Introduction to the Immune System
(Innate Immunity)

BMS 3325

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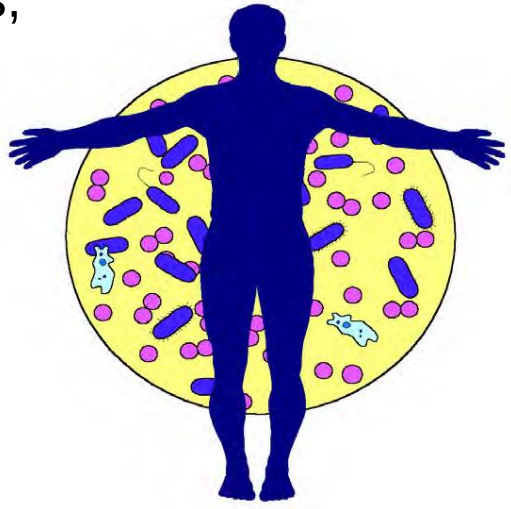
Lecture Structure/Objectives

- 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

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)

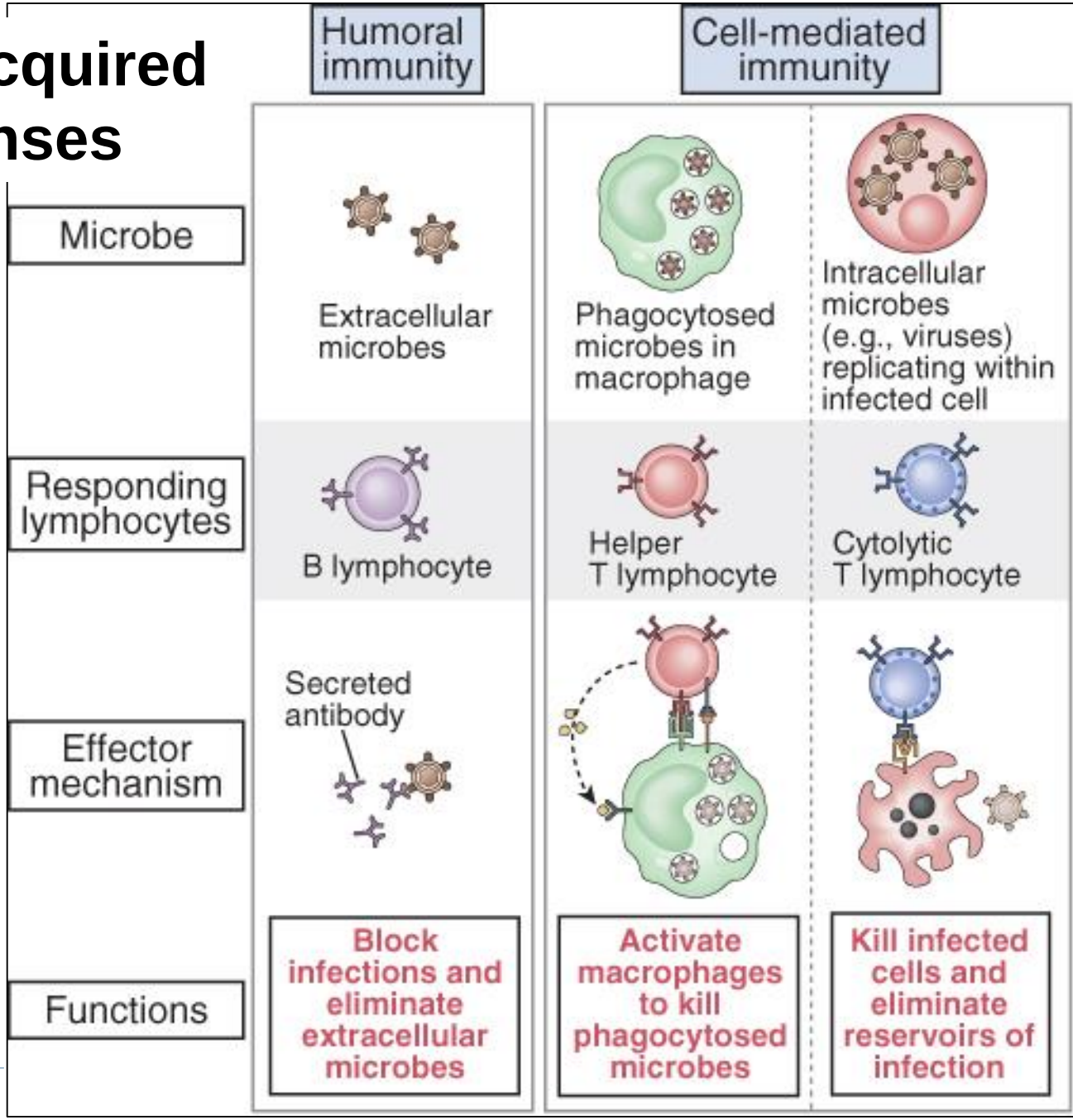
- Second line: innate immune cells
  - Phagocytes (monocytes/macrophages, neutrophils and dendritic cells)
  - Natural killer cells (NKCs)
  - Inflammatory cells (mast cells, basophils, eosinophils)

- Third line: adaptive immune cells
  - Lymphocytes (T cells and B cells)
  - **Humoral immunity**: Immunoglobulins (antibodies)
  - **Cell-medicated immunity**: T cells
    - Effector and memory responses

