Lymphatic System Functions:
1. Reclaim lost fluid for return to cardiovascular system
2. Protect against pathogens & cancer cells
   - nonspecific defenses: general protection, does not distinguish threat specifics
   - specific defenses = immune response, identify and defend against one particular threat
(Immunity = resistance to infection through activation of specific defenses)

Lymphatic System Components:
1. Lymph: fluid similar to plasma but less proteins
2. Lymphatic vessels: carry lymph from tissues to veins
3. Lymphoid tissues and organs: site of development of lymphocytes and screening for pathogens
4. Lymphocytes and Phagocytes: provide defense

Lymphatic Vessels
- histologically most like veins
- all three tunics
- large ones have vasa vasorum
- many valves
- many anastomoses
- lymph nodes present along vessels

Lymph & Lymphatic Vessels
- lymph originates as fluid lost from blood capillaries
- collected in blind end lymphatic capillaries
- overlapping endothelial cells create one way mini-valves
- fluid, solutes, large objects driven into lymphatic capillary by pressure in interstitial space (arteries, skeletal muscle)
Lymphatic Vessels
- converge, return fluid to blood stream:
  lymphatic capillaries →
  lymphatic collecting vessels →
  lymphatic trunks →
  subclavian veins

*Lymphangitis* = inflammation of a lymphatic vessel, due to toxins or infection, vasa vasorum swell with blood due to pressure, appears as red line under skin

Lymphoid Cells:
- Macrophages: phagocytosis and T cell activation
- Dendritic cells: antigen presentation (found in CT)
- Lymphocytes: (3 classes)
  1. T cells - “Thymus dependent”, 80%
     - cytotoxic T cells: kill “foreign” cells directly (cell mediated immunity)
     - helper T cells: activate T & B cells
     - suppressor T cells: inhibit T & B cells
  2. B cells - “Bone marrow derived”, 10-15%, when activated → plasma cell
     → secretes antibodies, antibodies bind specific antigens (foreign molecules)
      (antibody mediated or humoral immunity)
  3. Natural Killer Cell: 5-10%, attack abnormal cells: cancer cells, or virus-infected cells
     (nonspecific defense)

Lymphocytes constantly circulate between blood, lymph, tissues; can survive 20+ years
*LYmphopoiesis* = production of lymphocytes
- occurs in bone marrow, thymus, and lymphoid tissues
-Hemocytoblast → Lymphoid stem cell
- one type of lymphoid stem cell stays in bone marrow → B cells and NK cells
- one type migrates to thymus → T cells

Both B and T cells can divide to produce more of same type (clones)
both can migrate to all lymphoid tissues for division and development

Lymphoid Tissue
- reticular CT & lymphocytes & other lymphoid cells
- functions:
  1. Proliferation site for lymphocytes
  2. Surveillance point for lymphocytes and macrophages
- two types: lymphoid follicles and lymphoid organs
  1. **Lymphoid Follicles / Nodules**
     - CT packed with lymphocytes (T, B, and dendritic cells)
     - no capsule
     - germinal center in middle: dividing B cells
     - germinal center surrounded by dendritic cells, T cells and some macrophages
- follicles associated with respiratory, digestive, and urinary tracts
- special lymphoid nodule/follicle collections:
  A. MALT (mucosa-associated lymphoid tissue): deep to intestinal epithelium, made up of individual nodules called Peyer’s Patches

B. Appendix
   tubular offshoot of beginning portion of large intestine

2. Lymphoid Organs
   - have fibrous CT capsule around outside
   - contain many lymphoid follicles
   - include: lymph nodes, thymus, and spleen

A. Lymph nodes
   - bean shaped, 1-25mm
   - have associates blood vessels and nerves

structure:
- capsule: CT, surrounds outside
- trabeculae: folds of capsule creating partitions inside
- cortex = outer edge
  - superficial cortex = lymphoid follicles: B cells & dendritic cells
  - deep cortex = T cells, transit between lymph and blood
- medulla = center: houses T, B & plasma cells
- sinuses: spaces throughout, house macrophages, allow lymph flow through node

Lymph flow through node:
- lymph enters via afferent vessels (many)
  - flows slowly through sinuses where it is surveyed for pathogens and antigens
  - Macrophages engulf pathogens
  - Dendritic cells bind antigens and stimulate lymphocytes
- “clean” lymph exits via efferent vessels (few)

*Lymph nodes clustered mostly along lymphatic trunks: function to purify lymph before returning it to blood

