



Introduction to the Immune System (Cells and Tissues)

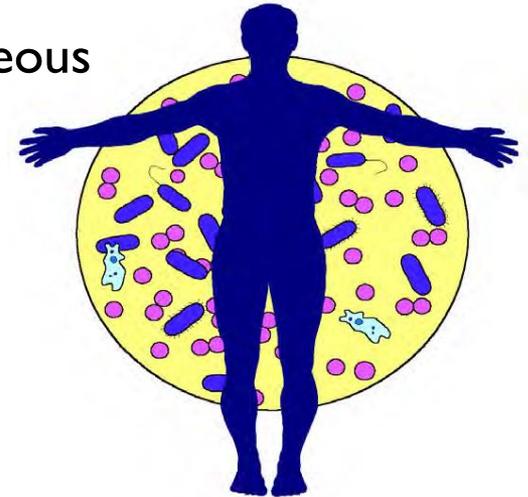
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Lecture Structure/Objectives

- ▶ **Cells and tissues of the immune system**
 - ▶ Lymphocytes, antigen presenting cells and granulocytes
 - ▶ Primary and secondary lymphoid organs
 - ▶ Bone marrow, thymus, spleen, lymph nodes, mucosal associated lymphoid tissues and cutaneous associated lymphoid tissues
- ▶ **Basic development morphology and function of the immune system and immune cells**
- ▶ **Introduction to infectious disease**



Historical perspective

- ▶ From birth we are exposed to microorganisms that can potentially cause disease, also cancers
- ▶ 430BC: Historian Thucydides in Athens recorded that only those who recovered from plague could nurse the sick and not contract the disease (*immunis*- 'exempt')
- ▶ Fifteenth century: Chinese and Turks performed **variolation**
 - ▶ Dried smallpox pustules were inhaled or inserted in the skin
- ▶ 1798: **Edward Jenner** improved variolation
 - ▶ Injected fluid from cowpox patient into healthy individuals
- ▶ 1881: **Louis Pasteur** describes attenuation of *B anthracis*
 - ▶ 1885: Louis Pasteur administered **Rabbis vaccine** (first vaccine)



Structure of the Immune System

▶ First line:

- ▶ Anatomical /Mechanical barriers (Skin and mucous membranes)
- ▶ Chemical barriers (acid and antibacterial peptides)
 - ▶ Complement proteins, lysozyme and defensins
- ▶ Physiological barriers (temperature, pH)

▶ Second line: innate immune cells

- ▶ Phagocytes (monocytes/macrophages, neutrophils and dendritic cells)
- ▶ Natural killer cells (NKC's)
- ▶ Inflammatory cells (mast cells, basophils, eosinophils)

▶ Third line: adaptive immune cells

- ▶ Lymphocytes (T cells and B cells)
- ▶ **Humoral immunity:** Immunoglobulins (antibodies)
- ▶ **Cell-mediated immunity:** T cells

- ▶ Effector and memory responses

Comparison Between Innate and Acquired Immunity

- ▶ Innate Immunity: 1st and 2nd line of defense
 - ▶ Immediate response with no improvement with repeated exposure
 - ▶ React against microbes but not against noninfectious substances or host tissue
- ▶ Adaptive or acquired immunity (3rd line of defense)
 - ▶ **Specificity**: ability to recognize different microbes (self/non-self recognition)
 - ▶ Flexibility (**adaptability**): ability to recognize newly evolved microbes (diversity)
 - ▶ **Memory**: ability to remember previous responses and to react more quickly and more intensely



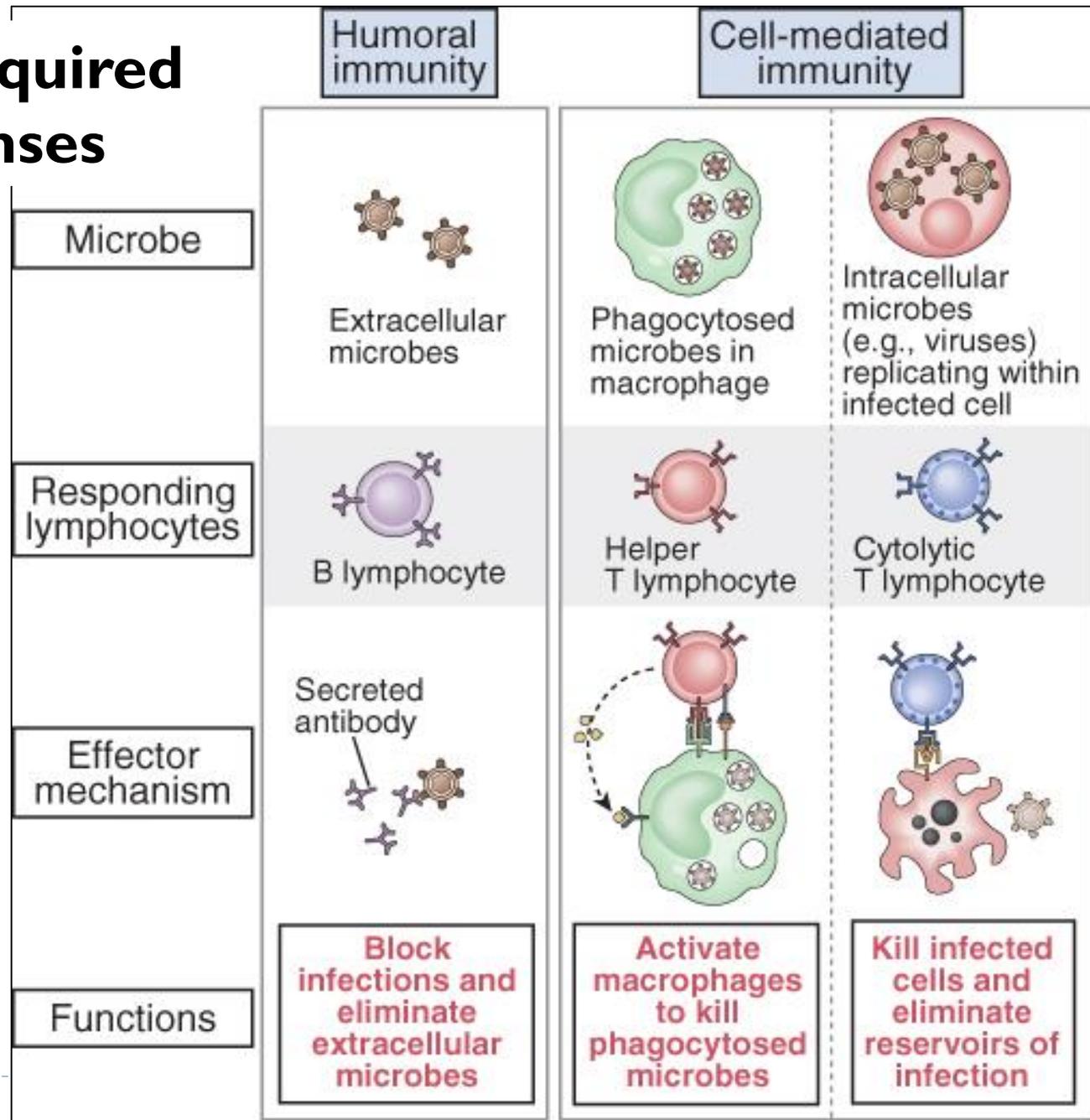
Two Types of Acquired Immune Responses

• **Humoral immunity:**
Antibodies in circulation eliminate infectious agent

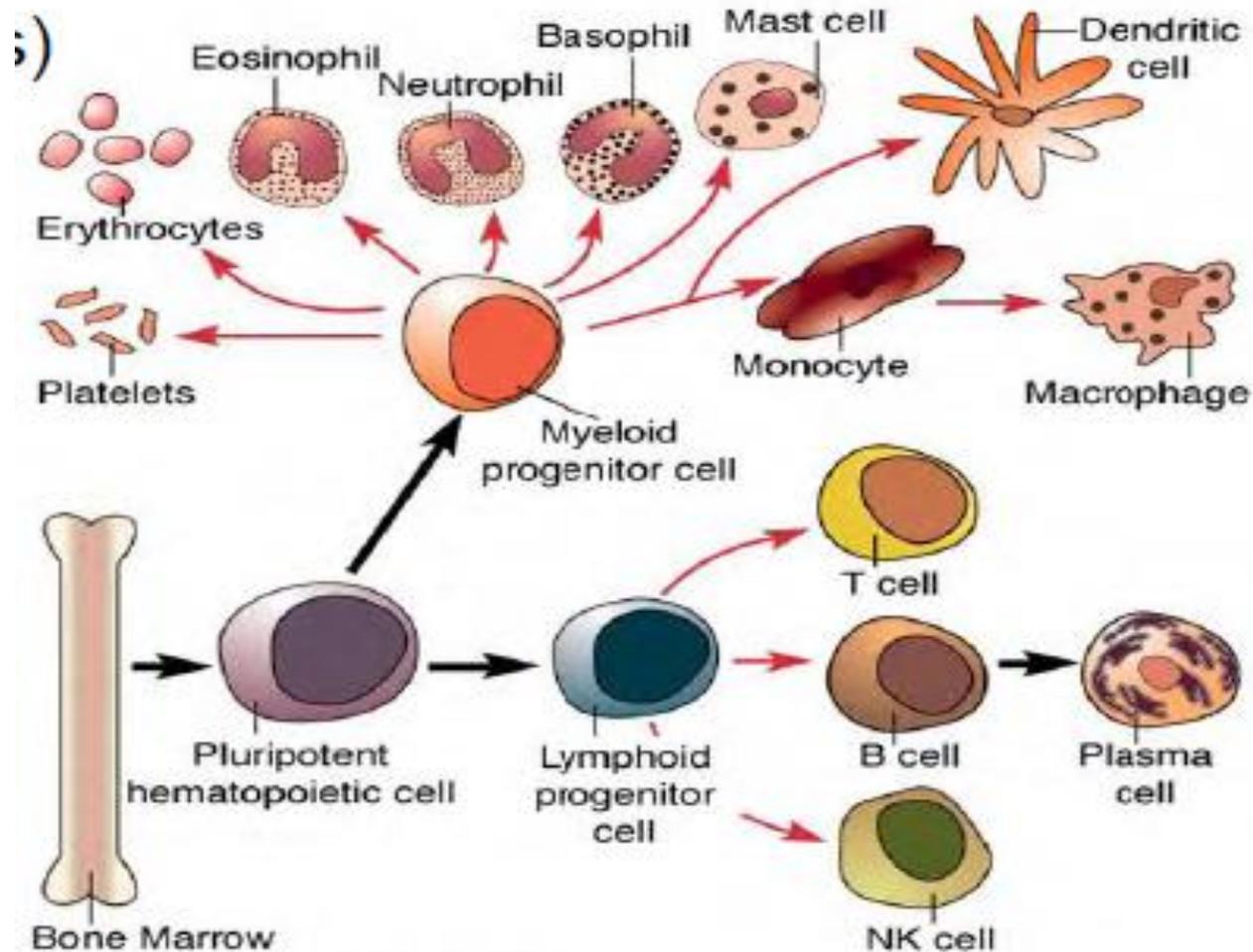
• **Mechanisms**

- Neutralization/blocking
- Antibody dependent-cell mediated cytotoxicity (ADCC)
- Opsonization
- Complement fixation

• **Cell-mediated immunity:** T cells activate macrophage to kill phagocytosed microbe or kill infected cells

