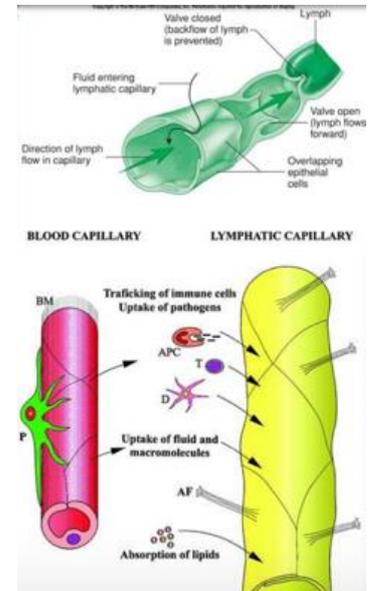
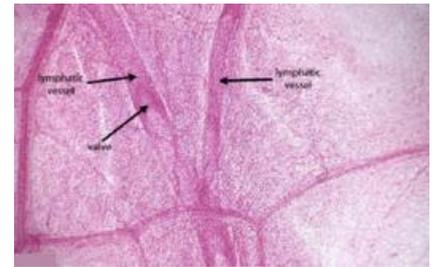


LYMPHOID SYSTEM – TISSUES AND CELLS OF IMMUNE RESPONSE

Lymphatic Vessels:

- Similar to blood vessels.
 - Inner endothelium
 - Incomplete BM
 - Smooth muscle (circular)
 - Valves – carries lymph in single direction.
 - Return of ISF to blood.
 - Transport absorbed fat.
 - Return filtered plasma proteins.
 - Lymphocyte circulation.
 - Adventitia
- Lymph capillaries more simple.
 - Open system
 - No pump. Moves via muscle contraction (skeletal & smooth).
- Lymph fluid – contains immune cells and is white bc of fat content.
- Closed end vessels.
 - Anastomose & form larger lymphatic vessels.
 - Thoracic duct & right lymphatic duct – return fluid back to cardiovascular system.
 - Terminate near heart – subclavian/jugular.
- Thin walled.
 - Blind-ended sacs – initial lymphatics, which forms the pre-collecting lymphatic.
 - Then you have the larger lymphatic vessels forming the collecting lymphatic which returns to heart.
 - Along these lymph vessels are frequent valves, and will be interrupted by lymph nodes.



Primary Lymphatic Organs: Red Bone Marrow, Thymus:

- Sites of stem cell division: Red bone marrow, Thymus.
- Develop immuno-competence: In bone marrow, stem cells are dividing. B cells stay here and develop immuno-competence. T cells leave bone marrow as pre-T cells and mature in thymus.
- Maturation: Red bone marrow: Found in flat bones and epiphyses of long bones, Thymus: Bi-lobed.

SUMMARY: Lymphatic Organs and Tissues:

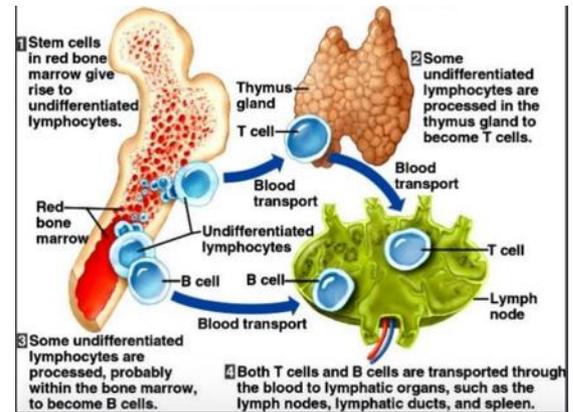
- Lymphatic vessels: return of ISF to blood.
- Primary lymphatic organs: BM & thymus. Generative environment, Competence, Maturation.
- Secondary lymphatic organs: In-line filter, Concentrates Ag, optimise immune cell interactions, Immune cell activation – lymphocyte activates to become effector/memory cell.

Primary Lymphoid Organ – Thymus:

- Atrophies in adult.
- T lymphocyte.
 - Development/education/maturation.
 - Terminal differentiation.
 - Differentiation.
- Thymus is the site of T lymphocyte maturation.
- Pre-T cells (precursors).
 - From bone marrow stem cells.