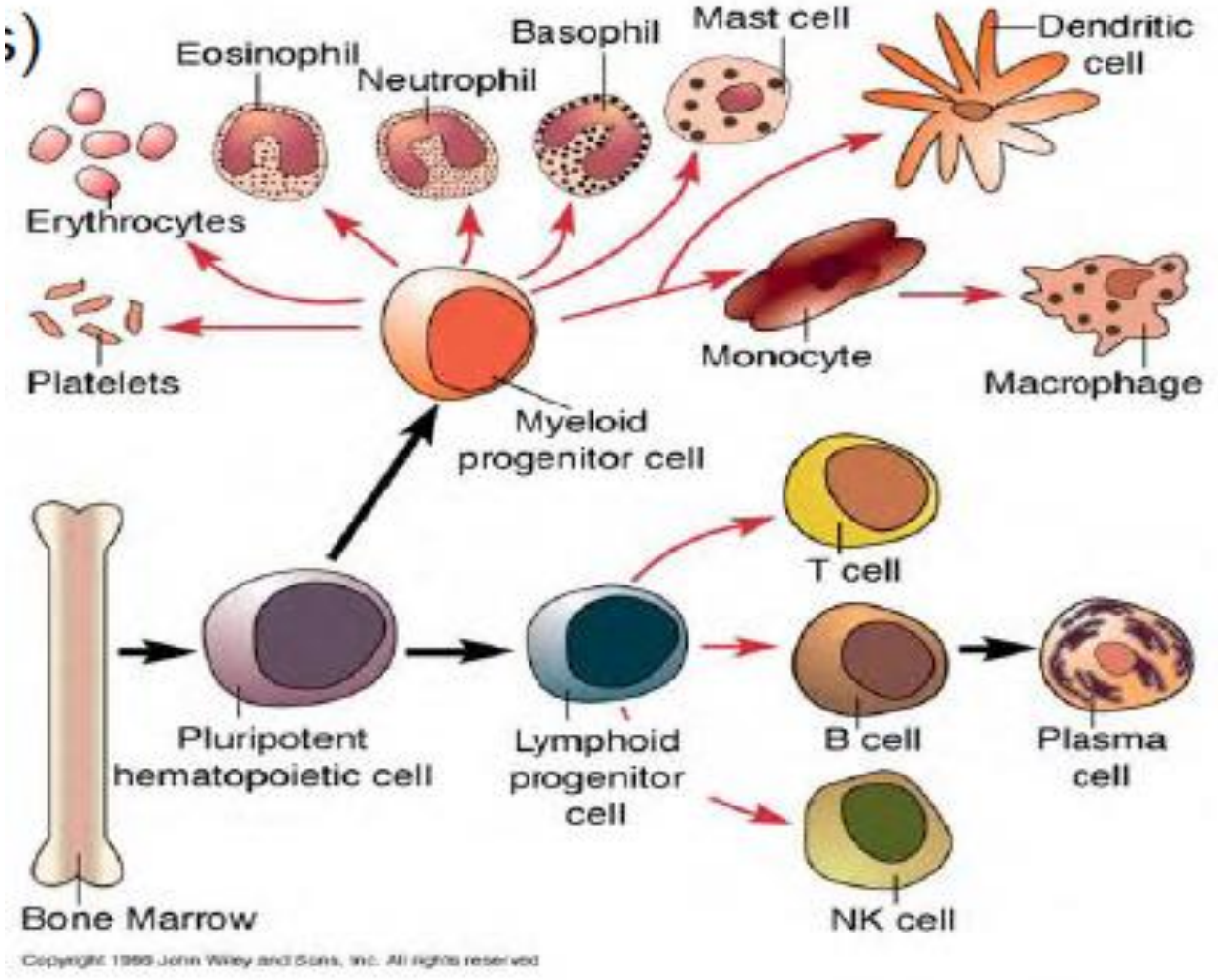
Two Types of Acquired Immune Responses

- **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

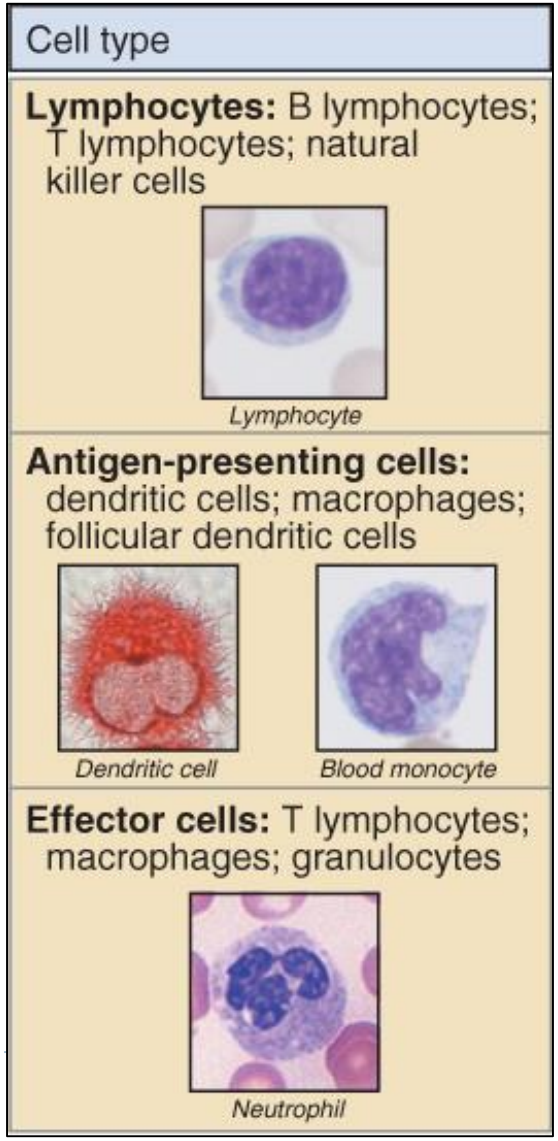


Development of Cells of the immune system



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



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

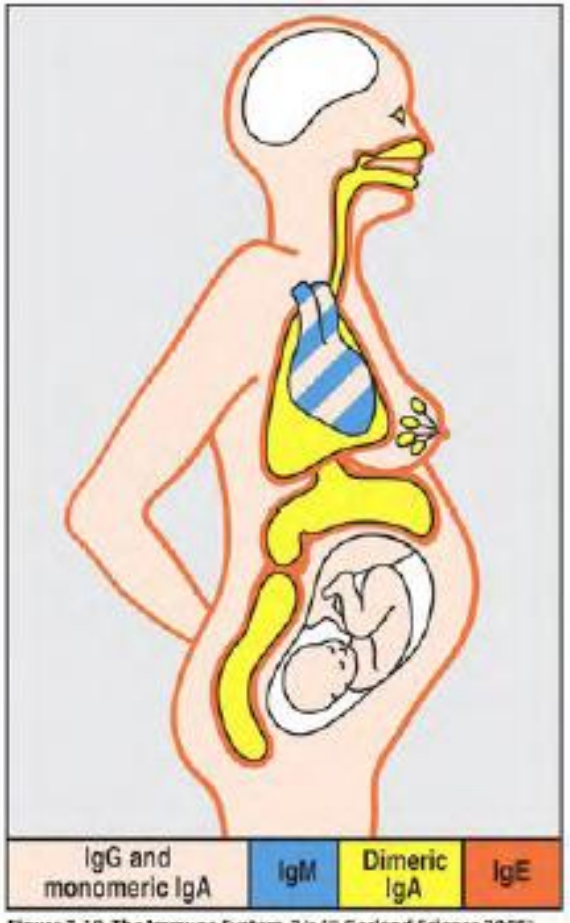
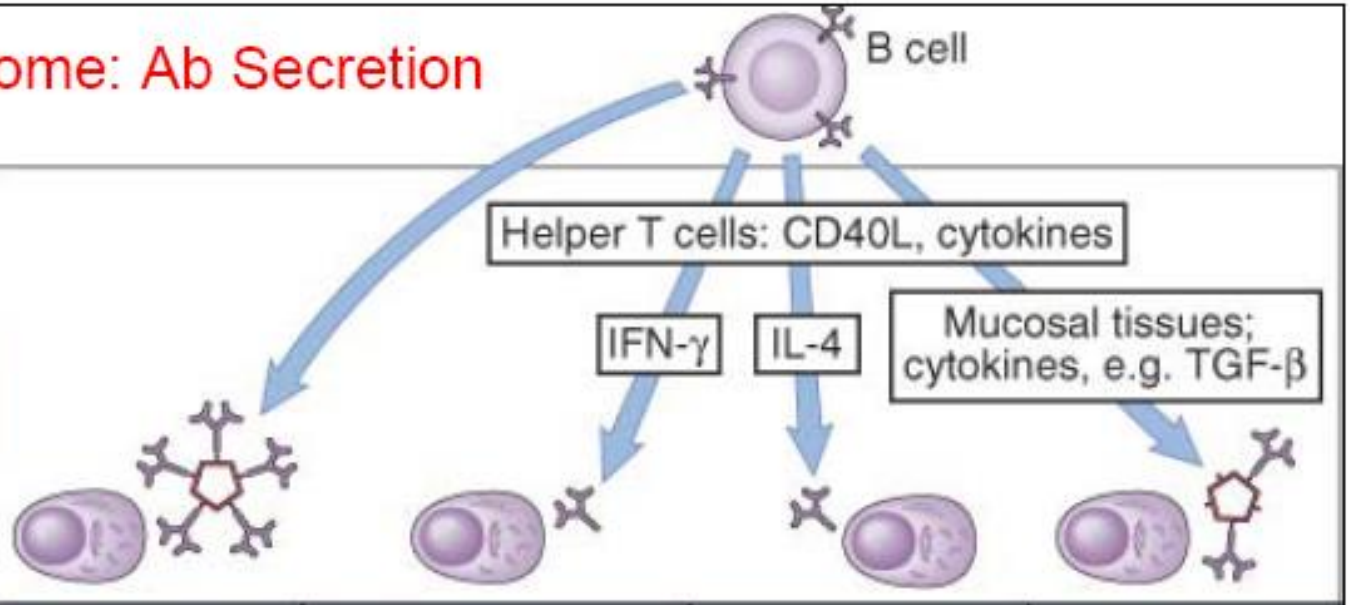