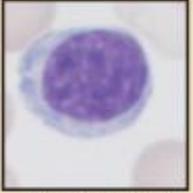
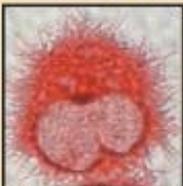
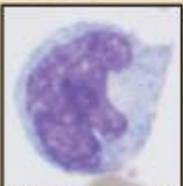
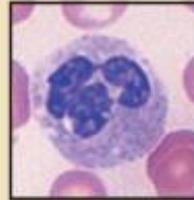


Development of Cells of the immune system



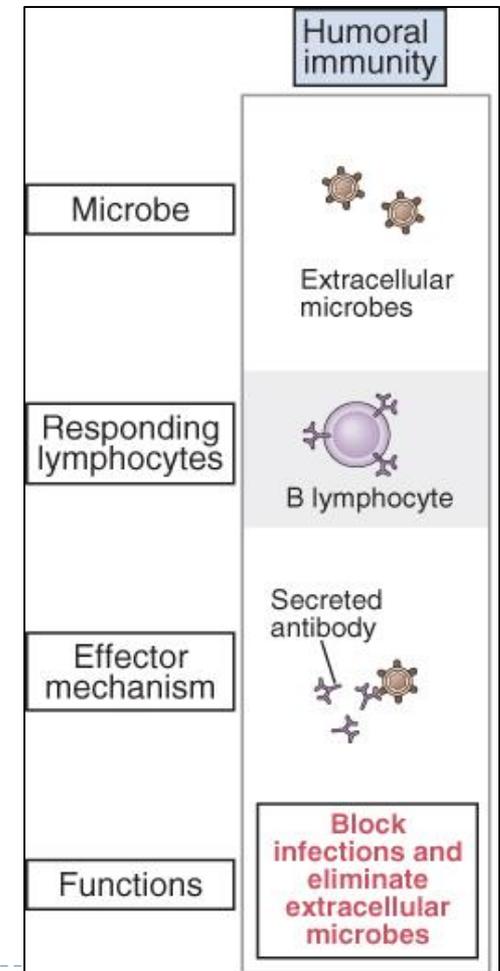
Cells of the immune system

- ▶ **Lymphocytes**
 - ▶ B and T cells (Th/CD4 and Tc/CD8 cells)
 - ▶ Natural killer cells (NK cells)
- ▶ **Antigen presenting cells**
 - ▶ B cells, monocytes/macrophages, dendritic cells
- ▶ **Cells that produce inflammatory mediators (granulocytes)**
 - ▶ Neutrophils, basophils, eosinophils, mast cells
 - ▶ Important in helminth and protozoan infections
 - ▶ Involved in allergy

| Cell type |
|--|
| Lymphocytes: B lymphocytes; T lymphocytes; natural killer cells  <i>Lymphocyte</i> |
| Antigen-presenting cells: dendritic cells; macrophages; follicular dendritic cells  <i>Dendritic cell</i>  <i>Blood monocyte</i> |
| Effector cells: T lymphocytes; macrophages; granulocytes  <i>Neutrophil</i> |

B Cells

- ▶ Mature within the bone marrow
 - ▶ Mature in the bursa of Fabricius in birds
- ▶ Express B cell receptor (**immunoglobulin/antibody molecules**) on the surface
- ▶ Upon encounter with antigen, B cells differentiate into effector B cells (**plasma cells**) that secrete antibodies and **memory B cells**.



Ab Isotypes

- 5 main classes of Ab due to different C regions

- C γ
 - IgG
- C μ
 - IgM
- C δ
 - IgD
- C α
 - IgA
- C ϵ
 - IgE

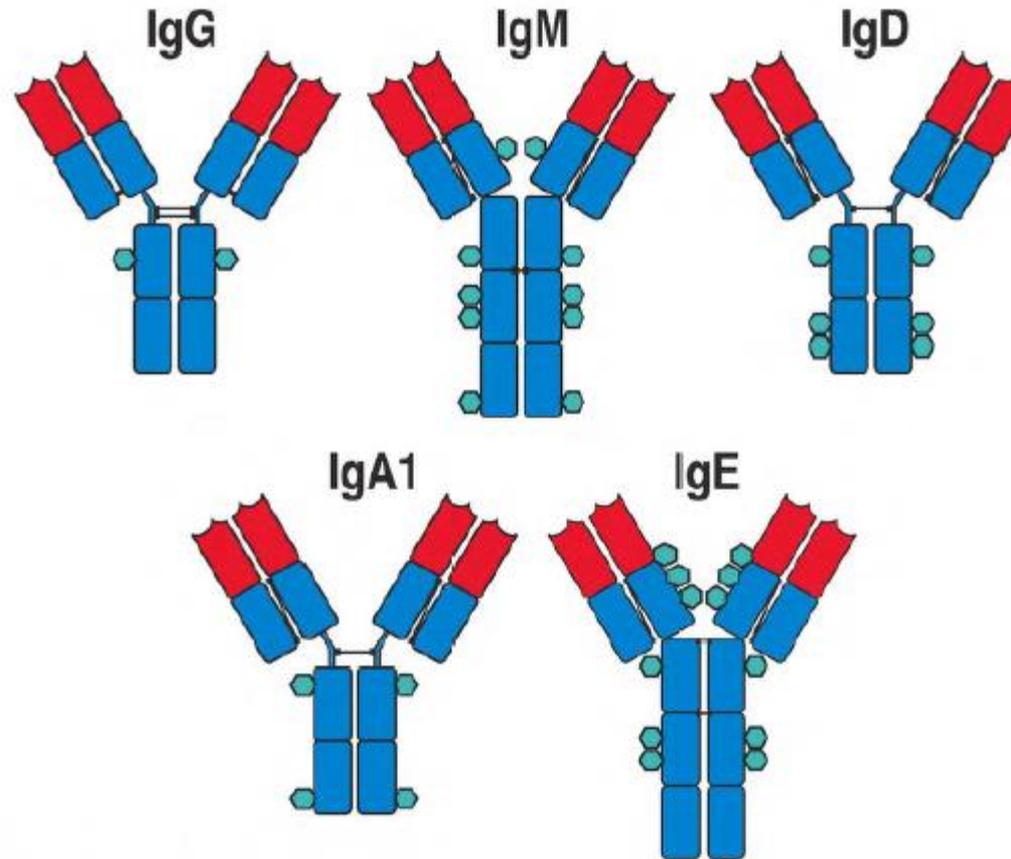
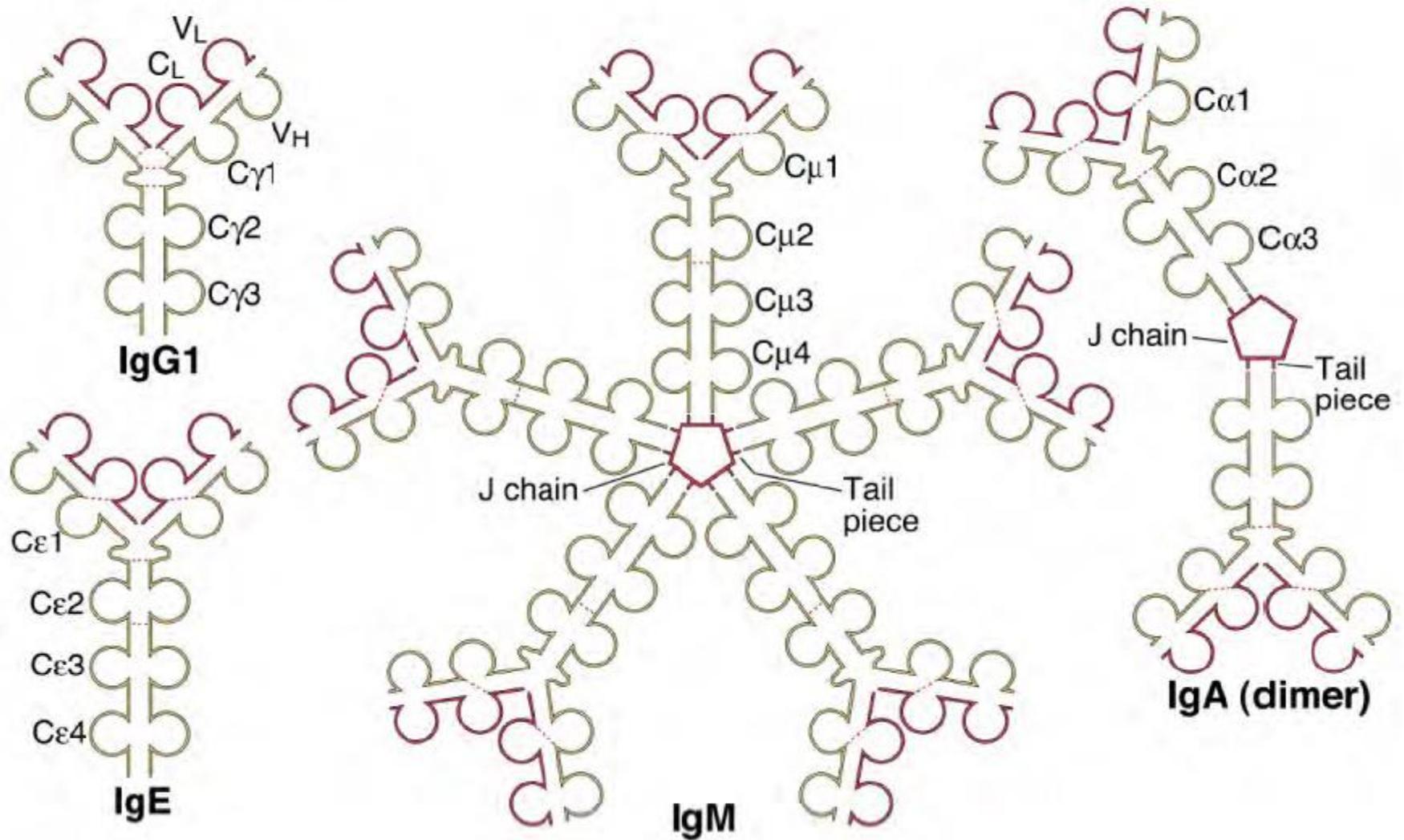


Figure 4-18 Immunobiology, 6/e. (© Garland Science 2005)

Ab Isotypes



Antibody Effector Functions

- IgM, IgG and IgA antibodies protect the blood and extracellular fluids
- IgA and IgG are transported across epithelial barriers by specific receptor proteins