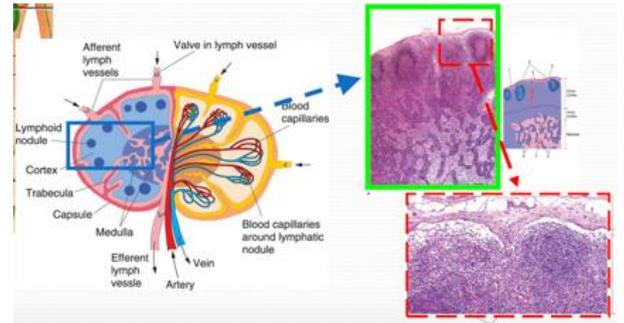


- Do not express Lymphocyte markers.
- Migrate from bone marrow to thymus gland.
 - Divide and proliferate.
 - Not dependant on stimulation/activation.
 - Mature.
 - Rearrangement of genes.
 - 99% deleted/die.
 - Removes self-reactive T cells.
 - Central tolerance.
 - Prevents autoimmunity.



Secondary Lymphoid Organ: Lymph Nodes:

- Found along lymphatic vessels.
- 600 bean shaped organs.
- 2 basic functions: both concerned with body protection:
 - **They act as lymph “filters” – Macrophages** in the nodes remove and destroy microorganisms and other debris that enter the lymph from the loose connective tissues, effectively preventing them from being delivered to the blood and spreading to other parts of the body.
 - **They help activate the immune system – Lymphocytes**, also strategically located in lymph nodes, monitor the lymphatic stream for the presence of antigens and mount an attack against them.

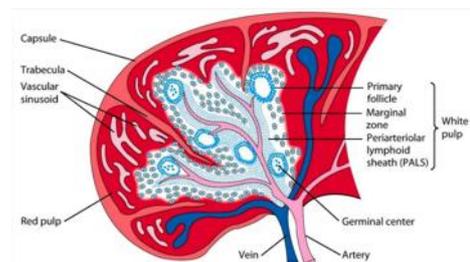


What happens in Lymph Nodes?

- Antigen is filtered out of lymph fluid.
- Present the antigen to ‘virgin’ lymphocytes – presented by dendritic cells (LN).
- Activation of T & B cells.
- Virgin or naive cells differentiate into either memory cells or effector cells → become activated cells → enter division stage of cell cycle → increase in cell size → proliferate by cell division.
- T helper cells will stimulate B cells to differentiate into plasma cells → produce antibodies in medulla.

Secondary Lymphoid Organ: Spleen:

- Has 2 sections: Red pulp (breaking down RBCs and storing platelets) & white pulp (immunity).
- Reticular CT.
- Blood filter:
 - Mononuclear phagocytic centre.
 - Removes old RBCs.
 - Clears microbes & particulate matter.
 - Concentrates antigens & microbes.
 - Blood reserve.
 - Recycles iron.
- White pulp:
 - Filters blood (not lymph like in lymph nodes).
 - Contains B lymphocytes.
 - Many plasma cells – Ig production.
 - Phagocytes – Removes Ig coated bacteria.
 - Stores platelets.
 - Presents antigen in blood.



Spleen Functions:

- Major site of immune response to blood borne antigens.

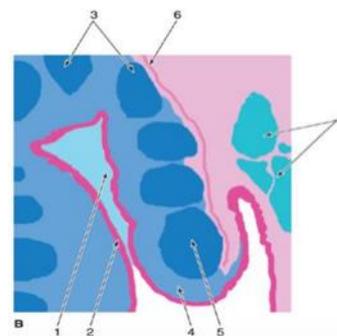
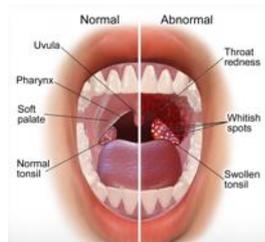
- Important filter for blood.
- Red pulp macrophages clear microbes & particles.
- Major site of phagocytosis.
- Antibody coated microbes. (Opsonised → readily phagocytosed).