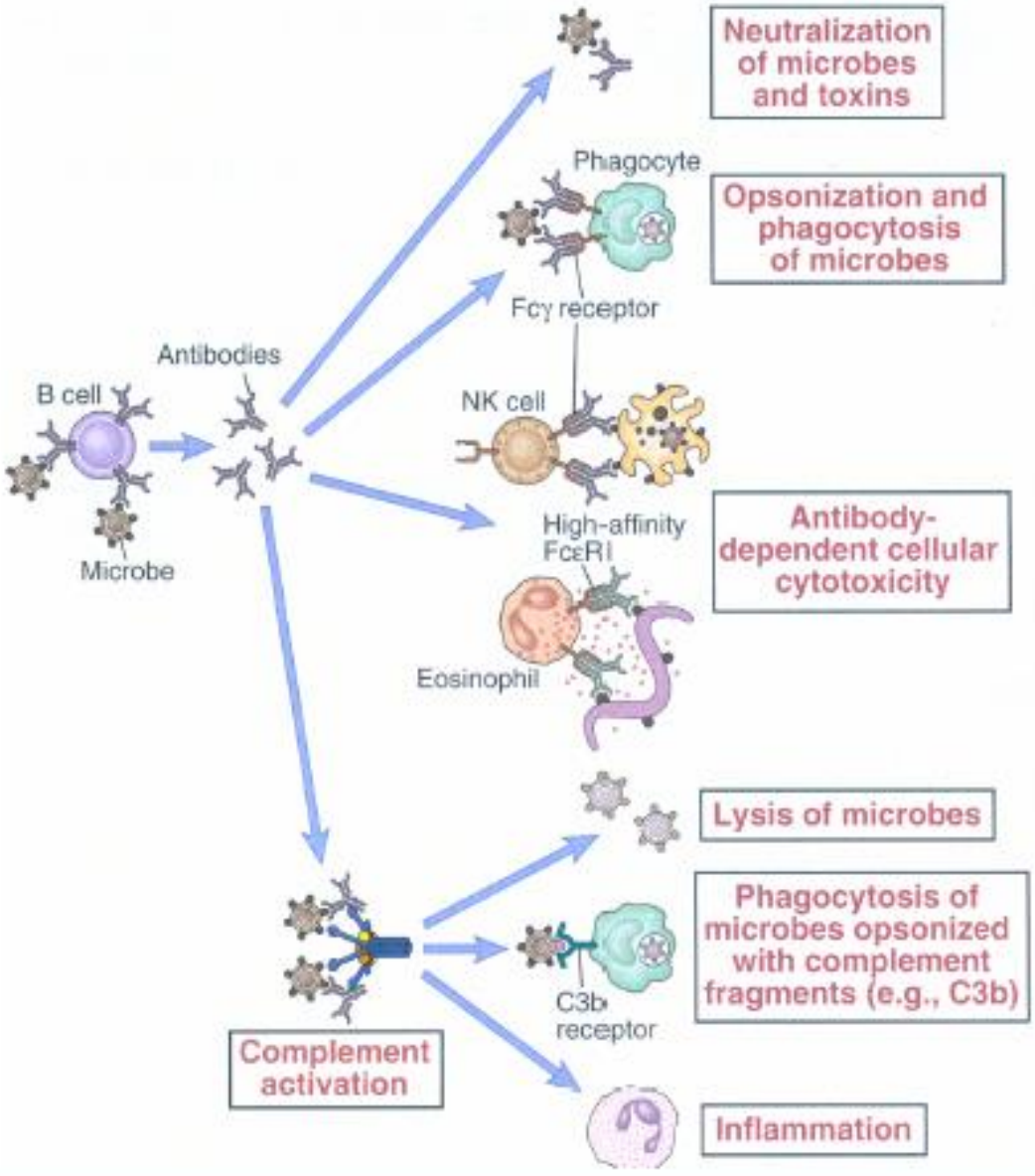
Figure 7-19 The Immune System, 2/e (© Garland Science 2005)

1st Outcome: Ab Secretion



Isotype switching	IgM	IgG subclasses (IgG1, IgG3)	IgE	IgA
Principal effector functions	Complement activation	Fc receptor–dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths (eosinophil-mediated) Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

Effector function of immunoglobulins



Effector T cells Molecules

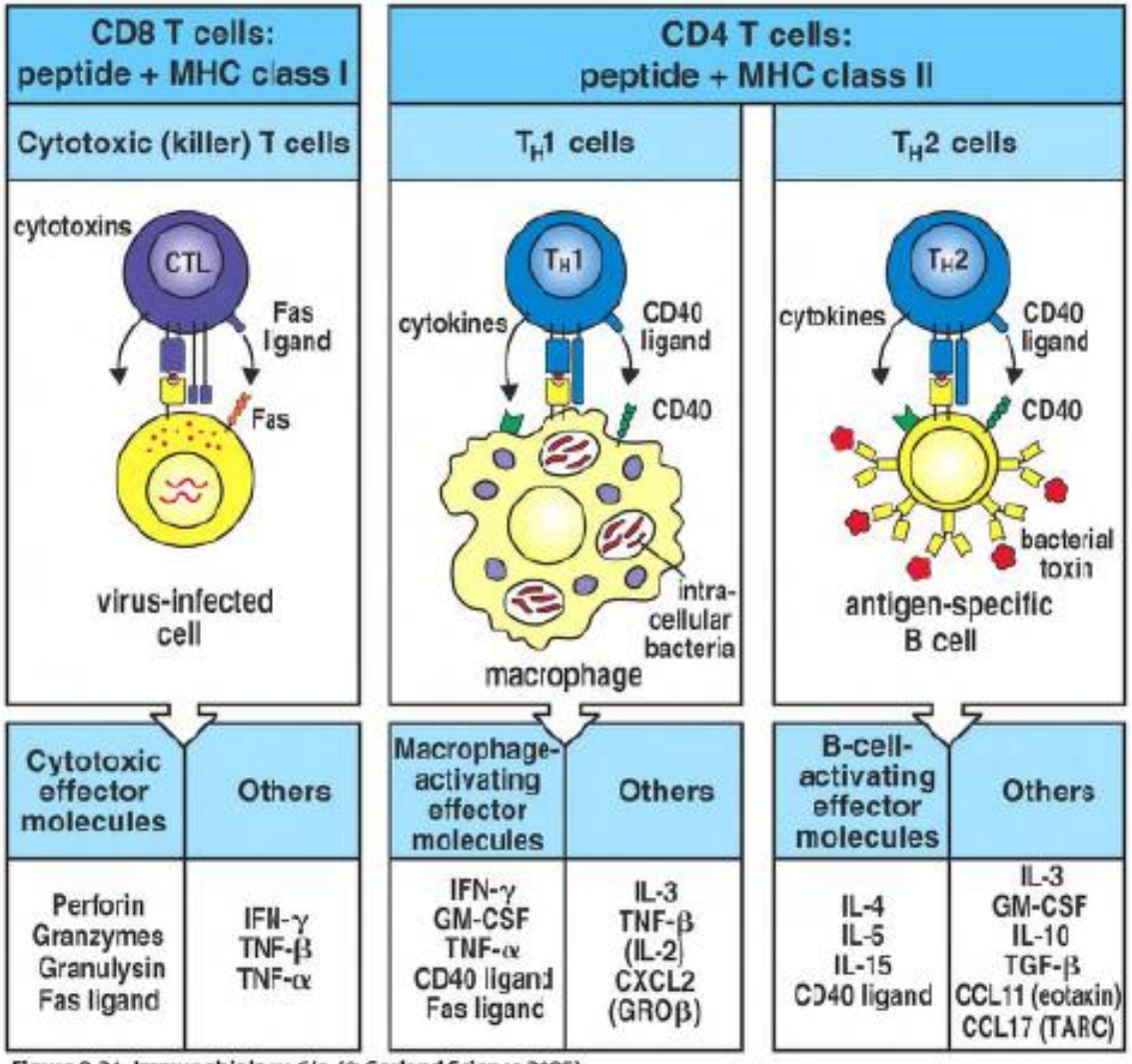
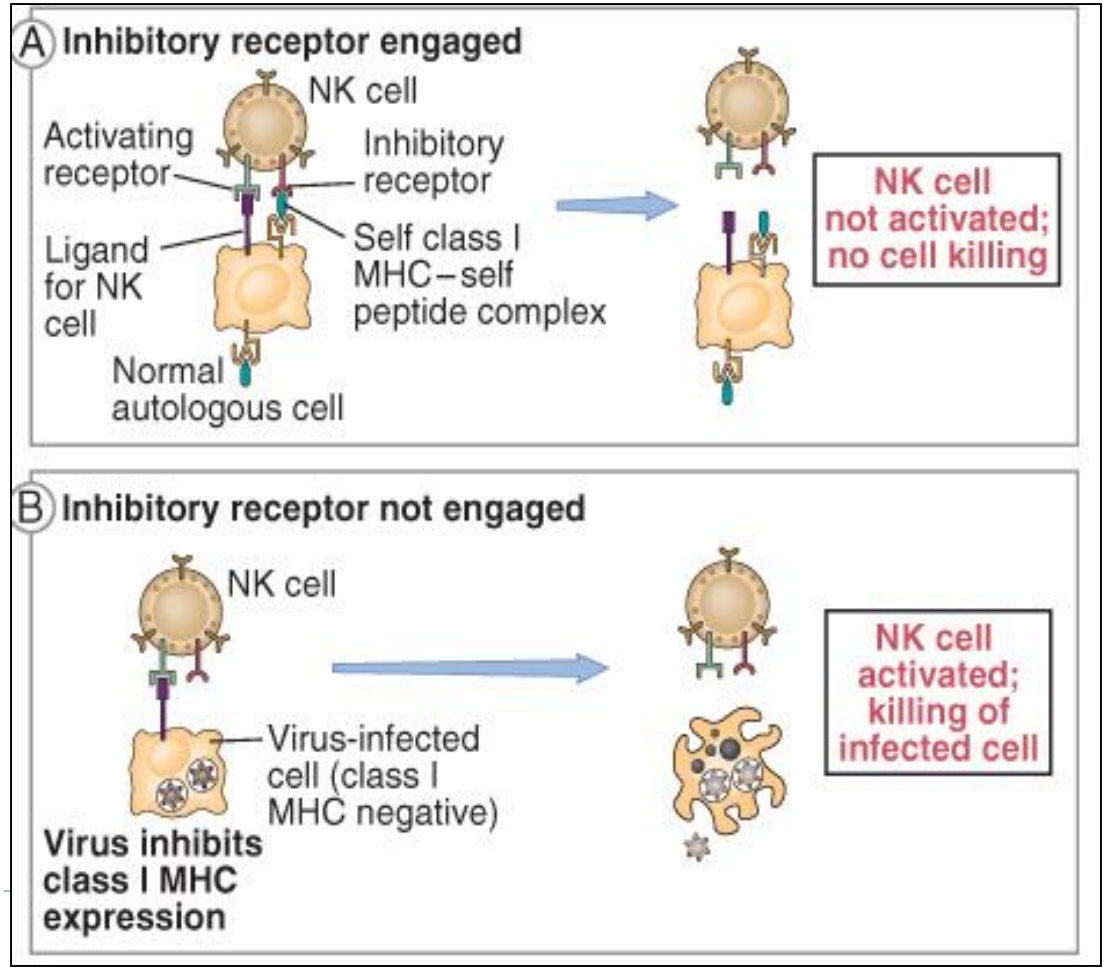