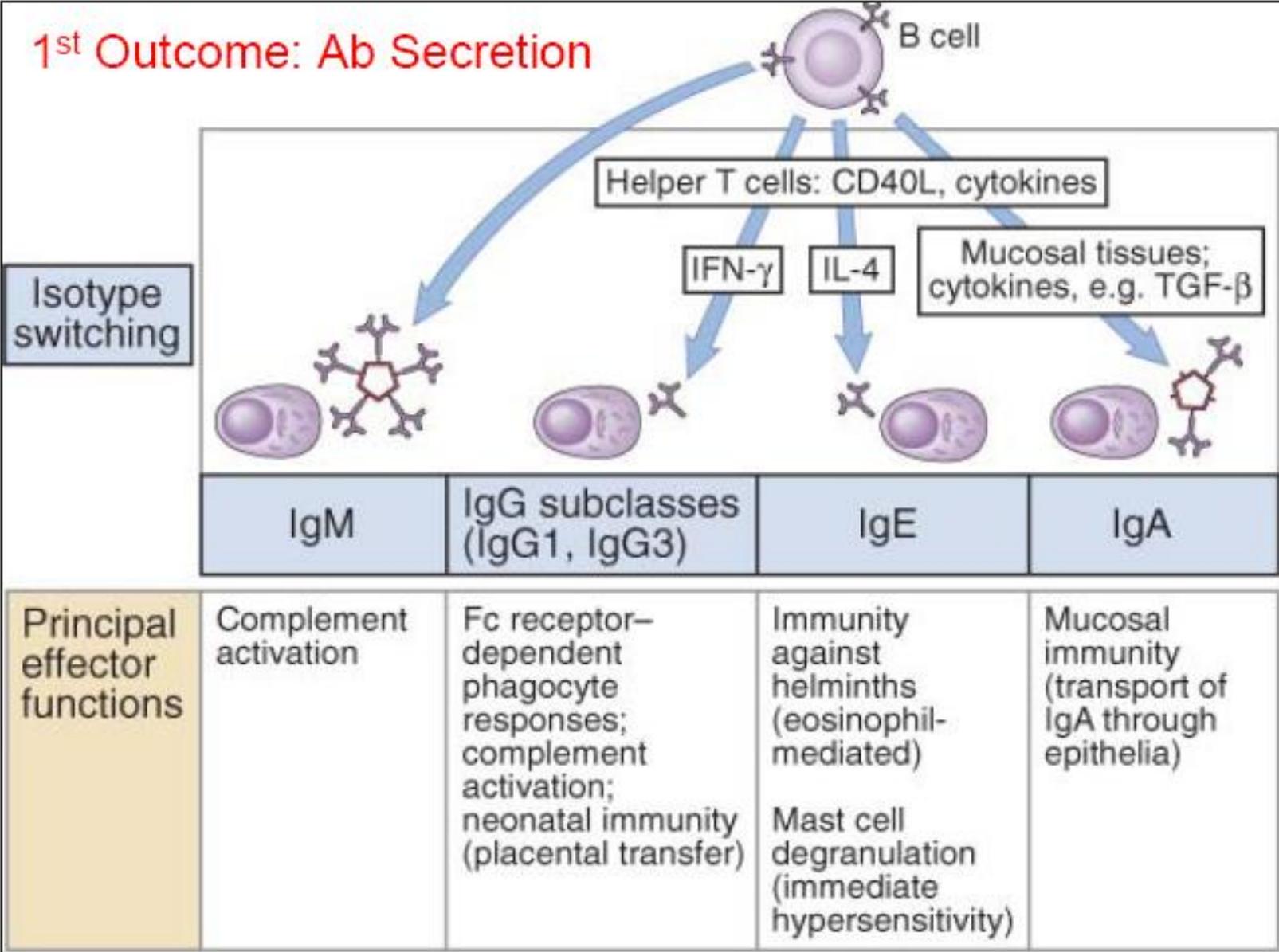
Figure 7-19 The Immune System, 2/e (© Garland Science 2005)

Specialized Properties of Different Ig Isotypes

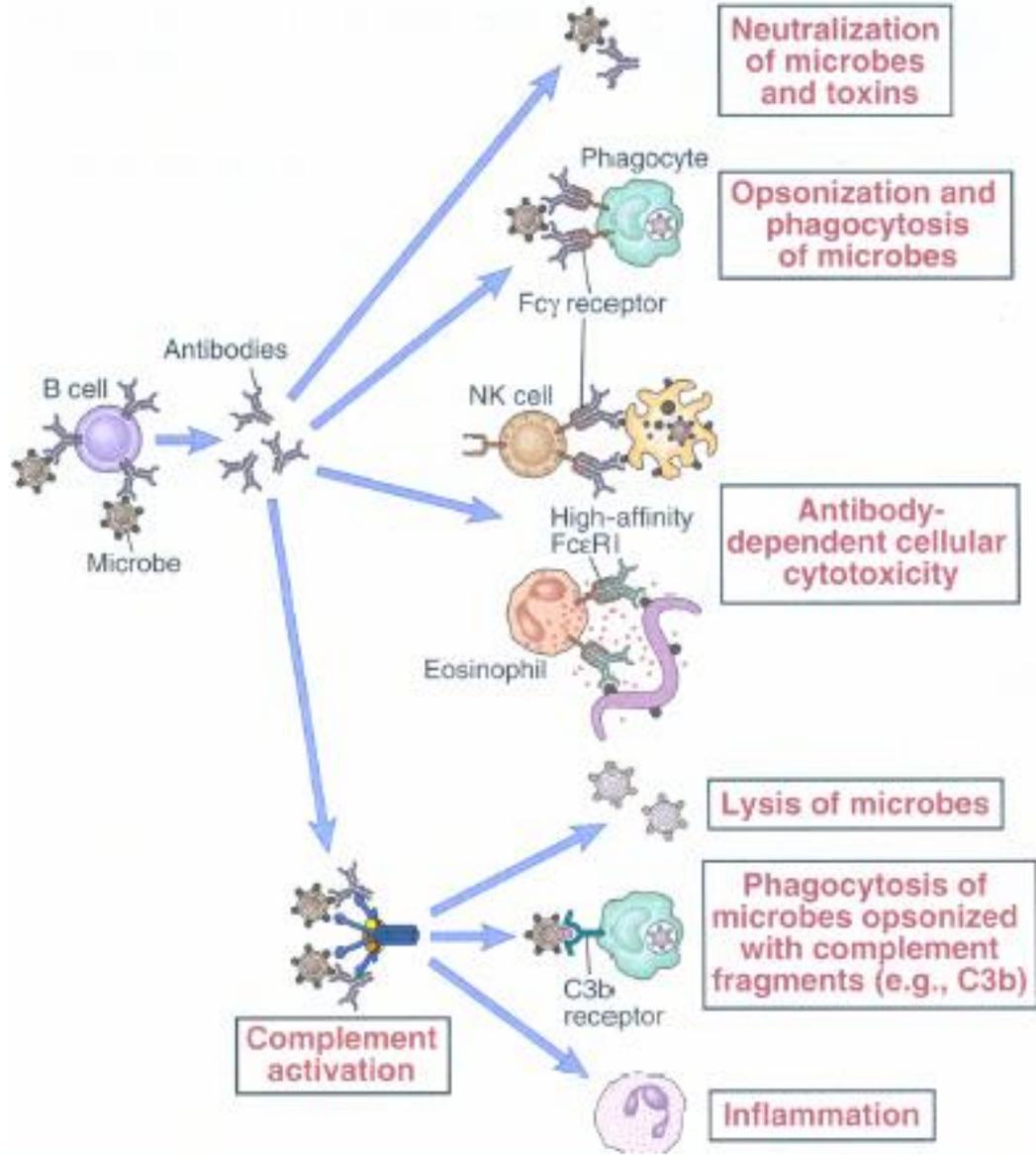
| Function | IgG | IgA | IgM | IgE | IgD |
|----------------------------|--|---|--|---|-----------|
| H chain symbol | γ | α | μ | ϵ | δ |
| Adult serum level (mg/ml)* | 13.5 | 3.5 | 1.5 | 0.05 | trace |
| Half-life in serum (days) | 23* | 6 | 5 | 2 | 2 |
| Activates complement | + | - | ++ | - | - |
| Placental transfer | + | - | - | - | - |
| Main function | Opsonization; complement activation; placental transfer; antibody dependent cytotoxicity | Mucosal immunity; neonatal passive immunity through breast milk | First in ontogeny, in immune response; naïve BCR; potent complement activation | Immunity against helminths; Mast cells, basophils, eosinophils activation | Naïve BCR |



1st Outcome: Ab Secretion

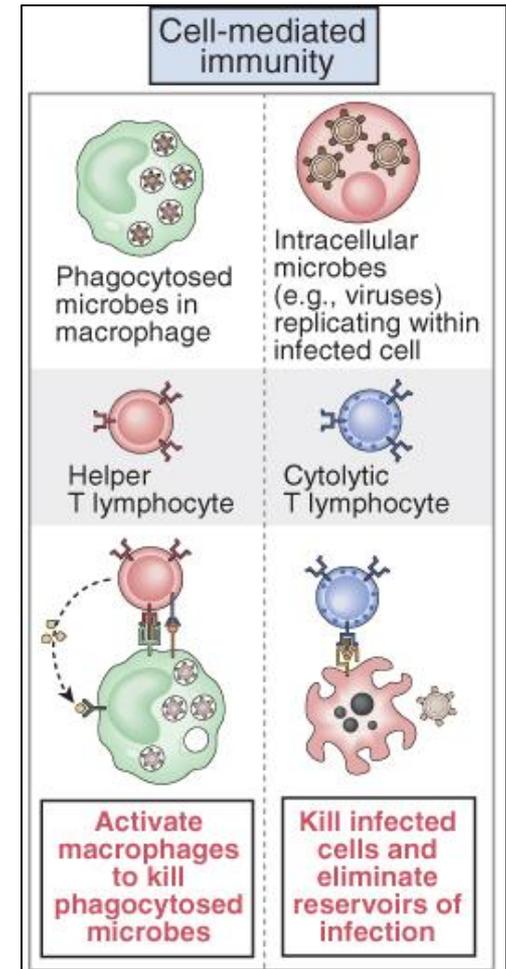


Effector function of immunoglobulins



T Cells

- ▶ Develop in the bone marrow but migrate and mature in the thymus
- ▶ Express **T cell receptor** on the surface
 - ▶ TCR recognize molecules bound on MHC/HLA molecules
- ▶ Main T cell populations: Th (CD4) and Tc (CD8)
 - ▶ **CD4 cells:** recognize antigens bound on MHC-II molecules, produces **cytokines/chemokines** that activate phagocytes (extracellular pathogens)
 - ▶ **CD8 cells:** recognize antigens bound on MHC-I molecules and proliferate into cytotoxic T lymphocytes (CTLs) (intracellular pathogens, tumor cells, foreign tissue grafts)