C. Tonsils: large nodules in pharynx, have crypts to trap bacteria → encourage development of immunity
   5 Total: 2 palatine tonsils
      1 pharyngeal (adenoid)
      2 lingual tonsils
B. Thymus
- glandular
- located superior to heart
- T cells mature in cortex and migrate to medulla to enter blood
Thymus produces hormones: thymosin & thymopoietin both promote development and maturation of lymphocytes (mostly the T cells in thymus)
Thymus most active in early childhood, atrophies with age

C. Spleen
- located lateral to stomach
Functions:
- remove abnormal blood cells
- store iron from recycled RBCs for reuse
- initiate immune response by B & T cells in response to antigens in blood
- store platelets
- site of fetal erythrocyte production

Spleen cleans blood:
- blood flows slowly through sinuses
- macrophages and lymphocytes detect and destroy foreign cells and antigens
Spleen = mostly sinuses
- bleeds profusely when damaged
- to fragile to stitch tears
- splenectomy to prevent fatal hemorrhaging
- liver and bone marrow can take over functions
Defense against pathogens:
1st line: prevent entry → skin & mucosa
2nd line: general antimicrobial actions when first line has been penetrated (nonspecific defense = innate defense)
3rd line: precision assault on a specific pathogen (immune response)

Non-specific or Innate defense (born with it) (handout)

1. Physical Barriers
   A. Cutaneous Membrane (Skin):
      - impenetrable layers of keratinized cells
      - impermeable to water and chemicals
      - acid pH due to sebum
      - high salt due to perspiration (acid & salt inhibit microbe growth)
   B. Mucosa:
      - produces antimicrobial secretions:
         - acid: inhibit microbe growth
         - lysozyme: lyse bacterial cell walls
         - mucus: traps microbes

2. Phagocytes
   A. Microphages
      - neutrophils and eosinophils:
         - either phagocytose pathogen or secrete defensins on pathogen
         - defensins cause membrane pores that cause lysis of target cell
   B. Macrophages
      - phagocytose pathogens, cell debris and other foreign material
      - fixed macrophages: non-traveling, associated with specific tissue or organ (e.g. microglia)
      - free macrophages: travel throughout body via blood
   All phagocytes:
      - emigrate from capillaries
      - display chemotaxis
      - have receptors to bind target for phagocytosis
4. Interferons
   = antiviral cytokines
     (cytokines = chemicals used for cell to cell communication)
   = proteins released by activated lymphocytes, macrophages, or virus-infected cells
Three types:
-α interferons:
  produced by leukocytes to attract and stimulate NK cells
-β interferons:
  produced by virus infected cells to trigger neighboring cells to produce antiviral proteins to slow viral replication
-γ interferons:
  produced by T and NK cells to stimulate macrophage activity

5. Complement (handout)
   - 11 complement proteins + 9 other factors & regulators act in cascade to cause foreign cell lysis (often target bacteria)
   *Classical pathway:*
     requires bound antibodies
   *Alternate Pathway:*
     no antibodies required
     -Factors P,B,D interact in response to foreign material
     -C3 converted to C3b
     -C3b binds foreign material
   -C1 binds antibody on bacteria
   -turns on C2 + C4
   -C3 converted to C3b
   -C3b binds bacteria

   Binding of C3b = “complement fixation” → triggers anti-microbial effects (on handout)

3. Immunological Surveillance
   = monitoring of tissues by NK cells for abnormal cells (cancer or virus infected)
   -abnormal cells express abnormal antigens on surface → detected by NK cells
   -NK cell binds abnormal cell and releases perforins from Golgi
   -perforins assemble on target membrane creating pores → lysis of target
6. Inflammation
- localized redness, swelling, heat, and pain in response to any tissue damage

Functions:
1. Help prevent injury/infection from spreading
2. Disposes of cell debris
3. Sets the stage for repair

Events: (on handout)

Puss = dead WBCs, pathogens, debris: failure to clear ⇒ abscess = puss walled off by CT
Necrosis = tissue degeneration due to lysosomal enzymes released by damaged cells (injury gets worse before better)
Apoptosis = controlled cell death (no necrosis)

7. Fever
= elevated body temperature (>99°F/37.2°C)
- triggered by pyrogens; released into blood by leukocytes, mostly macrophages, upon exposure to foreign antigens
- effect: increase metabolic rate to allow better defense and repair (rate ↑ 10% / 1°C)
up to 104°F: safe & productive
@106°F: nervous tissue dysfunctional
@110°F: proteins denature = death