Figure 8-31 Immunobiology, 6/e. (© Garland Science 2005)

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

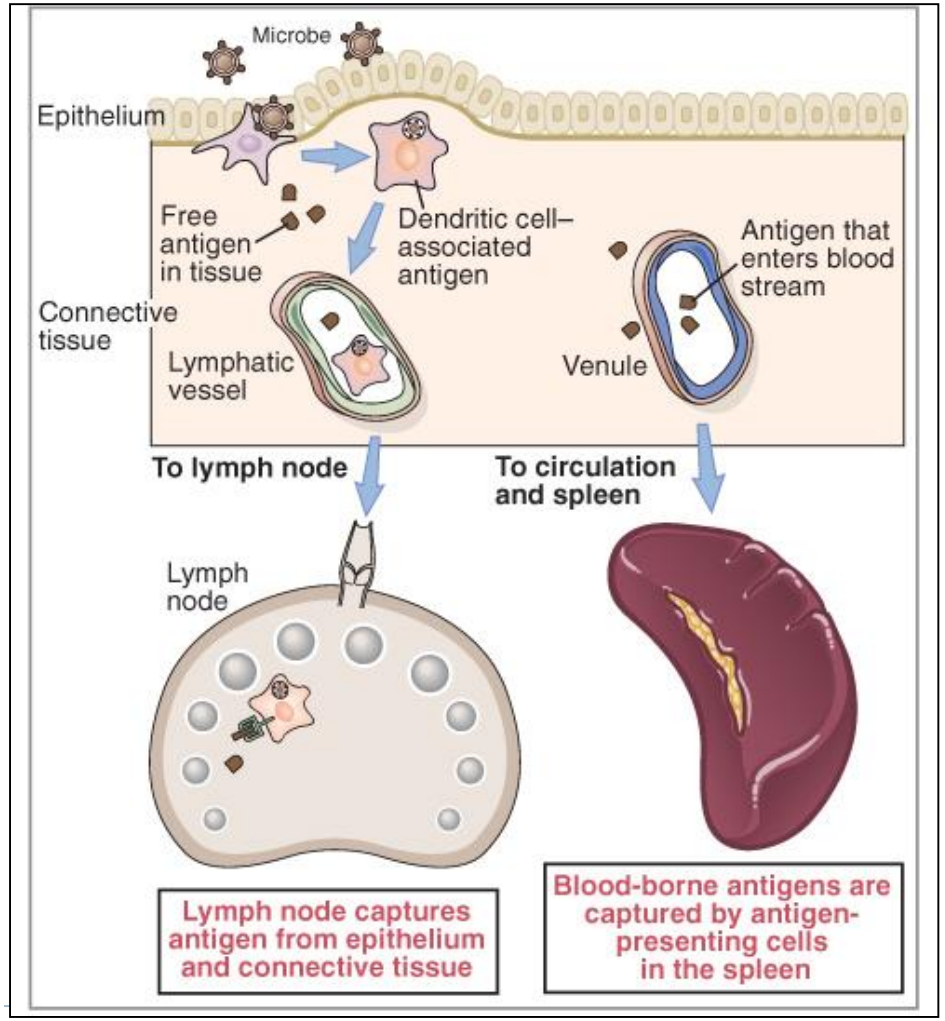


Monocytes/macrophages

- 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

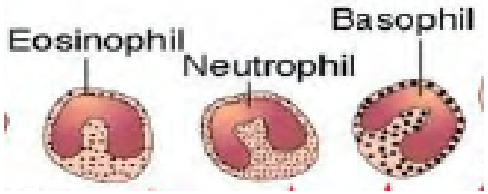
Dendritic cells

- 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

- **Neutrophil**s
  - 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

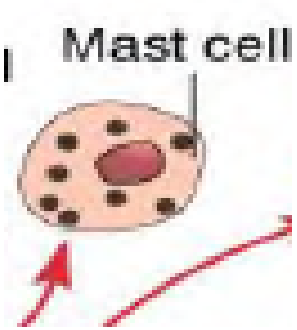


- **Eosinophils**
  - Phagocy*tic cells*
  - Important in parasitic infections
  - Produce inflammatory mediators that damage parasite cell membranes

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

Mast cells

- Found in a wide range of tissues
- Contain cytoplamic 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**)

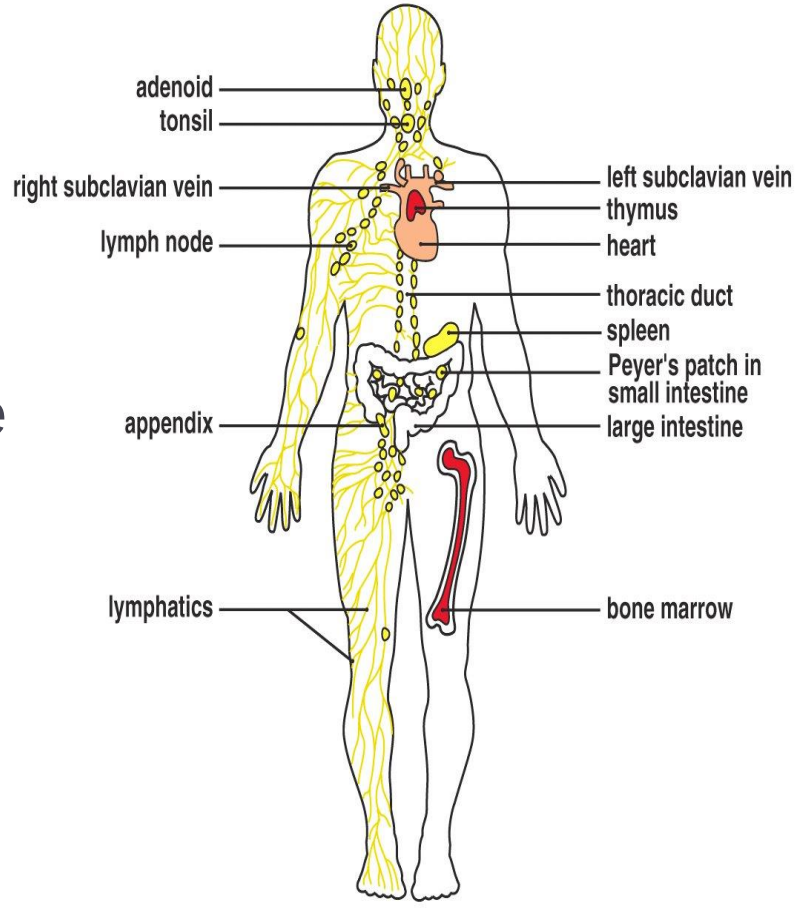


Figure 1-15 The Immune System, 2/e (© Garland Science 2005)