Effector T cells Molecules

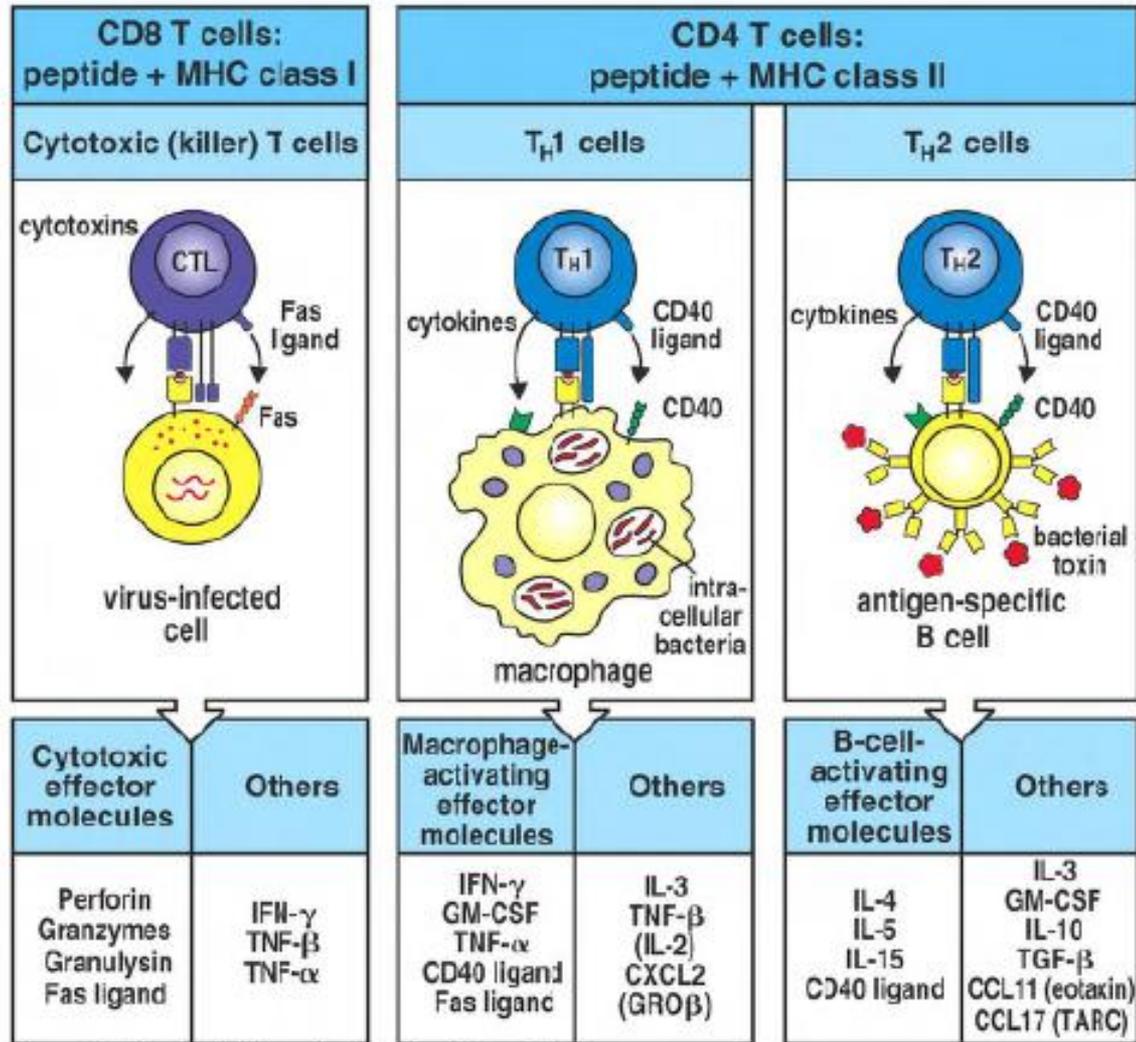


Figure 8-31 Immunobiology, 6/e. (© Garland Science 2005)

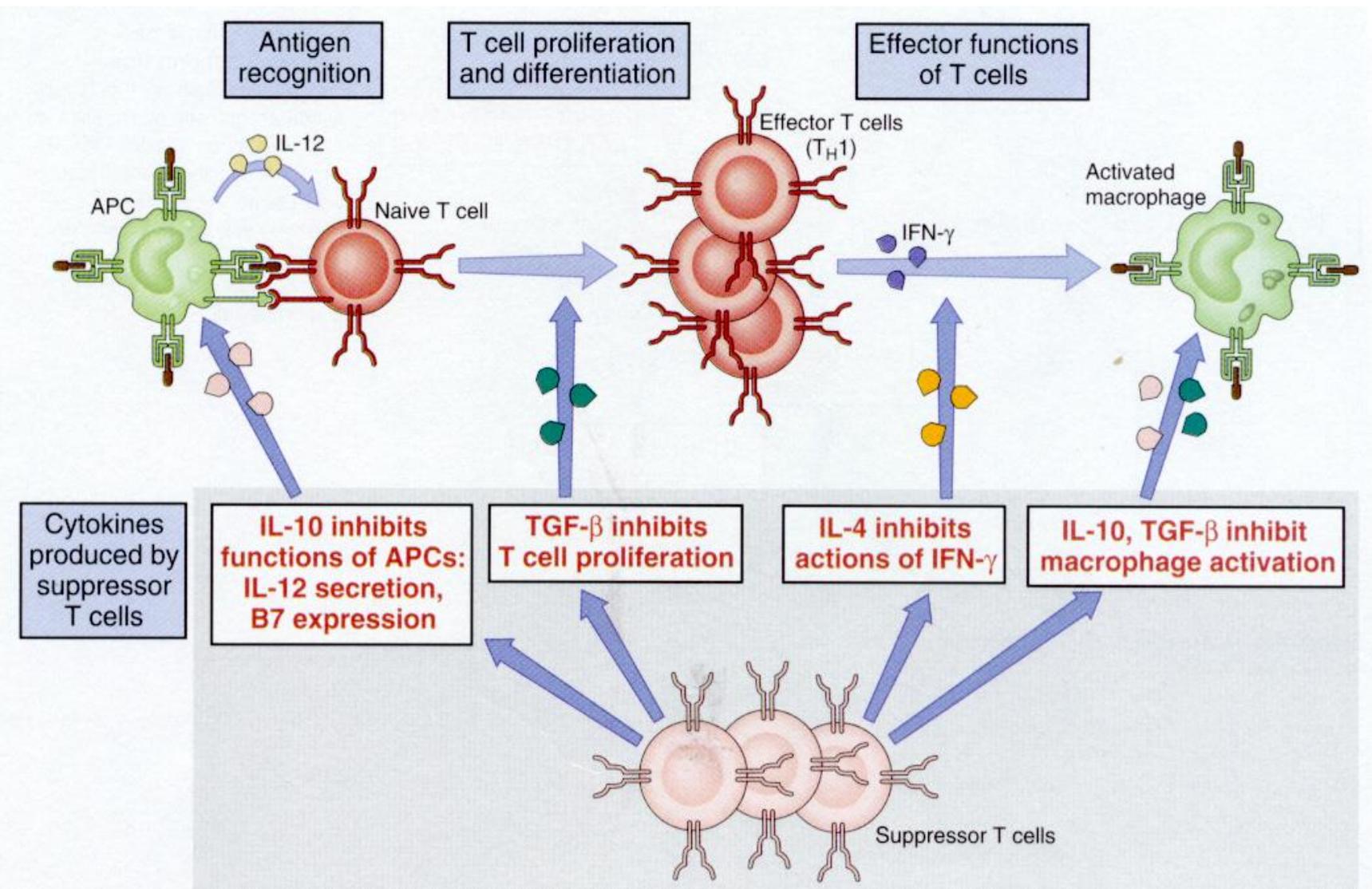
Other T cell subpopulations

- ▶ **Regulatory T cells (Tregs) or suppressor T cells**
 - ▶ Express CD4, CD25 and foxp3
 - ▶ Regulate T cell responses
 - ▶ prevent autoimmune disease and suppress other CD4+ effector cells by cell-to-cell contact and production of inhibitory cytokines

- ▶ **Th17 Cells**
 - ▶ Subpopulation of T cells that produce IL-17
 - ▶ Involved in mucosal immunity

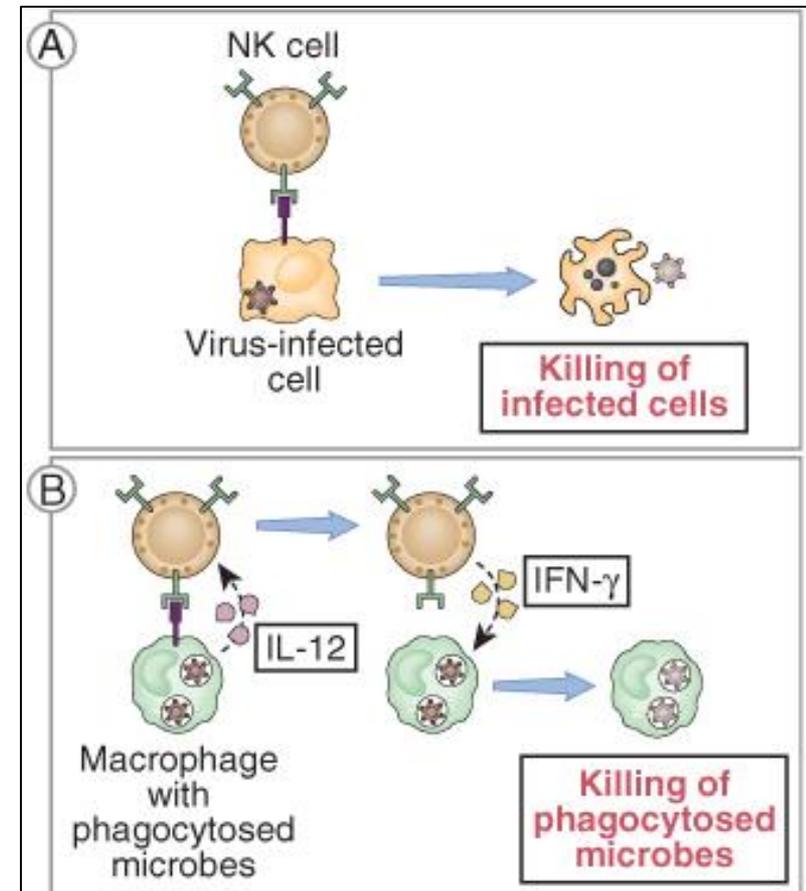


Suppressor (Regulatory) T cells elaborate inhibitory cytokines



Natural Killer Cells

- Lyse viral infected cells immediately
-
- Activated by macrophages that produce IL-12
- NK cells produce interferon- γ that, in turn, activates macrophages
- NK cells also have Fc receptors so function in antibody dependent cellular cytotoxicity (ADCC)



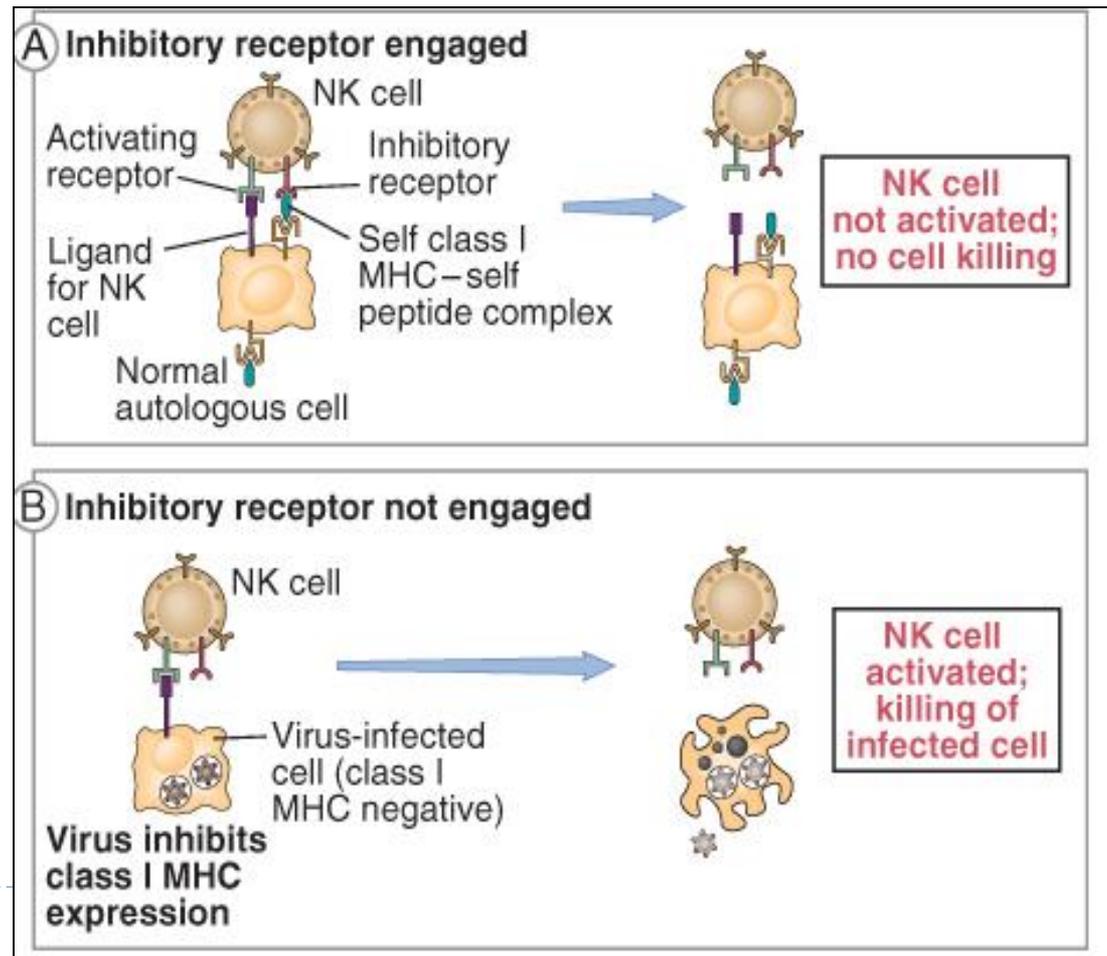
NK cells Have Inhibitory and Activating Receptors