Specific or Adaptive Defenses = The Immune Response

T cells = cellular immunity; function to amplify the inflammatory response
B cells = humoral immunity; responsible for most complement activation/fixation
- Each B/T cell covered in receptors that recognize and bind only one specific antigen

Antigen = foreign substance that can activate the immune system and provoke an immune response
- usually large complex molecules: proteins, nucleic acids, some lipids, some polysaccharides
Simple chemical structures like plastic and metal are not immunogenic / antigenic

Forms of Immunity
(on handout)

Properties of Immunity
1. Specificity: immune response targets particular antigens; each B and T cell responds to and destroys only one specific antigen.
2. Versatility: a large diversity of lymphocytes prescribed by genes exist to respond to almost any antigen; when a particular antigen is encountered the one lymphocyte specific to it divides by clonal selection to produce many cells specific to that particular antigen
3. Memory: response after second exposure to the same antigen is faster, stronger and lasts longer; during the initial exposure memory cells were created to respond quickly upon second exposure
4. Tolerance: immune system responds only to non-self antigens; B and T cells that recognize self antigens are destroyed by clonal deletion to insure self-tolerance
**T Cells and Cell Mediated Immunity**
- targets virus or parasite infected cells, cancer cells, and cells of foreign grafts

3 main types of cells:
1. Cytotoxic T (T\(_C\)) cells: carry out cell mediated immunity, physically attack foreign cells
2. Helper T (T\(_H\)) cells: activate B and T\(_C\) cells
3. Suppressor T (T\(_S\)) cells: moderate the immune response by inhibiting T\(_C\) and B cells

-T cells must be activated by exposure to antigen
- Do not recognize free antigen
- Antigen must be bound to special glycoprotein receptors on target cell: Major Histocompatibility Complex (MHC)

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**Class I MHC (on handout)**

Found on all nucleated cells: secreted by Golgi
Bind endogenous antigens: contain small peptides present in cytoplasm
Abnormal peptides (cancer, virus, bacterial) trigger cell destruction by T\(_C\) cells

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**Class II MHC (on handout)**

-Each T cell detects only one antigen and only when it is in either class I MHC or class II MHC

- Class recognized is determined by CD (cluster of differentiation) markers on the T cell (glycoprotein receptors)
  - CD8 → T\(_C\) and T\(_S\): respond to antigen in class I MHC
  - CD4 → T\(_H\): respond to antigen in class II MHC

Activation of CD8 / T\(_C\) cells / Killer T
1. Cell finds target antigen in class I MHC
2. T\(_C\) Cell undergoes clonal selection: proliferation producing many identical cells (often requires stimulation from a T\(_H\) cell that was activated by an APC)

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Found on lymphocytes and antigen presenting cells (APC) (e.g. dendritic cells, Langerhans cells, macrophages, activated B cells)
Bind exogenous antigens: materials that have been phagocytosed and broken down
Activate T\(_H\) cells which activate B cells and T\(_C\) cells
3. Some clones remain inactive as memory T<sub>C</sub> cells

4. Some clones (active cells) destroy target cell:
   A. release perforin: lyse target
   B. release lymphotoxin: disrupt DNA
   C. induce apoptosis: “self destruct”

Activation of CD4 / T<sub>H</sub> cells
1. Bind antigen in class II MHC
2. Proliferation / clonal selection
3. Memory cells
4. Active T<sub>H</sub> cells

Activated T<sub>H</sub> cells secrete cytokines which coordinate specific and nonspecific defense:
- stimulate production of memory T cells
- accelerate production of active T<sub>C</sub> cells
- attract and stimulate macrophages and NK cells
- promote activation of B cells resulting in antibody production

Activation of initial cell and clonal selection take time: memory cells are ready to go upon second exposure to same antigen

T<sub>S</sub> Cells activate more slowly than T<sub>C</sub>
function to release inhibitory cytokines to reduce immune response

Organ transplants
Graft rejection:
tissue typing = attempt to match MHC, but antigens in MHC will always be foreign, thus attacked;
need immuno-suppressive drugs to suppress T<sub>C</sub> cell activity to save graft

B Cells and Antibody Mediated Immunity
- targets bacteria, bacterial toxins, and free viruses

Activation of B cells: T dependent antigens
1. B cells have antibodies (IgD) on surface as receptor for antigen: binding causes B cell to become sensitized

2. Bound antigen is internalized and expressed back on surface in Class II MHC
3. A specific T<sub>H</sub> cell recognizes the antigen+MHC complex and releases cytokines to activate the B cell
4. Activated B cell proliferates (clonal selection) to produce memory B cells and plasma cells.