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

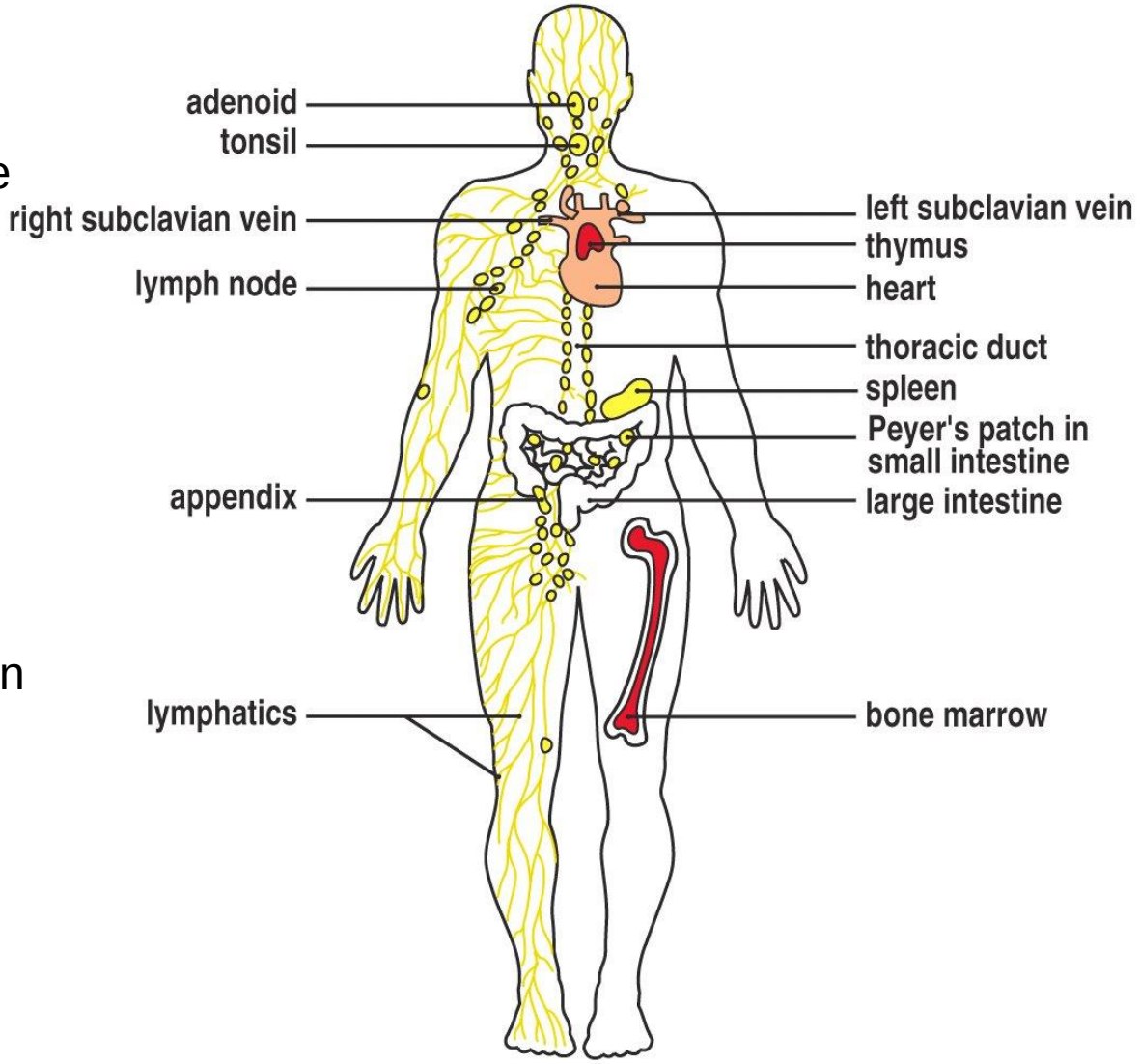


Figure 1-15 The Immune System, 2/e (© Garland Science 2005)

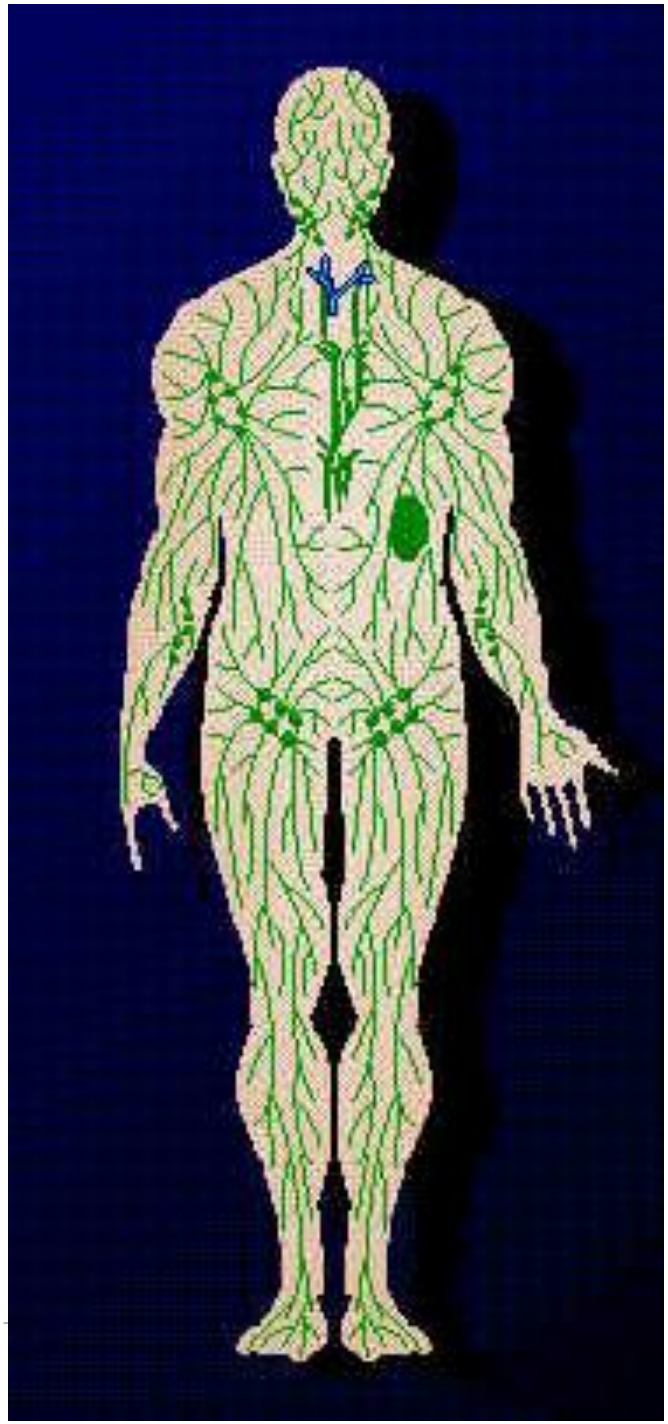
Lymphatic circulatory system innervates all tissues

•Lymphatic vessels begins as dead-end capillaries; extend into most tissues side by side with blood capillaries

•Collects fluid bathing tissues

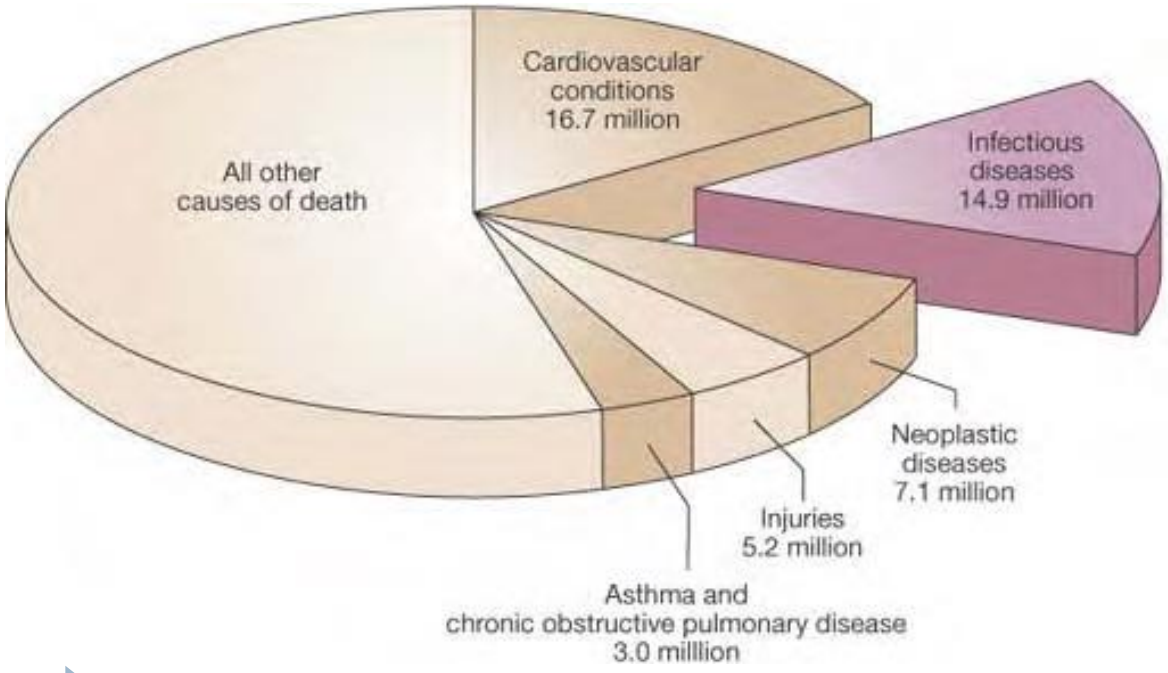
•Vessels merge forming afferent lymphatic vessels which enter lymph node