▶ Inhibitory receptors

- ▶ Recognize class I MHC (major histocompatibility) molecules)
- ▶ Transmit an inhibitory signal that blocks activation

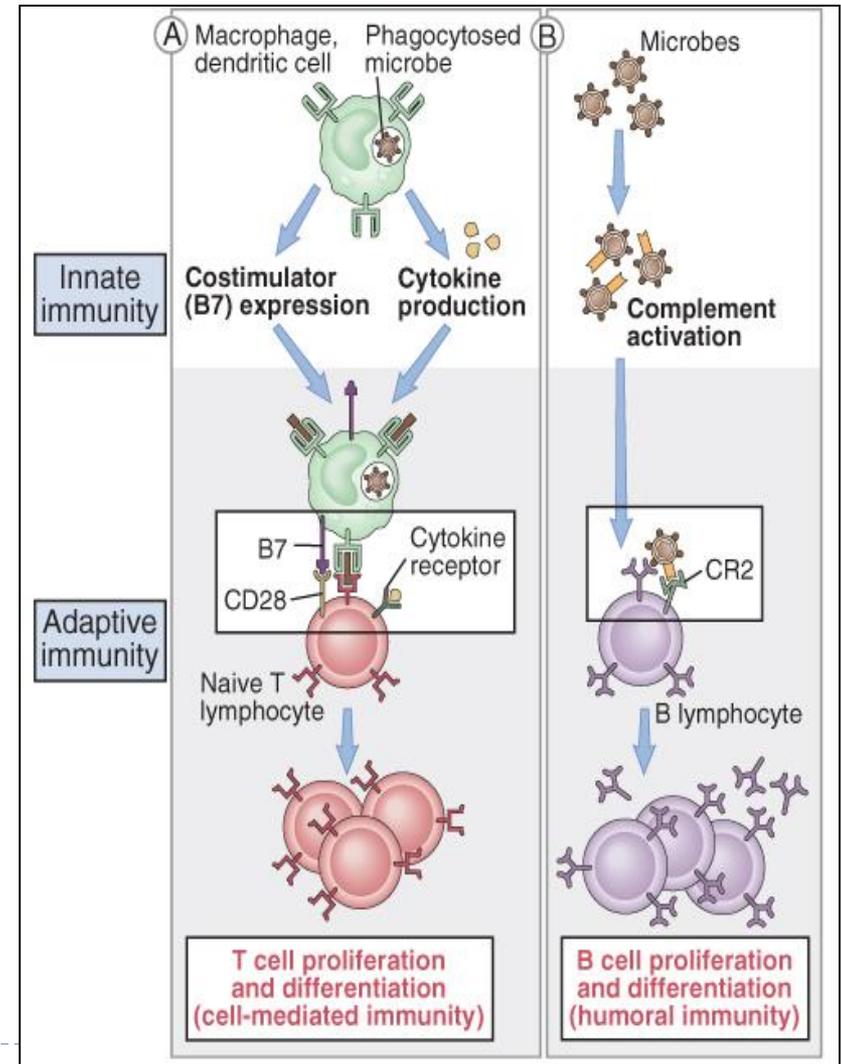
▶ Activating receptors

- ▶ Works only when MHC I expression is lost
- ▶ Virus infected and tumor cells often lose class I MHC expression



Antigen presenting cells

- ▶ B cells, monocytes/macrophages and dendritic cells
 - ▶ Express MHC-II molecules
 - ▶ Can produce co-stimulatory molecules to activate Th cells
- ▶ Bridge between innate and adaptive immune responses



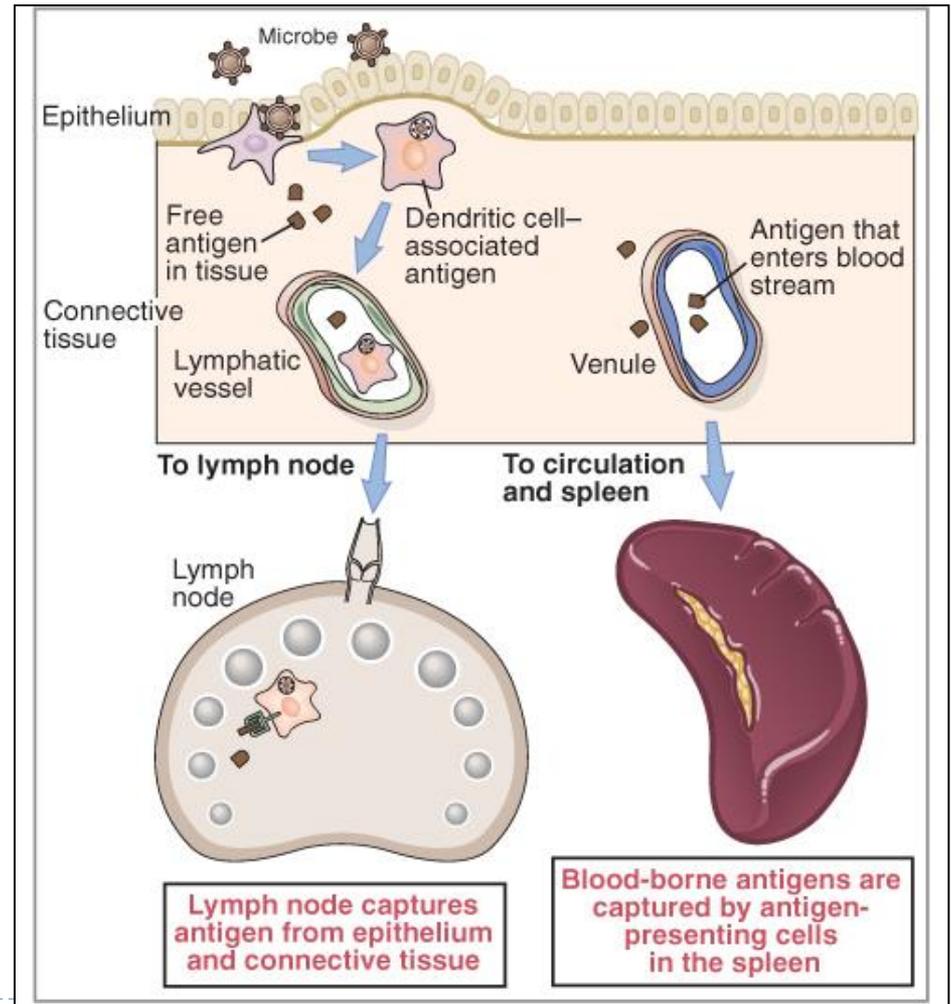
Monocytes / macrophages

- ▶ Monocytes originate from the bone marrow and mature in the blood (blood monocytes)
- ▶ Circulate in blood a few days and migrate into tissues where they differentiate into tissue macrophages
 - ▶ Alveolar macrophages in lungs
 - ▶ Histiocytes in connective tissue
 - ▶ Kupffer cells in the liver
 - ▶ Mesangial cells in the kidneys
 - ▶ Microglia in the brain
 - ▶ Osteoclasts in the bones
- ▶ Function as antigen presenting cells and phagocytes
 - ▶ Express MHC-II
 - ▶ Activated by IFN- γ



Dendritic cells

- ▶ Resemble dendrites of nerve cells
- ▶ Process and present antigens to Th cells
- ▶ After capturing antigens in tissues, they migrate into lymphoid organs, via blood or lymph, where they present antigens to Th cells



Granulocytes

▶ Neutrophils

- ▶ Have multi-lobed nucleus
- ▶ Respond to infection in tissues (mostly bacterial)
- ▶ Have potent phagocytic activity
- ▶ Kill by lytic enzymes, oxygen and oxygen independent pathways, lysozyme etc

▶ Eosinophils

- ▶ Phagocytic cells
- ▶ Important in parasitic infections
- ▶ Produce inflammatory mediators that damage parasite cell membranes



▶ Basophils

- ▶ Non-phagocytic granulocytes
- ▶ Produce pharmacologically active compounds (Histamines)
- ▶ Involved in allergic reactions



Mast cells

- ▶ Found in a wide range of tissues
- ▶ Contain cytoplasmic granules that contain histamines and other pharmacologically active compounds
- ▶ Involved in allergic reactions



Tissues/organs of the immune system

- ▶ **Primary lymphoid organs**
 - ▶ Where immune cells mature
 - ▶ Thymus (T cells)
 - ▶ Bone marrow (B cells)
- ▶ **Secondary lymphoid organs**
 - ▶ Where mature immune cells are housed/function
 - ▶ Lymph nodes
 - ▶ Spleen
 - ▶ Mucosal associated lymphoid tissue (MALT) and cutaneous associated lymphoid tissue (**tertiary lymphoid organs**)

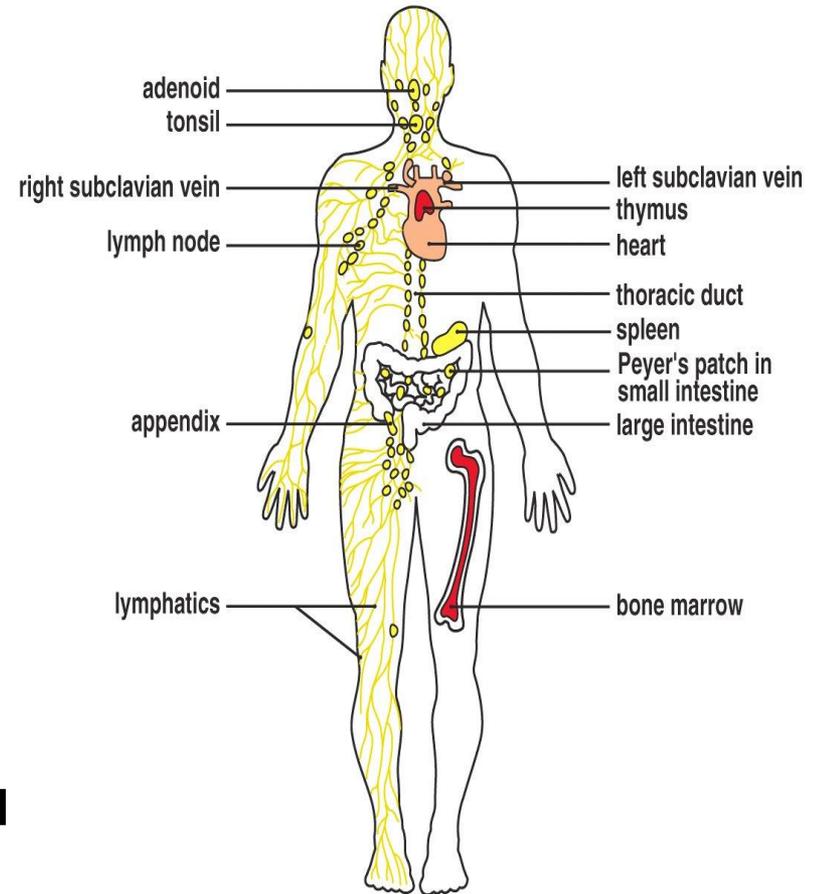
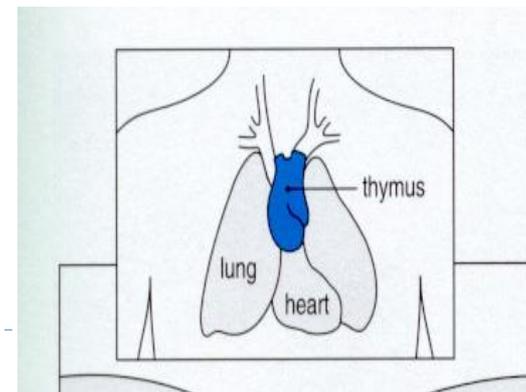
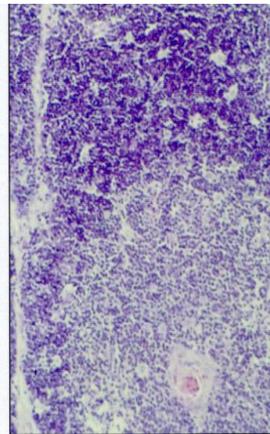
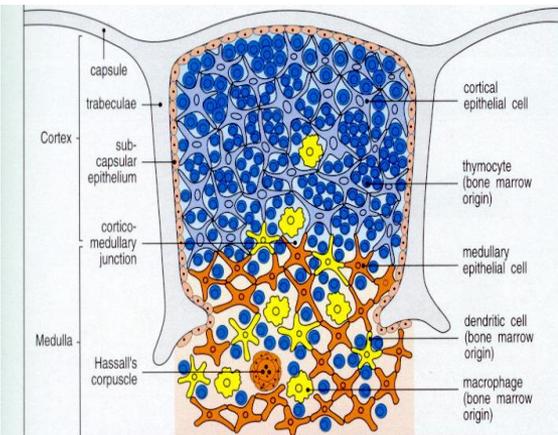