Secondary Lymphoid Tissue: Tonsils:

- Cluster of lymphatic tissue just under the mucous membranes that line the nose, mouth and pharynx (throat) called tonsils.
- Do not have CT capsule.
- MALT (mucosal associated lymphoid tissue).
- B cell areas and T cell areas (inter-follicular).
- Provide protection against harmful substances and pathogens that may enter the body through the nose or mouth (Inhaled antigen or Ingested antigen).
- There are 3 groups of tonsils: pharyngeal, palatine and lingual tonsils.
- Lymphoid tissue collections – Waldeyers tonsillar ring.
 - Tubal tonsils (2)
 - Palatine tonsils (2) (tonsil usually refers to palatine tonsils).
 - Situated at either side at the back of the throat. Adjacent to nasopharynx & oropharynx.
 - Lingual tonsil (1)
 - Adenoid or pharyngeal/Nasopharyngeal tonsil (1)

Secondary Lymphoid Organ: Palatine Tonsil:

- (1) Crypt of tonsil
- (2) epithelium
- (3) lymphoid nodules
- (4) diffuse lymphoid tissue
- (5) germinal centre

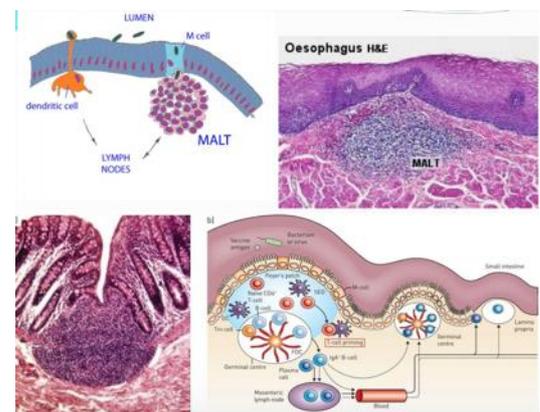


Tonsillitis:

- Causes: viral, bacterial.

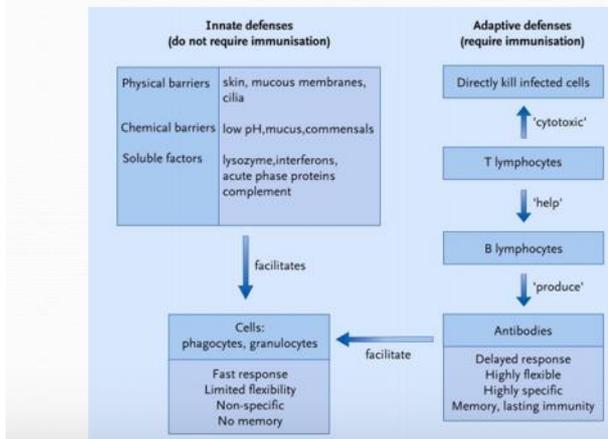
Secondary Lymph Tissue: What is MALT?

- Mucosal Associated Lymphoid tissue.
- Diffuse system.
- Small concentrations: GIT, Thyroid, breast, lung, Salivary glands, eye, skin, oral mucosa.
 - Referred to as: BALT, GALT, NALT, LALT, SALT.
- MALT is populated by lymphocytes such as T cells and B cells, as well as plasma cells and macrophages, each of which is well situated to encounter antigens passing through the mucosal epithelium



INNATE IMMUNITY

Functional division of the immune response



Immune Response:

- Innate immunity:
 - Does not improve with repeat contact.
 - Blocks entry, Rapidly eliminates microbes, Fast.
- Adaptive immunity 'Specific acquired'.
 - Learned through prior exposure
 - Slow

Innate Immunity:

- Non-specific, anti-microbial systems:
 - Epithelial barriers – if this is broken, microbes can enter.
 - In underlying loose CT: Professional phagocytic cells.
 - Natural killer cells – non-T, B lymphocyte. They kill cells that are infected or are an early tumour cell.
 - Antimicrobial factors: Complement, Acute phase proteins (inhibit microbe growth), Lysozyme, Interferon, Defensins, Toll-Like Receptors (PAMPS).

Barriers Against Infection:

- **Physical barriers: Skin surface:** Intact – Impermeable bc of keratin and closely packed cells.
 - If there is damage (skin loss/cuts/burns), then infection becomes a problem.
- **Chemical barriers:** Direct inhibitory factors: Sweat, sebaceous secretions.
 - Lactic acid & fatty acids, Low pH.

