (Foreign body) in form of**
- **Humoral** (activation of B-lymphocytes)
- **Cellular** (by activation of T-lymphocytes

1. **Innate (non-adaptive)**
   - first line of immune response
   - relies on mechanisms that exist before infection
2. **Acquired (adaptive)**
   - Second line of response (if innate fails)
   - relies on mechanisms that adapt after infection
   - handled by T- and B- lymphocytes
   - one cell determines one antigenic

Classification of Immunity



1. Natural Immunity

- *Innate immunity* or *natural immunity*
- The **non specific immunity** present from birth, It protects the body against any foreign invaders and does not show any specificity.
- It is also functionally matured in a new born.
- It does not become more efficient after subsequent exposures to same organism.

components

- Anatomic
  - Skin
  - Mucous membranes
- Physiologic
  - Temperature
  - pH
  - Chemical mediators

- Phagocytic
  - Cells specialized in the process of phagocytosis
    - **Macrophages**
      - **Reside in tissues and recruit neutrophils**
    - **Neutrophils**
      - **Enter infected tissues in large numbers**
  - Recognize common molecules of bacterial cell surface
    - using a few surface receptors
- Inflammatory

Components (Cell types) involved in immunity

- The cells of the immune system include leukocytes/ white blood cells (WBC).
- They developed from the bone marrow stem cells and give rise to two families of white blood cells
- ***Myeloid*** cells (named after bone marrow) *Basophils, Eosinophils and Neutrophils.*
  - The **monocytes** give rise to ***macrophages*** *when enter into the tissue space from blood circulation. Similarly,* ***Basophil*** *are transformed to* ***mast*** *cells.*

- ***Lymphoid* cells**, which take their name from the lymphatic system. Include **T and B lymphocytes** which get their **maturation in different lymphoid organs.**
- B-cell maturation begins in the liver (fetal) and continues within the bone marrow as maturation progresses (adult) and
- ***T cells*** complete their **maturation in the thymus.**

Mechanisms involved in Natural immunity

- **Skin barrier** covers and protects the body as a barrier to prevent invading pathogens.
- Intact skin prevents the penetration of most pathogens, by secreting lactic acid and fatty acids which lower the skin pH.
- **Mechanical barriers,** Mucous membranes form the external layer where body is not covered with skin and it plays an important role in the prevention of pathogen entrance by trapping them.
- Movement of the mucociliary process in the upper respiratory tract, the cilia in the eyelids act as escalators to remove the pathogens.

- **Secretions,** Sweat has antibacterial substances and tears contain lysozyme.
- Mucous secretion in nose prevents the dust and microorganism entry into the respiratory tract.
- Saliva contains lysozyme, thiocyante and lactoferrin.
- The HCl acid secreted in the stomach kills the microbes.
- **Phagocytosis,** The ingestion (endocytosis) and killing of microorganisms by specialized cells called as phagocytes. Phagocytes are polymorphonuclear leukocytes (eg. Neutrophils) and mononuclear cells (Monocytes and Macrophages).

- **Opsonization** -The process by which microbes are coated by a molecule called opsonin which aids attachment of microbes to the phagocytic cells which facilitates phagocytosis.
- **Stages of Phagocytosis**
- Opsonization (process by which microbes are coated by a molecule called opsonin). Attachment to the pathogen (so that pathogen movement can be restricted).

1. Formation of Pseudopodia (hand like projections).
2. Encircling of pathogen by pseudopodia leads to the formation of Phagosome.
3. Fusion of Phagosome with lysozyme vesicle leads to the formation of phagolysosome.
4. Killing of Pathogen.

- **Reticulo endothelial system (RES)**
- A diffuse system of cells that includes monocytes and macrophages, which are phagocytic in nature.
- The role of macrophage is consider as first order defence mechanism, as it engulf and kill more pathogens efficiently. Macrophages also takes part in antigen presentation.
- Apart from this, RES also involved in removing aged RBCs, denatured protein, steroids, dyes and drugs.

The macrophages derive the name according to their location.

- **Liver -** Kupffer cells
- **Brain -** Microglial cells
- **Kidney -** Mesangial cells
- **Spleen -** Splenic macrophages
- **Peritoneum -** Peritoneal macrophages.
- **Alveoli -** Alveolar macrophages.