•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



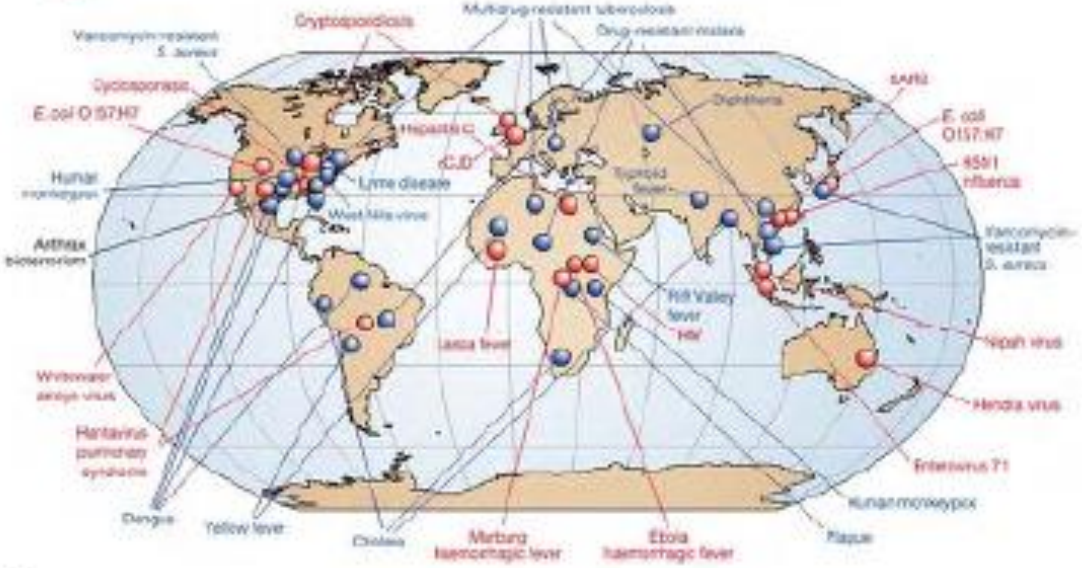
Introduction to infectious disease

- "…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 Toxogenic *Staph. aureus*
- 1982 *E. coli* O157:H7
- 1982 *Borrelia burgdorferi*
- 1983 HIV
- 1983 *Helicobacter pylori*
- 1985 MDR TB

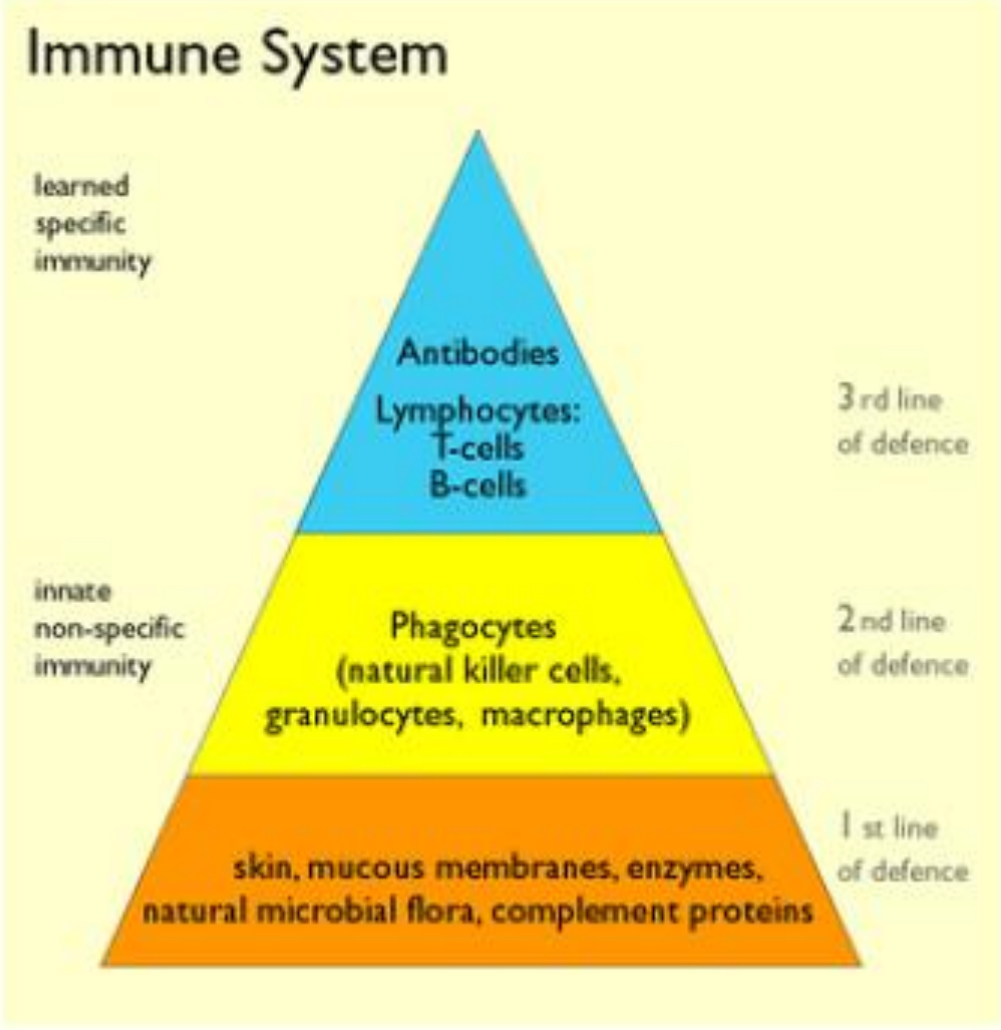
1989 Hepatitis C
1992 *V. cholerae O139*
1993 Hantavirus
1994 *Cryptosporidium*
1995 Hendra virus
1996 nvCJD
1999 Nipha Virus
2000 West Nile Virus
2003 SARS
2004 H1N5