Chemical Barriers to Infection:

- Body fluids: Bactericidal components.
 - Gastric juices → acidic.
 - Semen → spermine & zinc.
 - Milk → Lactoperoxidase.
 - Tears, Nasal secretion, Saliva → Lysozyme.
- Mucus secretion: Mucus lines the inner surfaces: GIT, Respiratory tract, UG tract.
 - Protective barrier: Blocks adherence, removes foreign particles. Strategies: cilia, coughing, sneezing

Physical and Chemical Barriers:

- Normal flora – Harmless bacterial growth.
 - Suppress pathogens.
 - GIT, vagina, skin [any surface].
 - Compete for essential nutrients, Produce inhibitory substance.
 - Commensal bacteria (harmless, provide advantage to health of that surface) → lactic acid.
 - Metabolism of glycogen.

- Disturbance by antibiotics.

What happens if microorganisms do penetrate the body?

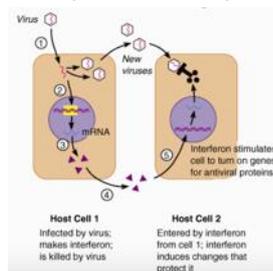
- Phagocytosis of invading antigen – Cellular response.
- Soluble chemical factors: Antimicrobial proteins, Bactericidal enzymes, Complement system, Interferon, Defensins.

Complement:

- Complement proteins produced by liver → circulate (inactive). When in contact w/pathogen → proteins interact w/each other and induce biochemical cascade of activations.
- Functions in both innate & adaptive immunity.
- When activated, it is involved in killing (Cell killing complex (MAC)), and amplification of response.
- 1. Lysis – forms pores in microbial membranes. Cells, bacteria & viruses.
- 2. Opsonisation – complement proteins promote phagocytosis by coating the pathogen.
- 3. Triggers inflammation.
- 4. Immune clearance – removes immune complexes & deposits in the spleen and liver.

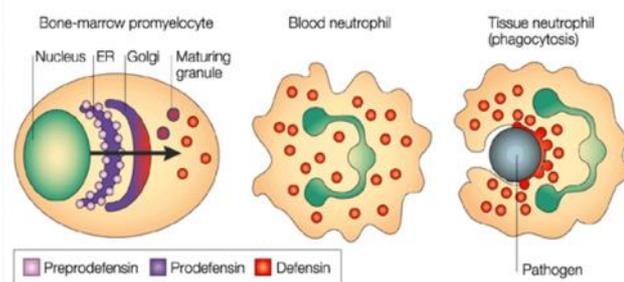
Interferon:

- Interferes with replication of viruses.
- Turns on anti-viral genes.



Defensins:

- Antimicrobial proteins stored in epithelial & PMN granules.
- Peptides.
- Kill bacteria, fungi, viruses.
 - Bind microbial cell membrane.
 - Damage cell membrane.
 - Stimulate insertion of pores.
- Pharmaceutical potential.
 - Strong antimicrobial.
 - Broad activity.
 - Resistance to proteolysis.



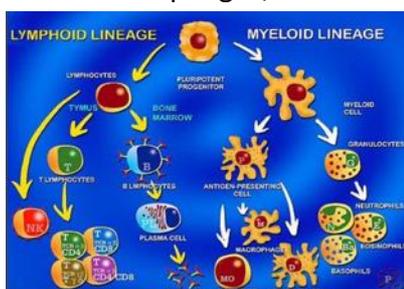
Toll-Like Receptors:

- A type of Pattern recognition receptor (PRR) – play a key role in immunity.
- Roles in Innate immunity (Inflammatory response), and Adaptive immunity (Antigen-specific response).
- Recognise fixed patterns on microbes. PAMPS – pathogen associated molecular patterns.
- Triggers a response. Signals pathway.
- Inflammatory mediators or antimicrobials.

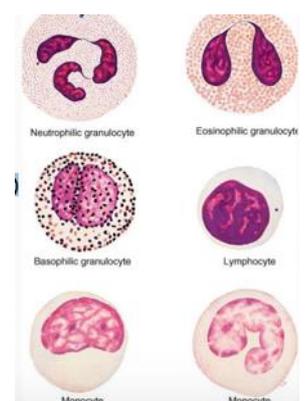


Cells of the Immune System:

- Leucocytes or derived from leucocytes. Also known as WBCs:
 - Neutrophils, Lymphocytes, Plasma cells, Mast cells, Monocytes, Macrophages, Dendritic cells.