- **Natural Killer Cells**
- Among the immune cells, natural killer cells (NK cells) are the most aggressive. They are first line of defense against infected and cancerous cells.
- They are lymphocytes (Large granular lymphocytes, LGL) with no immunological memory and are part of the innate immune system. It attaches to the target and releases a lethal burst of chemicals called as perforins that penetrate the cell wall.
- Fluids begin to leak in and out and eventually the cell explodes

- **Interferon**
- Interferons are proteins produced by body cells when they are invaded by viruses, is released into the bloodstream or intercellular fluid, in order to induce healthy cells to manufacture an enzyme that block viral replication.
- The complement cascade consists of two separate pathways that converge in a final common pathway .
- **classic pathway and alternative pathway the two** converge in a final common pathway .

Complement System

- **Complement System**
- It is a group of proenzymes. They circulate in serum in inactive form.
- The complement system is the part of innate immune system plays an important defense against microorganisms, especially gram-negative bacteria.
- The complement system consists of a set of over twenty serum proteins which are getting activated

- **Antigen presenting cells (APC)**
- B cell,dendritic cells (lymphnodes), Langerhans cells (from skin) and macrophages are called as antigen presenting cells.
- All these cells, process the antigen and express the antigen over the surface of its cell membrane along with a molecule called as Major Histo Compatibility Complex (MHC) class II molecule.

- **Major Histocompatability complex**
- A set of cell surface glycoproteins molecules.
- Generally, they take part in differentiating self and non-self-antigens and the presentation of processed foreign antigen to activate the T cells.
- MHC a section on chromosome # 6 containing a group of genes that produce molecules marking our own tissues as “self” (referred to as “self-antigens.”) These are referred to as HLA (human leukocyte antigens) because…

- There are two classes of MHC proteins, MHC class I and MHC class II.
- MHC class I molecule is expressed on the cell surface of all nucleated cells of the body. MHC class I molecules with processed antigen are expressed on the surface of the infected cells, which present the processed antigen to cytotoxic T cells
- (CD8). MHC class II molecule are expressed on APC cell surface which present the processed antigen to Helper T cells (CD4 cells).

General principles

- HLA antigens help the immune system to recognize pathogens and to mount an immune response
- HLA-A, HLA-B, HLA-C—Class I antigens
- HLA-DP, HLA-DQ, HLA-DR—Class II antigens
- Class II antigens are the immune response antigens

Complement system

- It's a set of interacting proteins released into the blood after production in the liver.
- The components act together as zymogens, activating one another in cascade fashion after initiation from a variety of stimuli.
- Three pathways of activation occur in the body and culminate similarly in the production of important split products that **mediate inflammation, enhance phagocytosis by opsonization, and cause lysis** of particles by membrane pore formation.