Dengue virus
H1N1
ZIKA

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

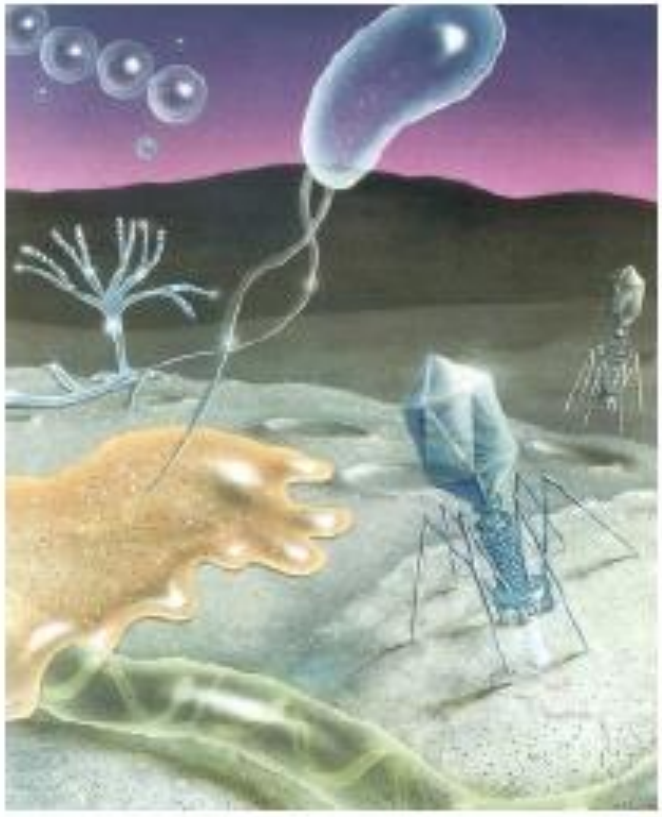


Intervention

- 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

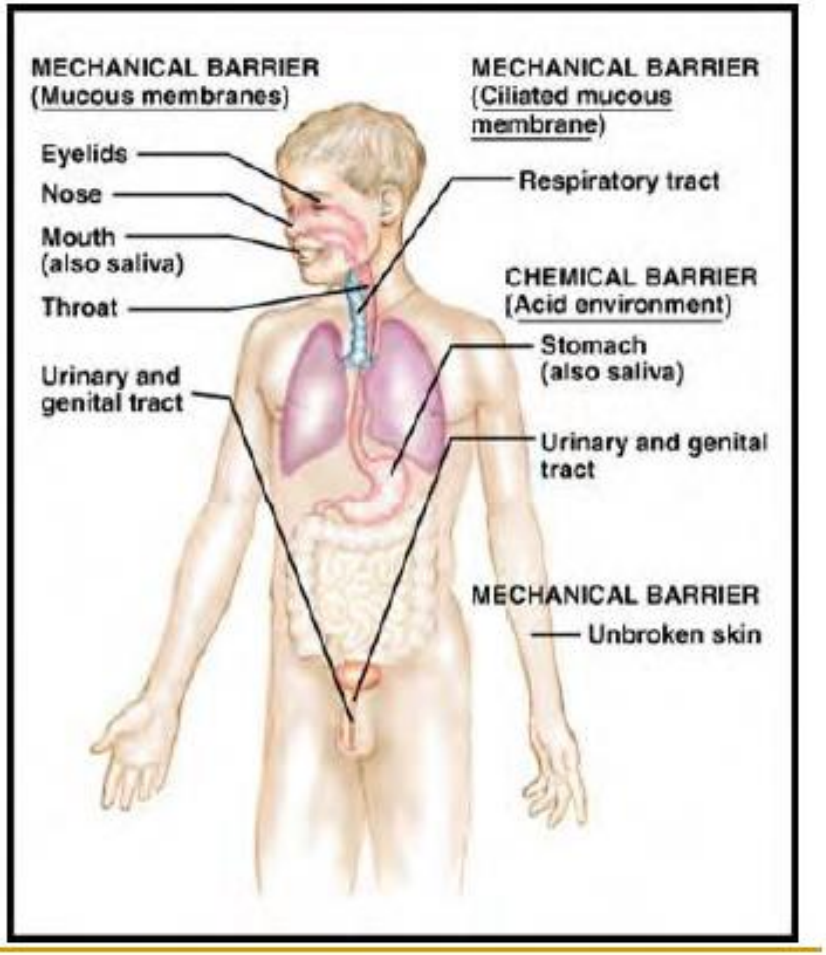


The Benefits of Normal Flora

- 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.

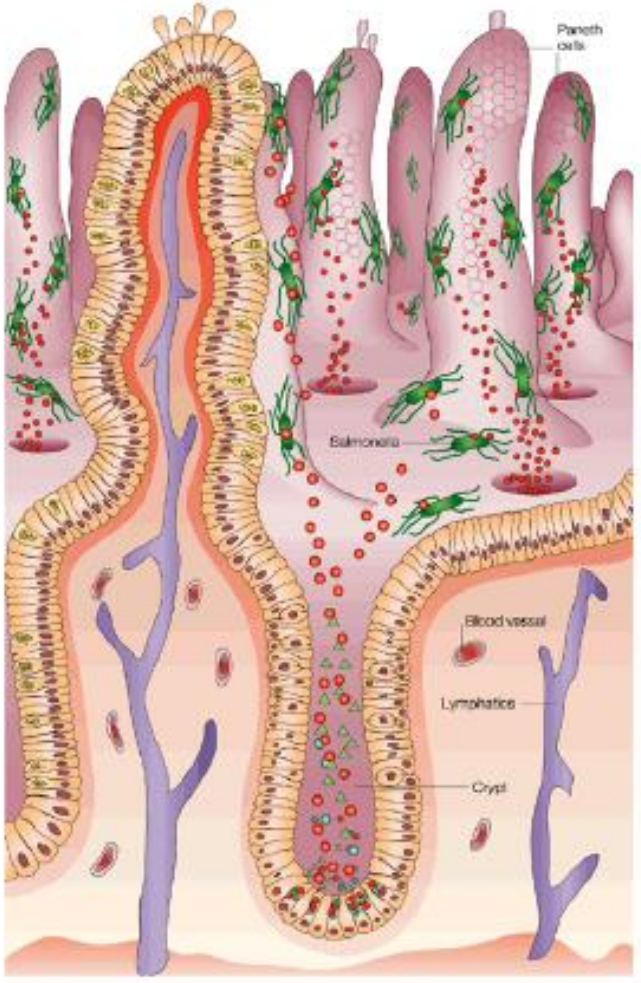
Innate Immunity

- Anatomical defenses
- Microbial antagonism
  - Normal Flora
- Antimicrobial peptides/Cytokines
  - Defensins
  - Type I Interferons
  - Complement
- Inflammation
- Phagocytosis
  - Killing



Antimicrobial Peptides

- Many different peptides
  - Defensins
    - αDefensins
      - neutrophils and intestinal Paneth cells.
    - β-defensins
      - epithelial tissues.
  - Collectin family proteins
    - Surfactant A and D
      - Liver and respiratory tract cells



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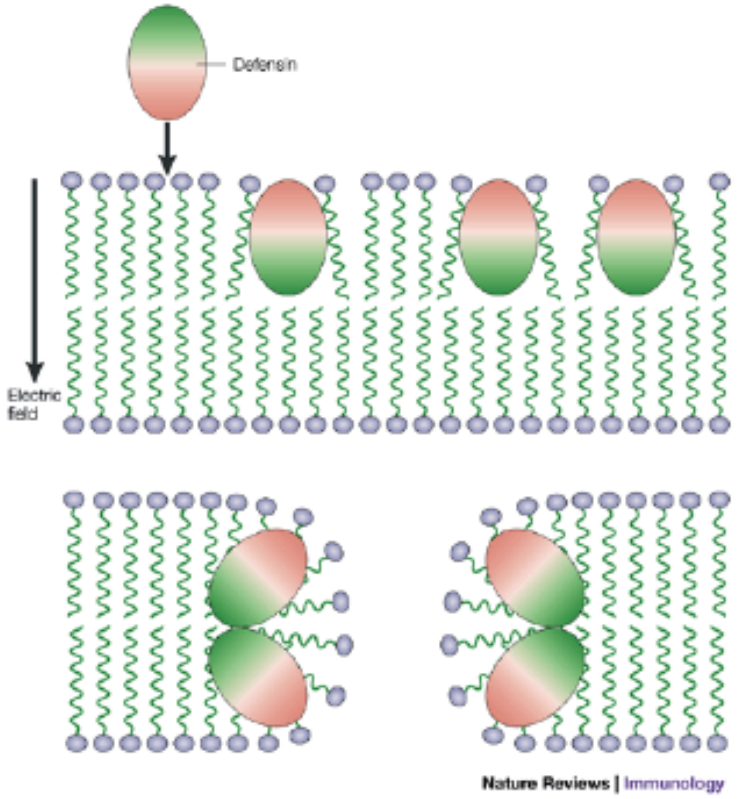
Defensins

- Defensins appear to act by binding to outer membrane of bacteria, resulting in increased membrane permeability.
- Act as chemokines
  - Attract immature dendritic cells, T cells



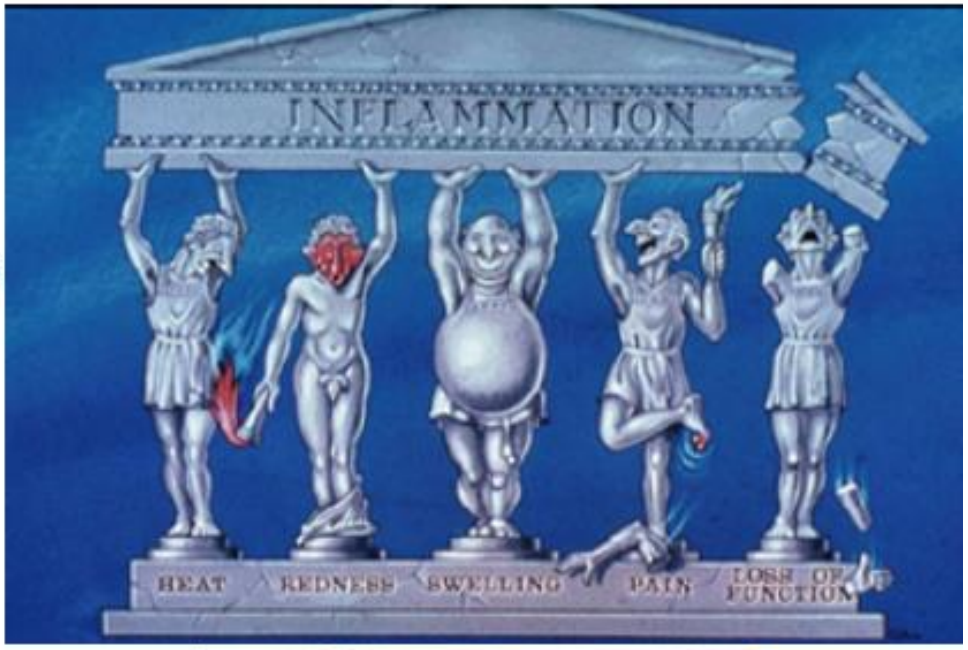
Nature Reviews Immunology 3; 710-720 (2003)