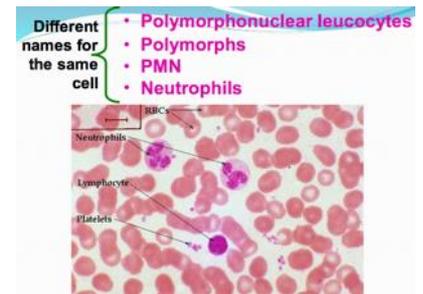
Agranulocytes: Lymphocytes subtypes: T lymphocyte: T helper, T cytotoxic.



Granulocytes: Basophils (allergy), Neutrophils, Eosinophils.

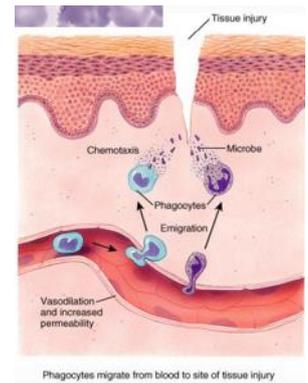
Polymorphonucleocyte/Neutrophil (Granulocyte):

- Produced in bone marrow from stem cells – live for about 4-5 days.
- PMN have a rapid turnover rate.
- Multi-lobed nucleus.
- In blood circulation.
- Phagocytose, release cytokines to activate other cells.
- Migrate to site:
 - Respond to chemical signal. Chemotaxis – movement in response to chemical gradient.
 - Diapedesis or extravasation or migration.
- Granules in cytoplasm:
 - Release at site of injury or antigen.
 - Many different chemicals. Antimicrobial effects.



Monocytes (Agranulocytes) – Macrophage Precursors:

- Differentiate into macrophages and Dendritic cells (DCs).
- Monocytes migrate from the circulation and extravasate through the endothelium.
- Monocytes, DCs, macrophages, neutrophils and mast cells, are 'professional' phagocytic cells.
- Professional phagocytes express many surface receptors:
 - That detect signals that are not present in healthy tissues.
 - Scavenger receptors to bind apoptotic, necrotic cells, opsonized pathogens and cell debris.
 - Toll-like receptors (TLRs), (facilitate mechanics of phagocytosis of microbes).
 - Synergistic & antagonistic interactions & downstream signalling mechanisms within phagocytic cell.



Macrophages:

- Bone marrow origin. Monocytes (blood WBC) become macrophages.
- Ingest and process foreign materials, dead cells and debris.
- Recruit additional macrophages.
- Local micro-environmental signals change function.

Phagocytes and Phagocytosis:

- For phagocytosis to occur, there needs to be specialized receptors and the cognate ligands should engage on the target particle.
- Receptor–ligand engagement.
 - Triggers an intricate signalling network.
 - Induces cytoskeletal and membrane remodelling.
 - Ends in particle engulfment.
 - Phagocytosis is completed when pseudopods reach the apex of the particle.
 - Contractile proteins contract in a purse-string fashion.
 - Severing the newly formed vacuole from the surface membrane.
- 1. Recognition of invading microbe.**
 - Macrophages have PRRs on plasma membrane → recognise specific molecular patterns on pathogen. These patterns are known as PAMPs.
 - Recognition occurs when PRRs react with PAMPs on pathogen surface.
- 2. Ingestion and formation of phagosome.**
 - Plasma membrane of phagocyte extends and surrounds bound pathogen.
 - Membrane surrounding pathogen pinches off and internalises the pathogen by forming a sac known as phagosome (phagocytic vesicle).
- 3. Formation of phagolysosome.**

- Phagosome fuses w/one or more of lysosomes in cytoplasm of phagocyte to form phagolysosome.
- Lysosome contains digestive and microbicide substances.
- This has acidic environment. There are also many enzymes and hydrolase-rich.
- **4. Microbial killing and formation of residual body.**
 - The acidic environment and many enzymes contribute to the killing and digestion of the pathogen.
 - Sac containing indigestible material is residual body.
- **5. Elimination or exocytosis.**
 - Residual body moves towards cell membrane and eliminates via exocytosis.

Phagocytosis: How are targets for phagocytosis identified?

- **Opsonin receptors:** Opsonin receptors are used to bind bacteria or other particles that have been coated with immunoglobulin or antibodies.
- **Complement system:** Complement proteins 'tag' the bacteria for phagocytosis.
- **Scavenger receptors:** Scavenger receptors bind to bacterial ECM molecules.
- **Toll-like receptors:** bind to specific patterns of molecules expressed by bacteria.
- **Antibodies:** bind to specific antigens to ID target.