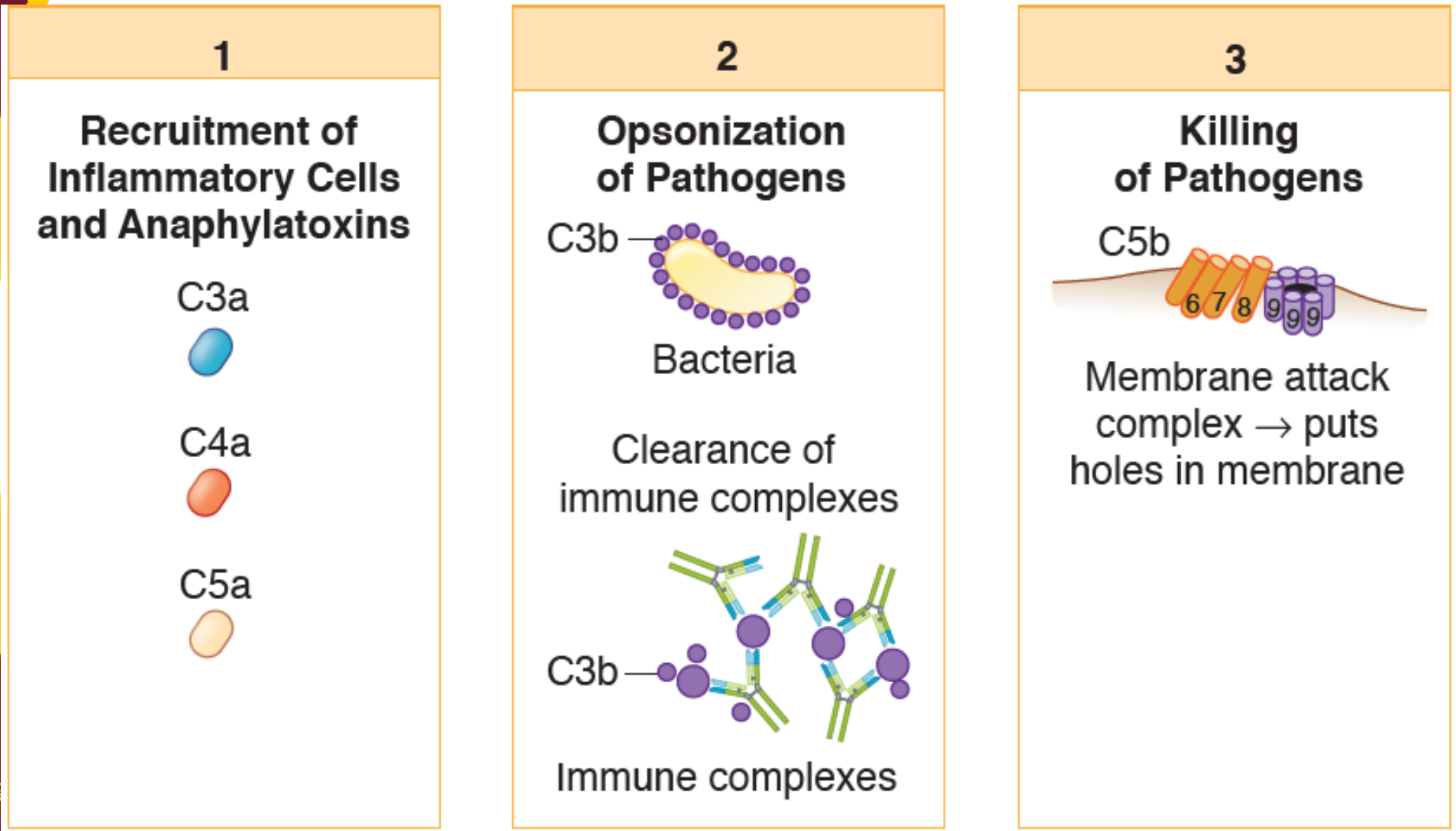


Figure I-4-5. Three Functions of the Complement System

The complement system

- A defensive system consisting of over 30 proteins produced by the liver and found in circulating blood serum.
- Complement kills microbes in three different ways
  - 1. opsonization
  - 2. inflammation
  - 3. Cytolysis

A Cascade system

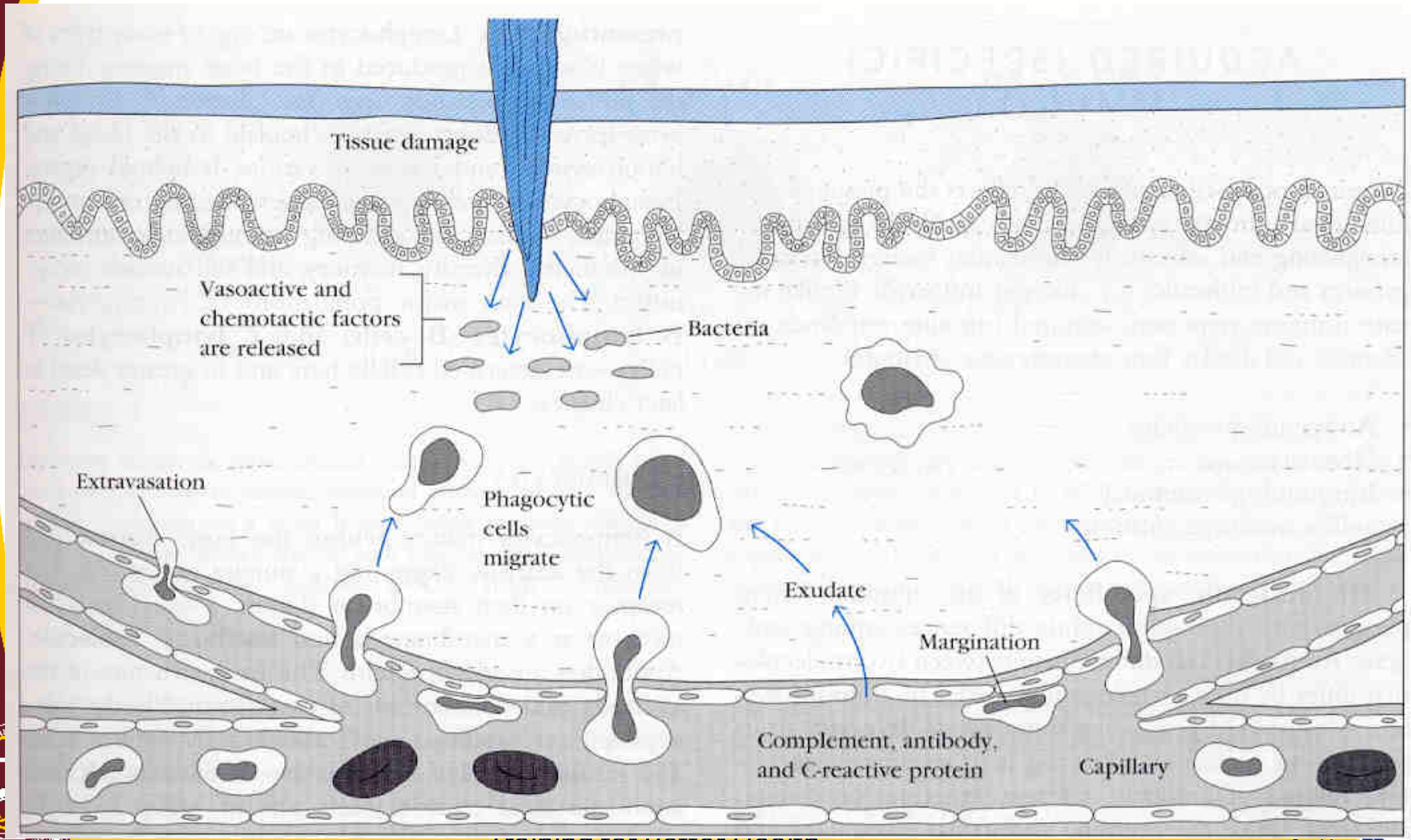
- The complement works as a cascade system.
  - Cascade is when one reaction triggers another reaction which trigger others and so on. These types of systems can grow exponentially very fast.