Figure 1-15 The Immune System, 2/e (© Garland Science 2005)

The thymus

- ▶ Flat bilobed organ situated above the heart
- ▶ The cortex is densely packed with thymocytes
- ▶ T cell selection and maturation occurs in the thymus
 - ▶ Thymocytes that fail to recognize self MHC or bind too tightly are eliminated by apoptosis
 - ▶ Only those that recognize self MHC and foreign peptides are allowed to mature

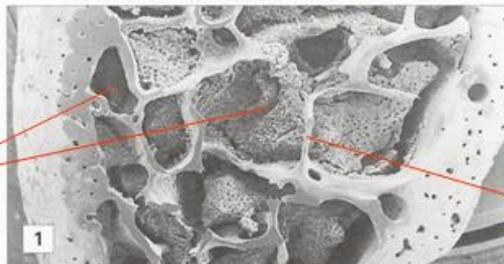


The bone marrow

- ▶ In birds the Bursa of fabricus is the site for B cell maturation
- ▶ In mammals the bone marrow is the site for B cell maturation
- ▶ Like T cell maturation, B cells under go selection and B cells that secrete self reactive antibodies are eliminated

Bone marrow

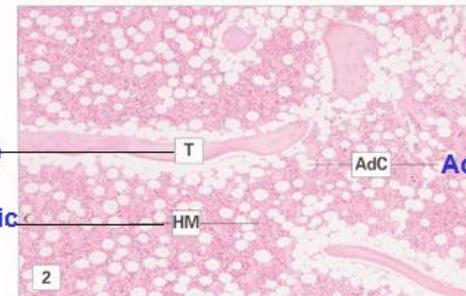
Hematopoietic areas



Bony trabeculae

Bony trabeculae

Hematopoietic areas



Adipocytes

Secondary lymphoid organs

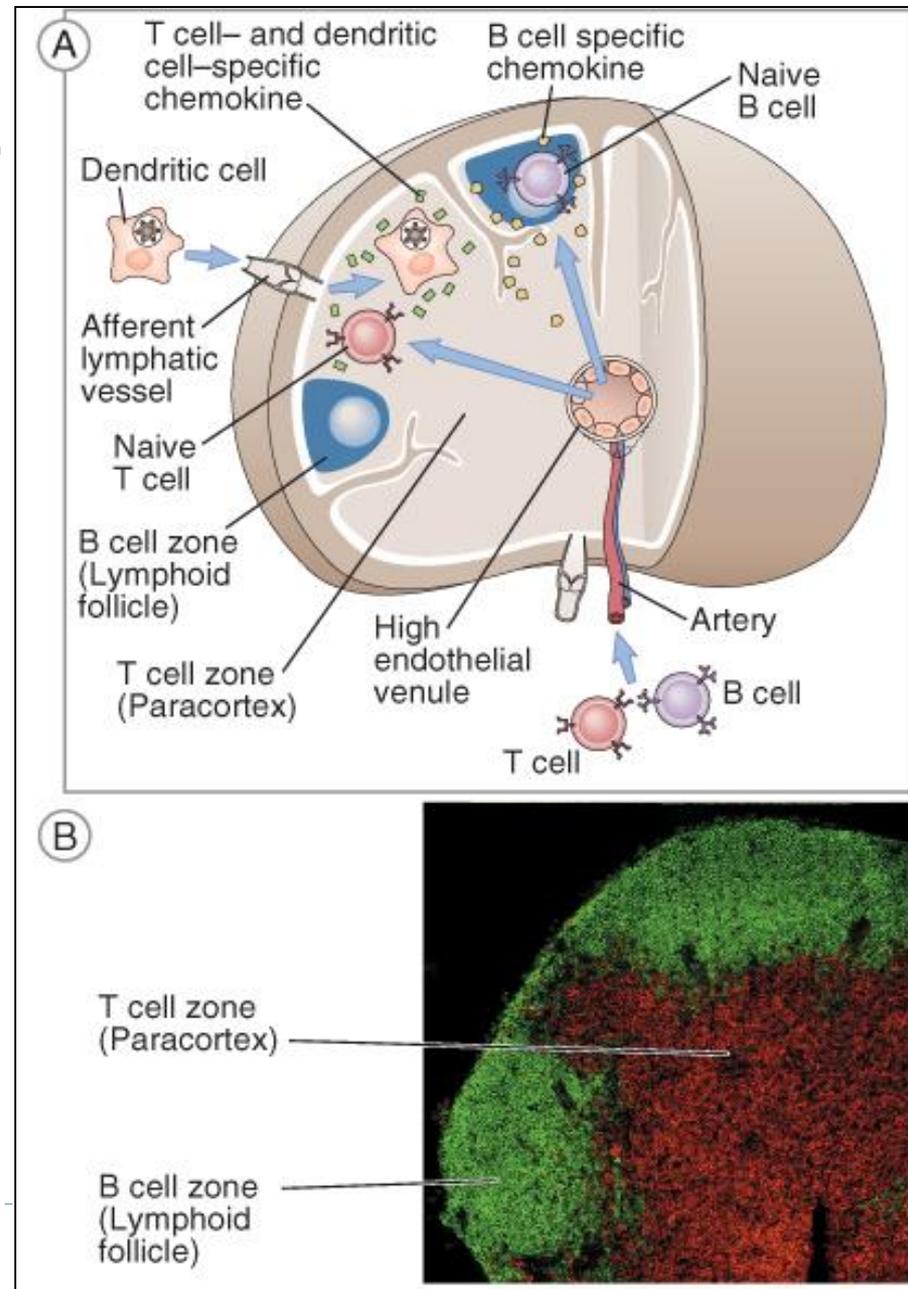
▶ Lymph nodes

- ▶ Encapsulated bean shaped organs
- ▶ Clustered in junctions of lymphatic vessels
- ▶ First to encounter antigens
- ▶ Contains macrophages, dendritic cells and lymphocytes
- ▶ The cortex contains B cells, macrophages and follicular dendritic cells
- ▶ The paracortex is populated with T cells and dendritic cells



Lymph nodes: nodular aggregates

- Naïve lymphocytes enter thru high endothelial venules
- B cells found in follicles in cortical region
 - Follicle develops into germinal center when stimulated
 - Contain follicular dendritic cells that elaborate chemokines attracting B cells
- T cells found in paracortex region
- Dendritic cells enter thru lymphatics or blood capillaries from periphery and migrate to T cell rich area

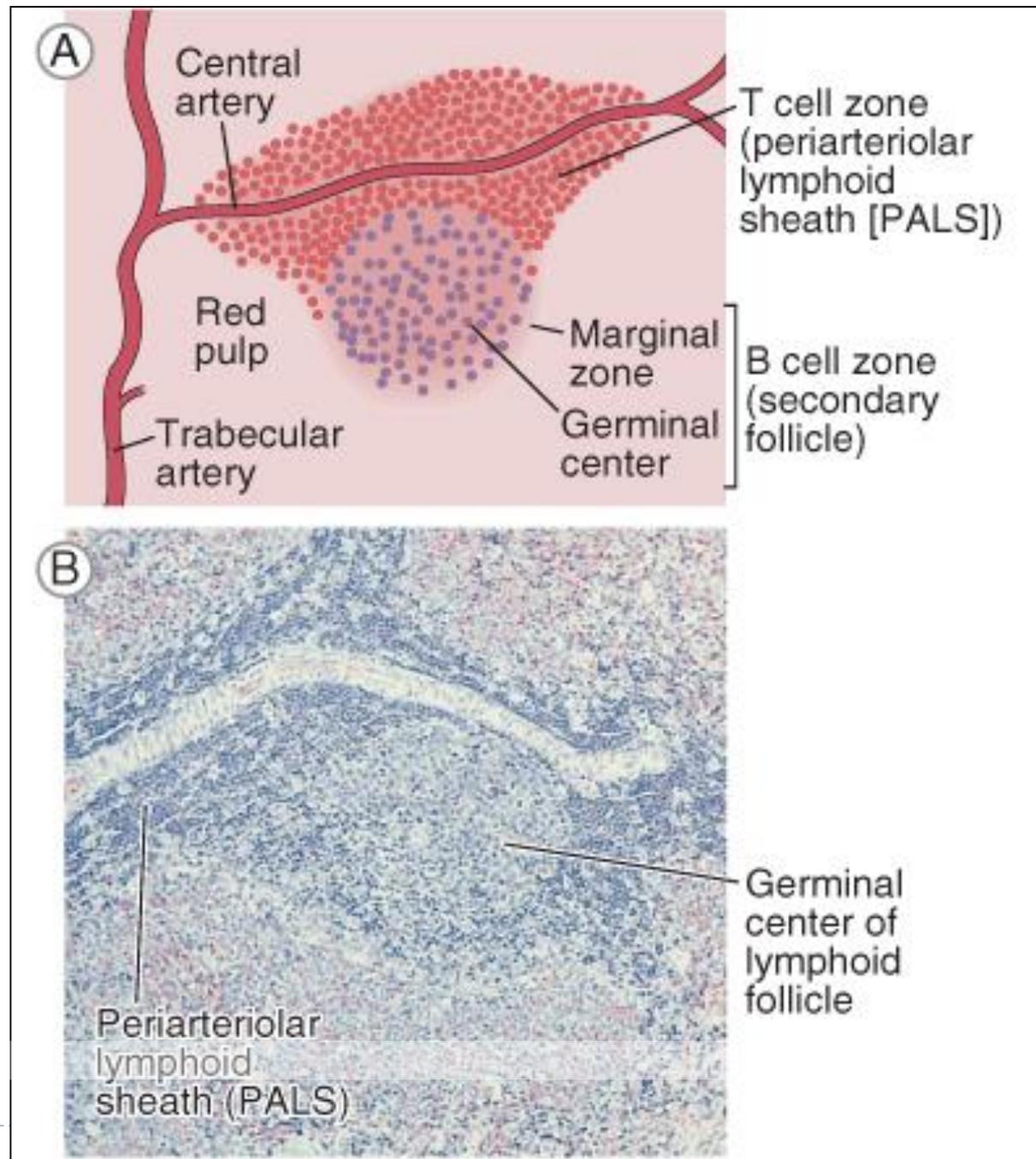


Spleen

Large ovoid organ situated high in the left abdominal cavity

Functions

- Clears blood born microbes, particulate antigens
- Removes abnormal rbc, stores rbc, platelets (in red pulp)
- Immune function (white pulp)
 - T cells found in periarteriolar lymphoid sheath
 - Follicles contain B cells that develop into germinal center