5. Plasma cells secrete antibodies specific to original antigen, ~2000/sec, for 4-5 days, then die (apoptosis).

Some B cells respond to T-independent antigens: they can self activate upon antigen binding without a T<sub>H</sub> cell.
T-independent activation is less common and produces much weaker response and less protection.

Initial exposure to antigen:
- ~5 days B cell → plasma cell
- ~10 days to peak antibody levels (titer) in blood
- antibodies (IgM) circulate ~ 2 weeks

Second exposure:
- memory cell → plasma cell ~1-2 days
- peak titer ~ 2-3 days, higher level antibodies (IgG) circulate weeks - months

Antibody (Ab) Structure (handout)
- two identical heavy chains (H)
- two identical light chains (L)
  - all held together by disulfide bonds
- hinge region: flexibility
- constant segments (C):
  - determine class of antibody molecule
  - have sites for complement binding (Fc region)
- variable segments (V):
  - determine antigen specificity of antibody
  - make up antigen binding sites (2 per monomer molecule)

Humans produce 100 million - 1 billion different Ab’s that each bind a different antigen.

Classes of Antibodies/Immunoglobulins (on handout)

IgG antibodies
- Monomer
- most common
- produced upon second exposure
- produced at high levels
- provides resistance against viruses, bacteria, toxins
- can cross placenta

IgM antibodies
- Pentamer
- first class produced upon initial exposure
- forms immune complexes (agglutination)

IgA antibodies
- Dimer
- in secretions

IgD antibodies
- Monomer
- on surface of B cells as receptor
- sensitizes or activates B cell upon antigen binding

IgE antibodies
- Monomer
- on mast cells and basophils as receptor
- triggers histamine release upon antigen binding
Antigen-Antibody Complexes:
- antibodies bind antigen via antigen binding sites
- antigen gets bound by its antigenic determinant site / epitope

complete antigen = two epitopes bound to the two antigen binding sites
incomplete antigen / hapten = only one epitope bound to one site (small molecules), can lead to allergies (combine with body proteins e.g. latex)

Effects of Antibody Binding: (on handout)
1. Agglutination and Precipitation
2. Opsonization
3. Neutralization: a. prevent attachment of pathogens, b. inactivate toxins
4. Complement fixation
5. Stimulate inflammation (IgE on Mast cell)
6. Ab-dependent cell mediated cytotoxicity

Immune Disorders
1. Autoimmune Disorders
   - immune response targets normal body cells, autoantibodies produced
e.g. Insulin dependent diabetes mellitus /Type I (attack cells of pancreas)
   Multiple sclerosis (attack white matter of CNS)
   Rheumatoid arthritis (attack joints)
   Graves Disease (stimulate thyroid)

2. Immunodeficiency Diseases
   - immune system fails to develop or immune responses are blocked
   - due to: genetics/development, infection by virus, exposure to radiation/drugs
e.g. SCID (severe combined immunodeficiency disorder) “Bubble Boy”: born without B or T cells
   Hodgkins Disease: lymph node cancer = ↓ B and T cells

AIDS (acquired immune deficiency syndrome): virus (HIV) infects CD4 (T_H) cells and replicates causing cell lysis.
- T_H cells necessary for both T_C and B cell activation
- ↓ T_H = patient has poor cell mediated and antibody mediated immunity
- patient dies of opportunistic infections

Allergies
= excessive immune response to non-harmful antigens, results in tissue damage
1. Immediate Hypersensitivity (most common) antibody based (antigen = allergen)
   A. Anaphylaxis:
      - initial exposure produces IgE
      - IgE binds Mast cells/basophils
      - 2nd exposure, allergen binds IgE, triggers release of histamine & heparin
      → inflammation
      (e.g. runny eyes and nose)
**Anaphylactic shock** = allergen circulates in blood → body wide inflammation (↓ BP = shock)

B. Atopy = full blown allergic response upon 1st exposure

2. Delayed Hypersensitivity
   - cell mediated
   - $T_C$, $T_H$, & macrophages activated by allergen resulting in cell death & local inflammation (e.g. poison ivy)

**Age Related Changes:**
- thymus size ↓, less T cells produced
- ↓ $T_H$ cells = less B and $T_C$ cell activation = ↓ immunity overall
- ↓ B cells = ↓ antibodies = ↑ susceptibility to viral and bacterial infections
- ↑ chance of cancer (↓ NK & $T_C$ cells)

**Overview Summary of Body Defense**
*Nonspecific defense and immunity are linked* (on handout)