Cascade activation

- Complement proteins are often designated by an uppercase letter C and are inactive until they are split into products.
  - Example: C1
- When the products are split they become active. The active products are usually designated with a lower case a or b.
  - Example: C1a and C1b

Two Pathways

- The complement pathway can be activated by either of two different pathways.
  - Classical pathway (specific immune system)
  - alternative (non-specific immune system)

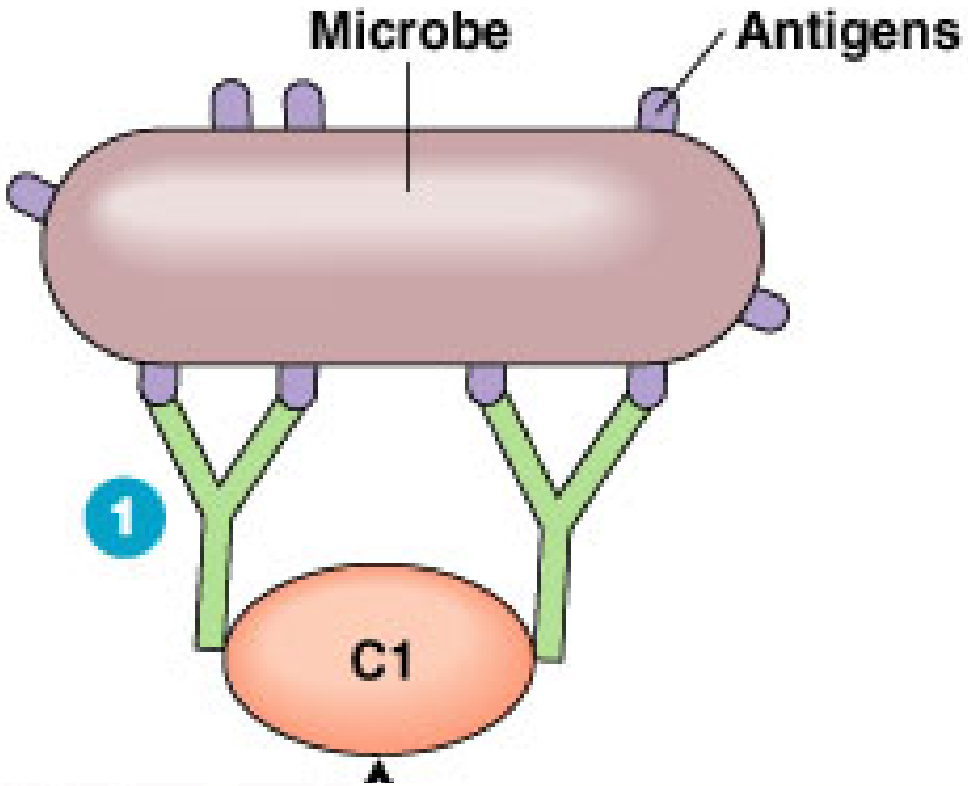

Tissue damage
Vasoactive and
chemotactic factors
are released
Bacteria
Extravasation
Phagocytic
cells
migrate
Exudate
Margination
Complement, antibody,
and C-reactive protein
Capillary

- Two of the pathways are considered part of the innate immune system: the alternate pathway and the lectin-binding or mannose-binding pathway (MBP).
- The alternate pathway for complement activation is shown below; the MBP activates the classical complement pathway but without the use of antibody, and is therefore considered part of innate immunity.
- The MBP is activated when mannose binding lectin binds to carbohydrates on the pathogen.