Mucosal associated lymphoid tissues (MALT)

- ▶ Found near mucosal surfaces of the respiratory, digestive and urogenital tracts
 - ▶ Peyer's patches in the digestive tract
 - ▶ Tonsils in the throat
- ▶ Antigen transport from luminal to the basal laminae is carried out by **M cells**
- ▶ Epithelial cells of mucous membranes play a key role in immune responses to foreign microbes
- ▶ Also important to maintenance of normal flora



MUCOSAL ASSOCIATED LYMPHOID TISSUES (MALT)

- Gut-associated lymphoid tissue (GALT): adenoids, tonsils, appendix, Peyer's patches
- Bronchial-associated lymphoid tissue (BALT): line respiratory epithelium
- Mucosal-associated lymphoid tissue (MALT): less organized on mucosal surfaces

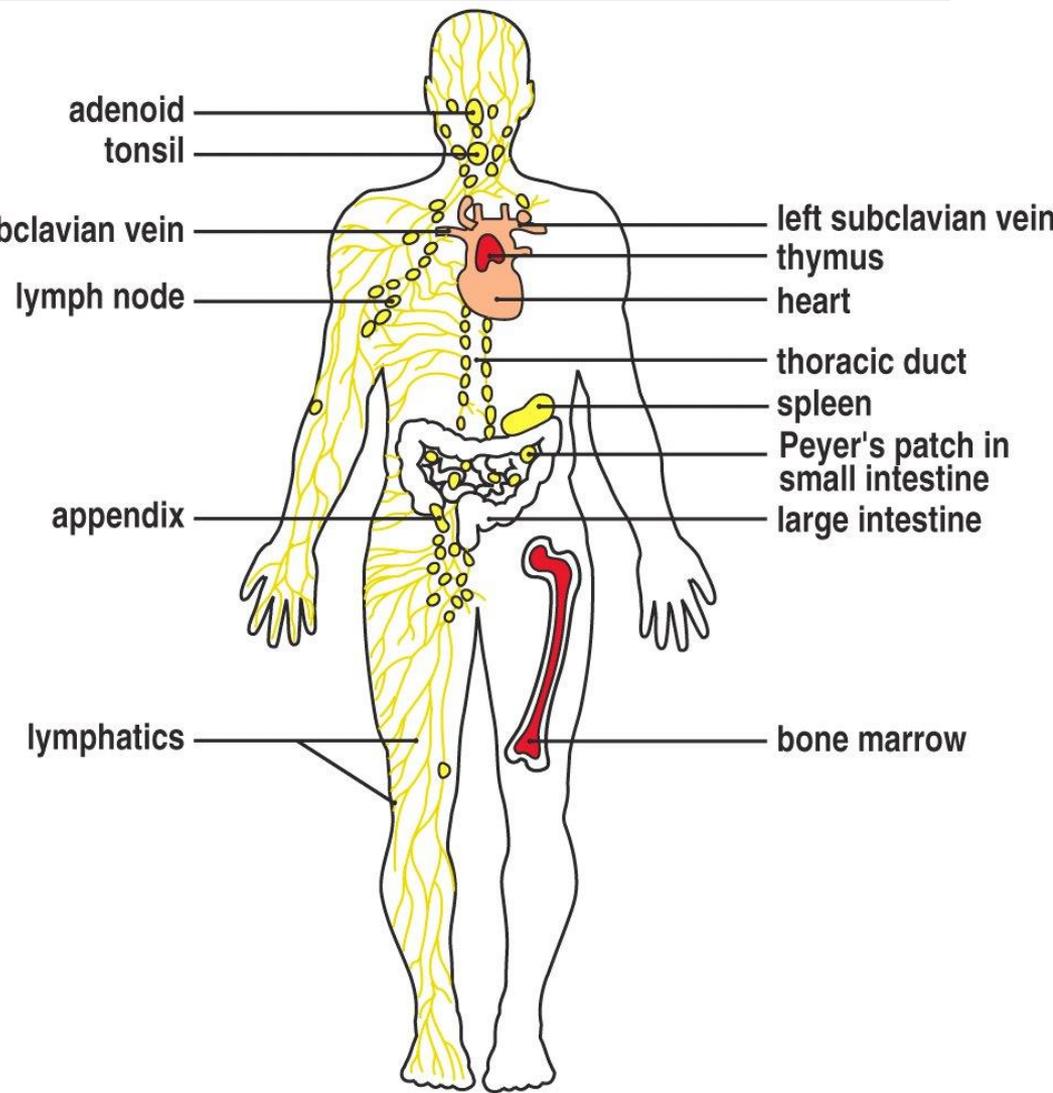
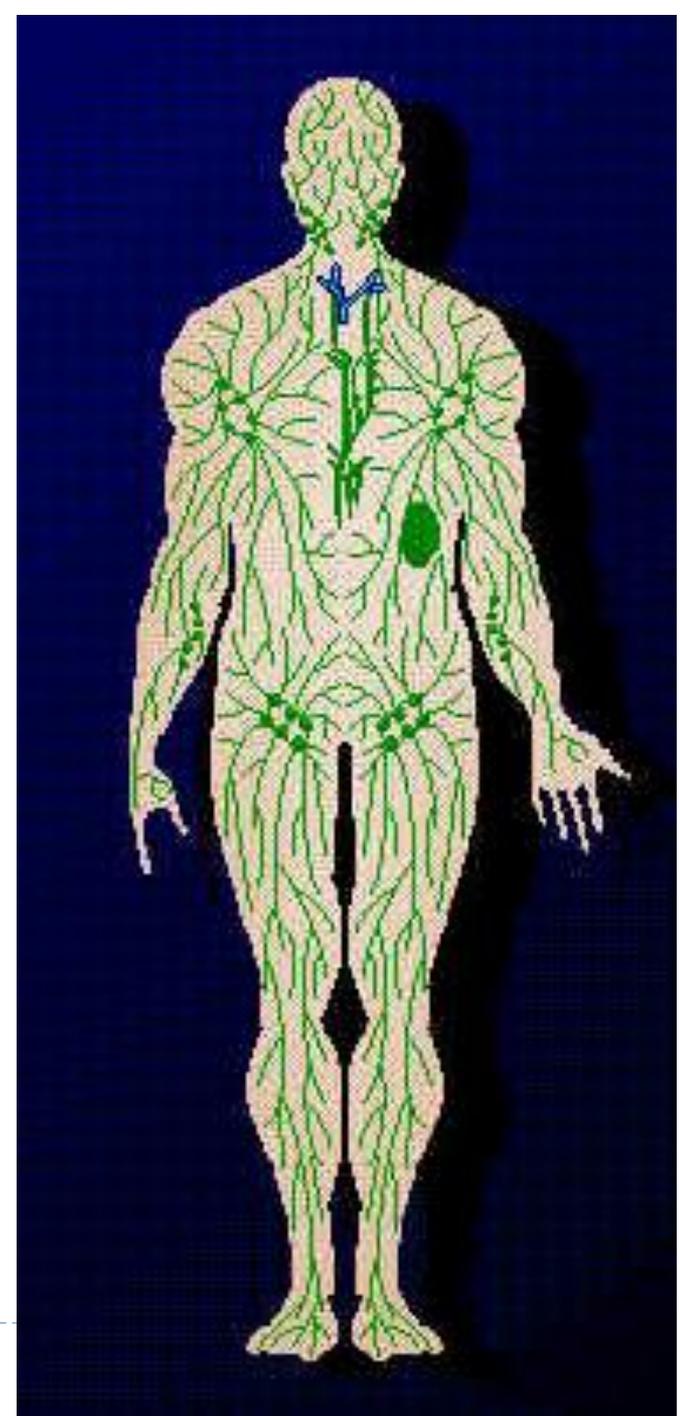


Figure 1-15 The Immune System, 2/e (© Garland Science 2005)

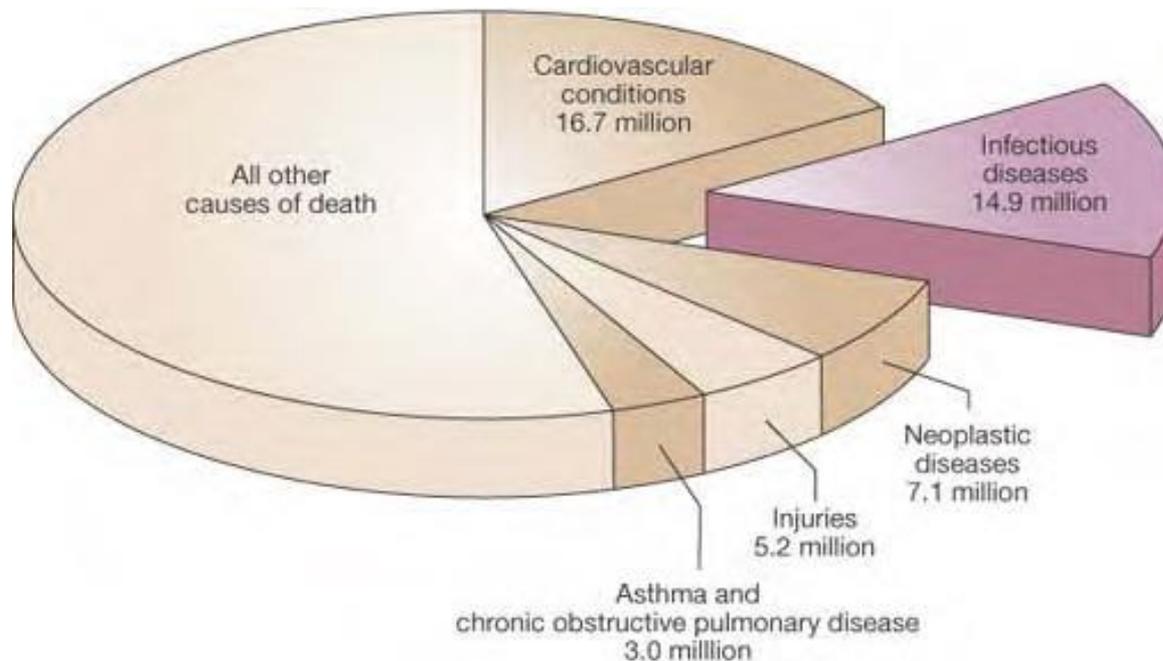
Lymphatic circulatory system innervates all tissues

- Lymphatic vessels begin as dead-end capillaries; extend into most tissues side by side with blood capillaries
- Collects fluid bathing tissues
- Vessels merge forming afferent lymphatic vessels which enter lymph node
- In lymph nodes, fluid picks up lymphocytes, leaves via efferent lymphatic vessels which merge to form lymphatic trunks eventually emptying into thoracic duct where lymph is added to blood