Phagocytosis and Destruction:

- Occurs in **acidic environment** – phagolysosome.
- Includes chemicals such as **Oxygen Radicals** (highly reactive molecules):
 - React with proteins, lipids and other biological molecules.
 - Causes Oxidative stress (physiological stress) which increases oxygen.
- **Nitric Oxide:** Reactive substance. Reacts with superoxide to create damaging molecules.
- **Antimicrobial Proteins** (specifically damage or kill bacteria):
 - Proteases, which kill various bacteria by destroying essential proteins.
 - Lysozyme, targets bacterial cell walls.
- **Antimicrobial Peptides:** they attack. Eg. defensins, target bacterial cell membranes.
- **Binding Proteins:** Competitively bind to proteins or ions.
 - Remove beneficial substances (bacteria or viral replication). Eg. Lactoferrin binds iron ions.

Dendritic Cells:

- Act as antigen presenting cell.
- Function:
 - Phagocytose.
 - Process antigen material. Present a fragment of that antigen on their surface to T, B cells so they become activated – but they are activated with co-stimulation of cytokines.
 - They also produce cytokines.
 - Act as messengers between the innate and adaptive immune systems.
- Located in tissues in contact with the external environment:
 - Skin, Respiratory tract, GIT, Mucosa.
 - Migrate to lymph nodes & present antigen to lymphocytes.
 - Initiate adaptive immune response.
 - Immature DC are 'veiled cells'. Mature have dendrites or tree-like extensions.

Plasma Cell (Agranulocyte):

- Mediators of humoral response.
- Produces antibodies.
- Once a B cell becomes a plasma cell, it is terminally differentiated/marked alteration.
 - Differentiation requires antigen presentation.
 - Its morphology changes. It changes its gene expression profile.
- Basis of most vaccination strategies.

Natural Killer Cells (NK):

- Derived from bone marrow.

- Large granular lymphocytes.
- Produce cytokines.
- Their role is **target killing** – they recognise a marker on infected/transformed cell → release granules (perforin or cytolytic) → punch holes in the infected/tumour cell → lysis/induce apoptosis.
- Remove virus/tumour cell: Recognise structure on infected cell → penetrate infected cell.

Eosinophils:

- Kill large parasites.
- Allergic conditions.
- Immunoregulatory function.
- Distinctive granules: Major basic protein (MBP), Cationic proteins, Enzymes: Peroxidase, Phospholipase, Histaminase, Growth factors.

Mast Cells:

- Powerful chemical mediators.
 - Chemotactic factors – Recruit PMN neutrophils.
 - Relaxation of blood vessel walls → increased blood flow, dilated vessels, exudation plasma proteins.
- Role in immune activity of mast cells:
 - Direct killing of cells/bacteria.
 - Phagocytosis.
 - Produce antimicrobial peptides.
 - Oxygen reactive species.
 - Smooth muscle facilitated expulsion of parasites.
 - Allergy/anaphylaxis.
 - Inflammation.
 - Stimulate mucus production.

INFLAMMATION

- Innate – Non-specific response. It is the host response.
- Leads to tissue damage or foreign invasion.
- Cardinal signs: **Redness** (due to increased blood flow – haem in RBCs causes redness), **Swelling** (more interstitial fluid coming from blood), **Heat** (increased circulation – water in blood carries heat), **Pain** (oedema stimulates receptors by APs), **Loss of function**.
- Goals are to isolate, destroy, inactivate invaders → Remove debris → Prepare for healing and repair.
- Damaged tissue release histamines → increase blood flow to area → histamines cause capillaries to leak, releasing phagocytes and clotting factors into wound → phagocytes engulf bacteria, dead cells and debris → platelets move out of capillary to seal wounded area.

Acute Inflammation: Causative Stimuli:

- Infections (bacterial, viral, parasitic) & microbial toxins.
- Trauma (blunt & penetrating).
- Physical (burns, frostbite, irradiation) & chemical agents.
- Foreign bodies (splinters, dirt, sutures).
- Immune reactions (hypersensitivity reactions).

What is Inflammation?

- Composite multiple immune responses against a stimulus that lead to a cardinal sign:
 - Complement activation.
 - Degranulation of mast cells & other granulocytes → Release inflammatory mediators → increase chemoattraction and activation of cells (neutrophils, phagocytes, lymphocytes).
 - Increased NK cell activity.
 - At end point, the body temp will increase.