The Classical Pathway

- The classical pathway is considered to be part of the specific immune response because it relies on antibodies to initiate it.

- C1 becomes activated when it binds to the ends of antibodies

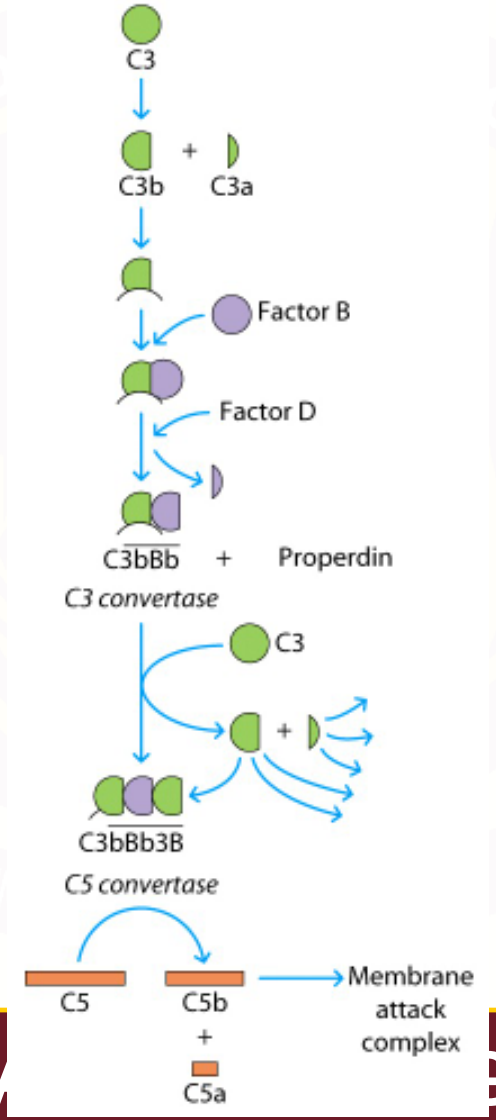


The alternative pathway

- The alternative pathway is part of the non-specific defense because it does not need antibodies to initiate the pathway.

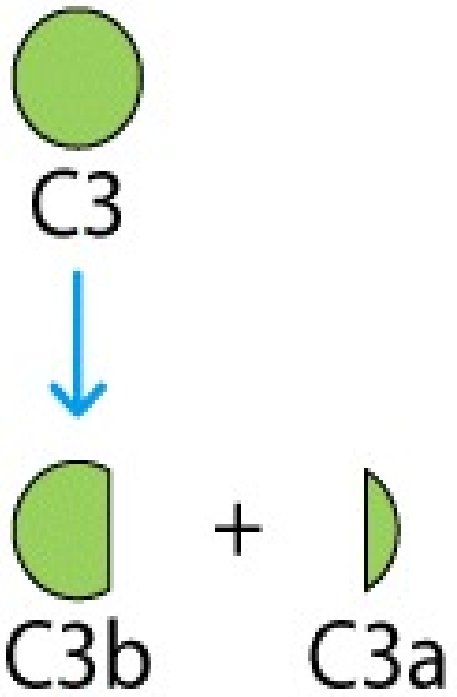
- The alternative pathway is slower than the Classical pathway

The Alternative complement pathway



Initiation of The Alternative pathway

- C3 contains in unstable thioester bond.
- This unstable bond makesC3 subject to slow spontaneous hydrolysis to C3b and C3a
- The C3b is able to bind to foreign surface antigens.
- Mammalian cells contain sialic acic which inactivates C3b



- The alternative pathway of complement activation is probably the more primitive of the pathways because it is initiated by simple attraction of the early factors to the surfaces of microbes.
- Bacterial polysaccharides and the lipopolysaccharide of the cell envelope of gram-negative bacteria both serve as potent, initiating stimuli.

Inflammation

–Vasodilation
–Capillary permeability

- **Inflammation** is a response to injury, infection, autoimmune, indeed any tissue site damage.
- It has two pathways -Exudative (liquid) and cellular.
- Autoimmune diseases are when the white cells destroy self tissue rather than bacteria or exogenous material, often autoimmune diseases will present as inflammation

Example causes of tissue injury:

- Trauma: broken bone, glass, crush injury, burn
- Bacterial infection
- Tumour
- Autoimmune destruction
- Coronary vascular disease: An atherosclerotic plaque

Assignment 1

- Read and make notes on inflammation