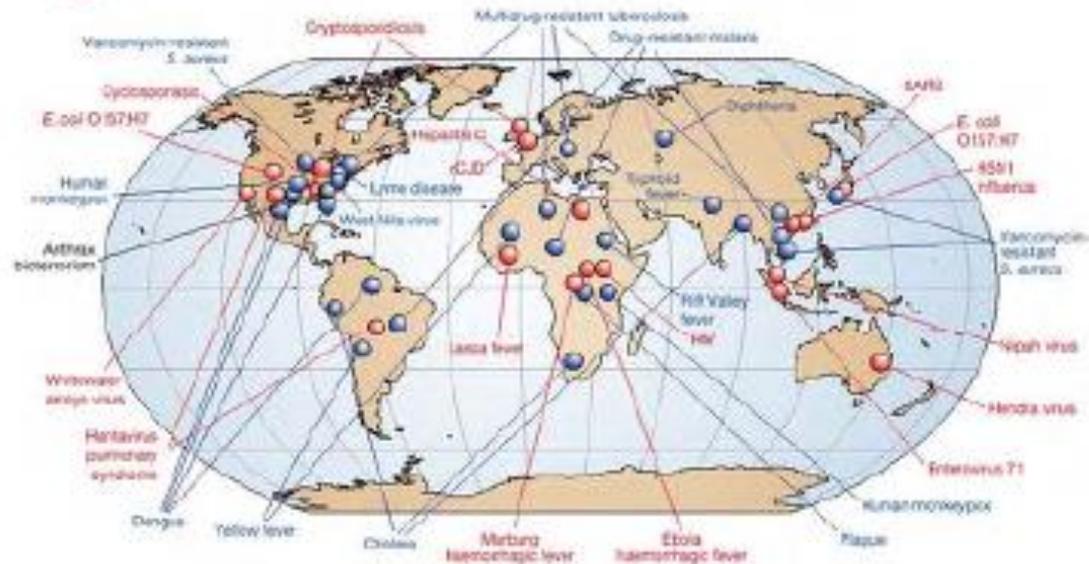
Introduction to infectious disease

- ▶ “...time to close the book on infectious diseases, declare the war on pestilence won and shift national resources to such chronic problems as heart disease and cancer.” US Surgeon General William H. Stewart 1969



| Infectious diseases | Annual deaths (million) |
|--|-------------------------|
| Respiratory infections | 3.96 |
| HIV/AIDS | 2.77 |
| Diarrhoeal diseases | 1.80 |
| Tuberculosis | 1.56 |
| Vaccine-preventable childhood diseases | 1.12 |
| Malaria | 1.27 |
| STDs (other than HIV) | 0.18 |
| Meningitis | 0.17 |
| Hepatitis B and C | 0.16 |
| Tropical parasitic diseases | 0.13 |
| Dengue | 0.02 |
| Other infectious diseases | 1.76 |

Emerging Infectious Diseases



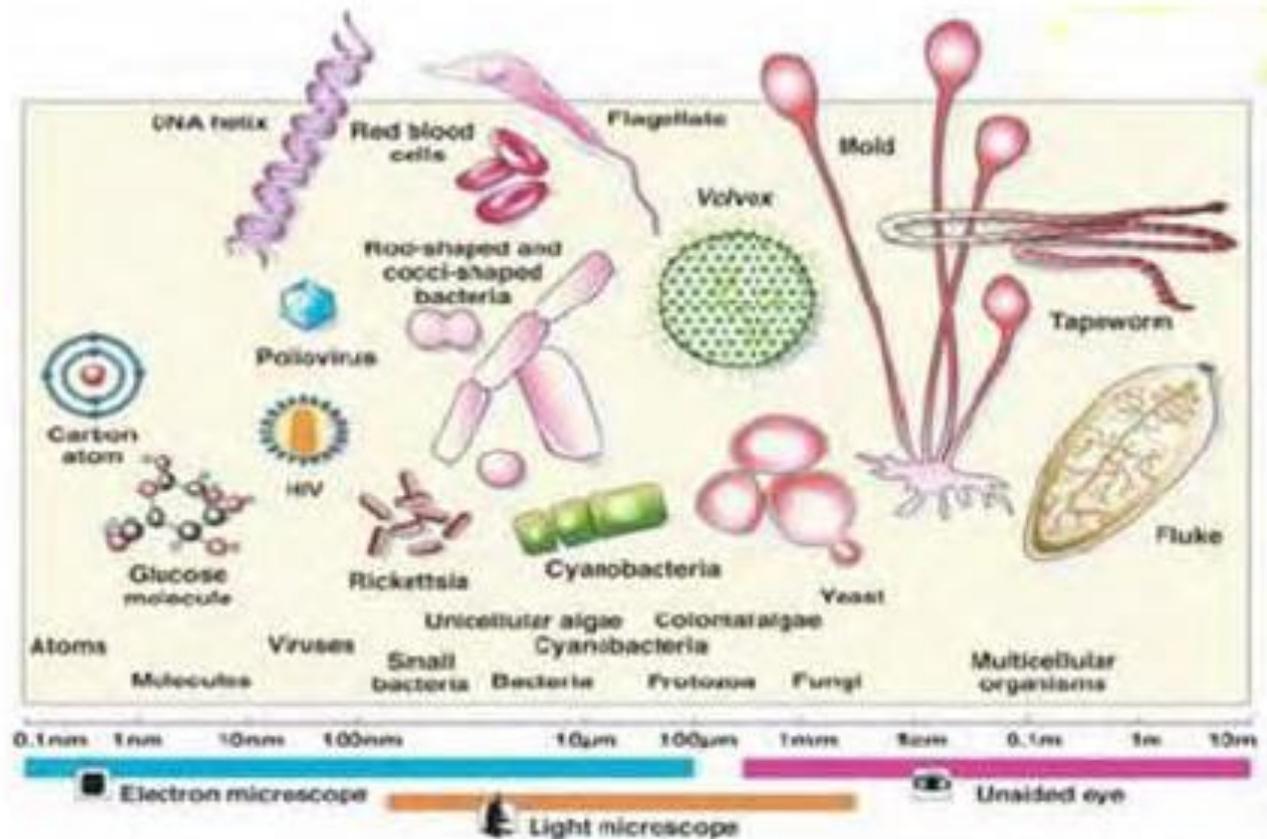
- 1973 Rotavirus
- 1977 Ebola virus
- 1977 *Legionella pneumophila*
- 1980 HTLV 1
- 1981 Toxigenic *Staph. aureus*
- 1982 *E. coli* O157:H7
- 1982 *Borrelia burgdorferi*
- 1983 HIV
- 1983 *Helicobacter pylori*
- 1985 MDR TB

- 1989 Hepatitis C
- 1992 *V. cholerae* O139
- 1993 Hantavirus
- 1994 *Cryptosporidium*
- 1995 Hendra virus
- 1996 nvCJD
- 1999 Nipha Virus
- 2000 West Nile Virus
- 2003 SARS
- 2004 H1N5

Dengue virus
 HINI
 ZIKA
 COVID-19

Microbiota

- Viruses
 - Mycoplasma
 - Chlamydia
 - Rickettsias
- Fungi
 - Protozoa
 - Helminthes



Infection and Disease

■ Disease

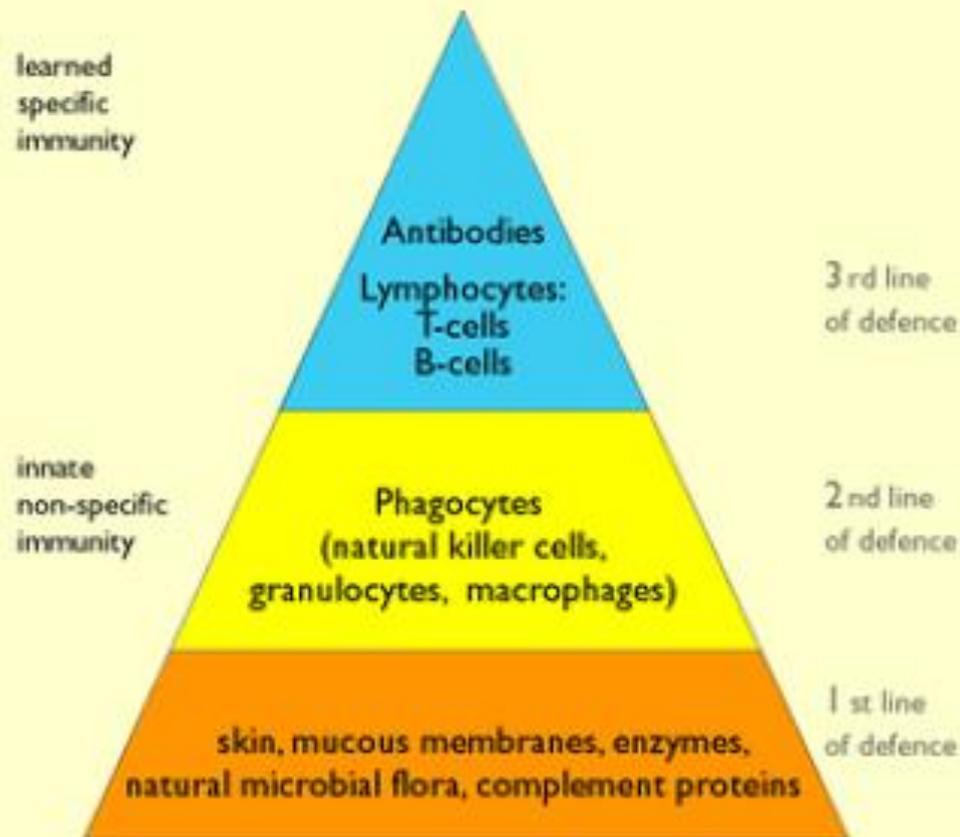
- an upset in the homeostasis of the host, resulting in generation of observable changes
- symptom - *subjective* evidence of damage to the host
 - headache, anorexia
- sign - *objective* evidence of damage to the host
 - fever, rash, vomiting

■ Infection

- The ability of an organism to establish itself in a host.
 - Infection **MAY NOT** represent DISEASE
-

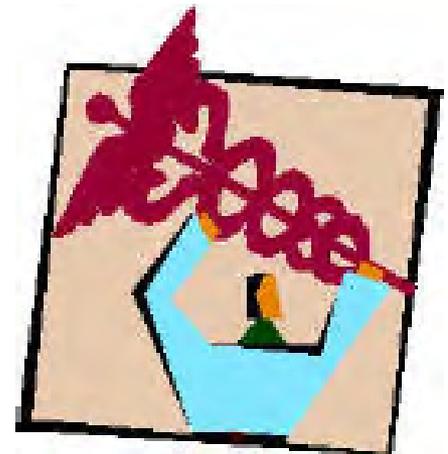
Host Response to the Microbial World

Immune System



Intervention

- Chemotherapy
 - Antimicrobials
- Immunization
 - vaccines
- Improving public health
 - better sanitation, nutrition



Host Microbe Interactions

- Host
 - harbours another organism
- Symbiosis
 - living together
- Mutualism
 - both benefit
- Commensalism
 - one benefits, the other unharmed
- Parasitism
 - one benefits, the other is harmed



The Benefits of Normal Flora

- Normal flora synthesizes and excrete vitamins
 - Normal flora prevents colonization by pathogens
 - Normal flora may antagonize other bacteria
 - Normal flora stimulates the development of certain tissues
 - Normal flora stimulates the production of cross-reactive antibodies.
-

In Summary

- Infectious Disease is a dynamic process
 - Emerging and Re-emerging pathogens
- Infectious Disease is a balance between
 - Bacteria virulence factors
 - Host immune response