Innate Antiviral

- Type I Interferons
  - IFN-α
    - Family of ~20 related polypeptides encoded by separate genes
    - Primarily produced by mononuclear phagocytes (a.k.a leukocyte interferon), also B cells, dendritic cell precursors
  - IFN-β
    - Single protein
    - Produced by many different cells, including fibroblasts (a.k.a fibroblast interferon)
  - Both IFN-α and IFN-β bind to same cell surface receptor and induce similar biologic response

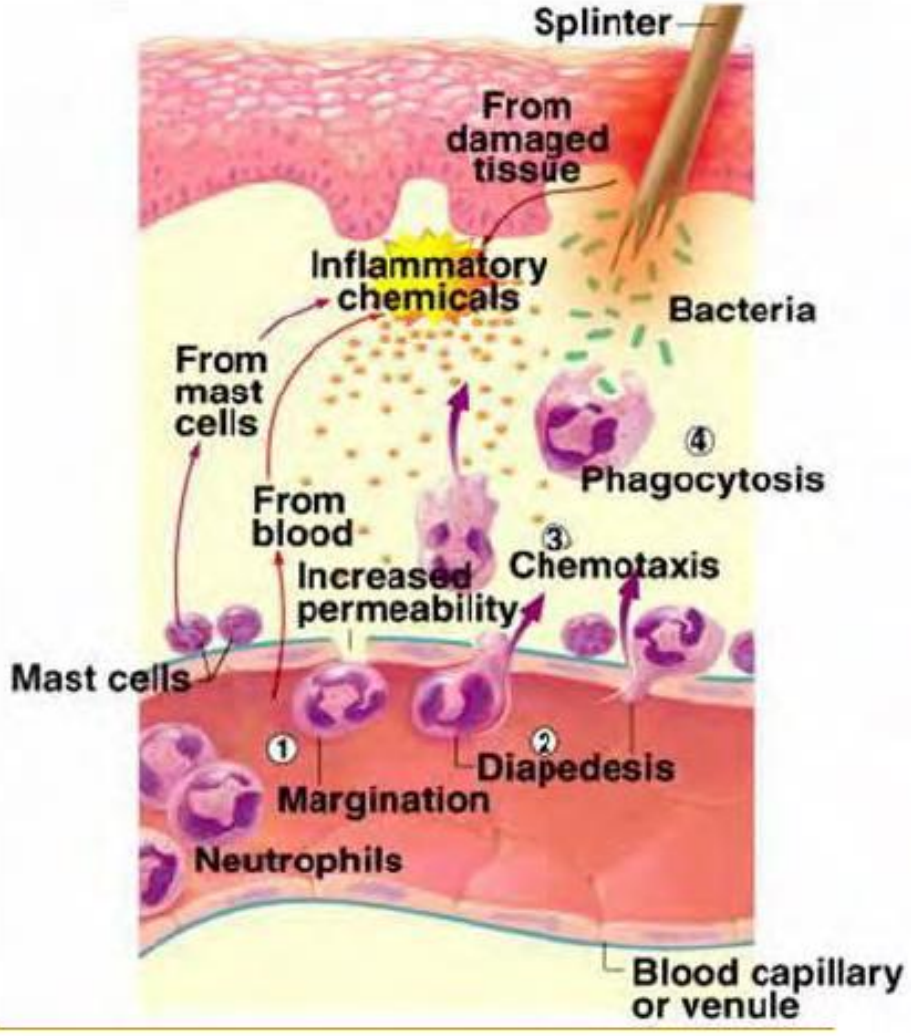
Inflammation

- Concept of inflammation has a colorful history due to the reason that it is closely linked to the history of infection
  - Inflammation is not the same as infection!
    - Infection means that bacteria, viruses or fungi have invaded the tissues
      - this usually causes inflammation
- ~30 A.D. Cornelius Celsus, definition of inflammation
  - Rubor et Tumor cum Calore et Dolore



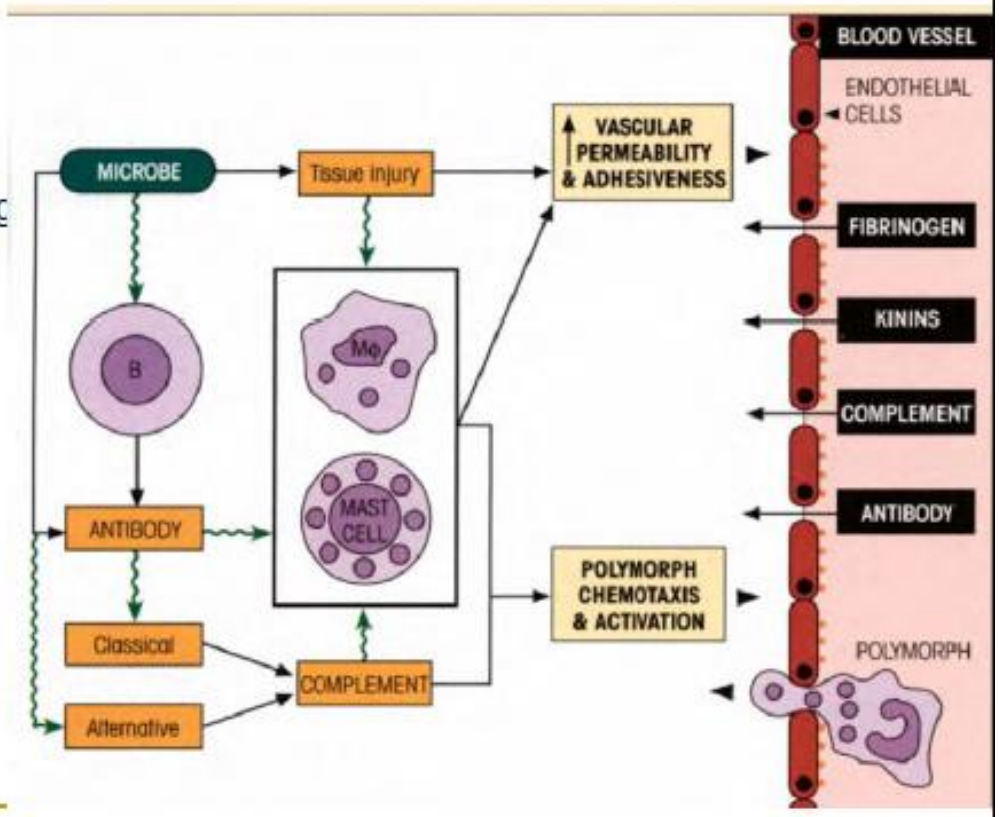
Inflammation

- Nonspecific localized response of the microcirculation designed to dilute, destroy or wall off pathogenic organisms.



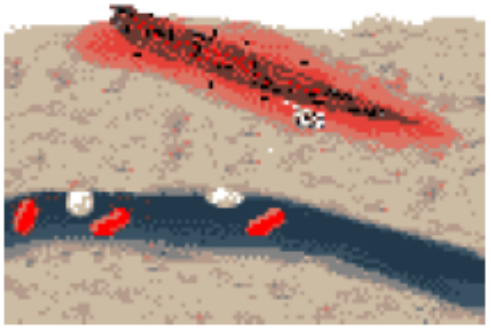
Benefits of Inflammation

- Increased permeability:
  - Plasma flows out of the blood into the tissue of beneficial molecules in the plasma:
    - Clotting factors.
      - Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding and chemotactically attract phagocytes;
    - Antibodies
    - Proteins of the complement pathways
    - Nutrients.
      - Feeding the cells of the inflamed tissue;
    - Antimicrobial peptides
      - Lysozyme β-defensins Transferrin
  - Leukocytes enter tissues via diapedesis or extravasation.



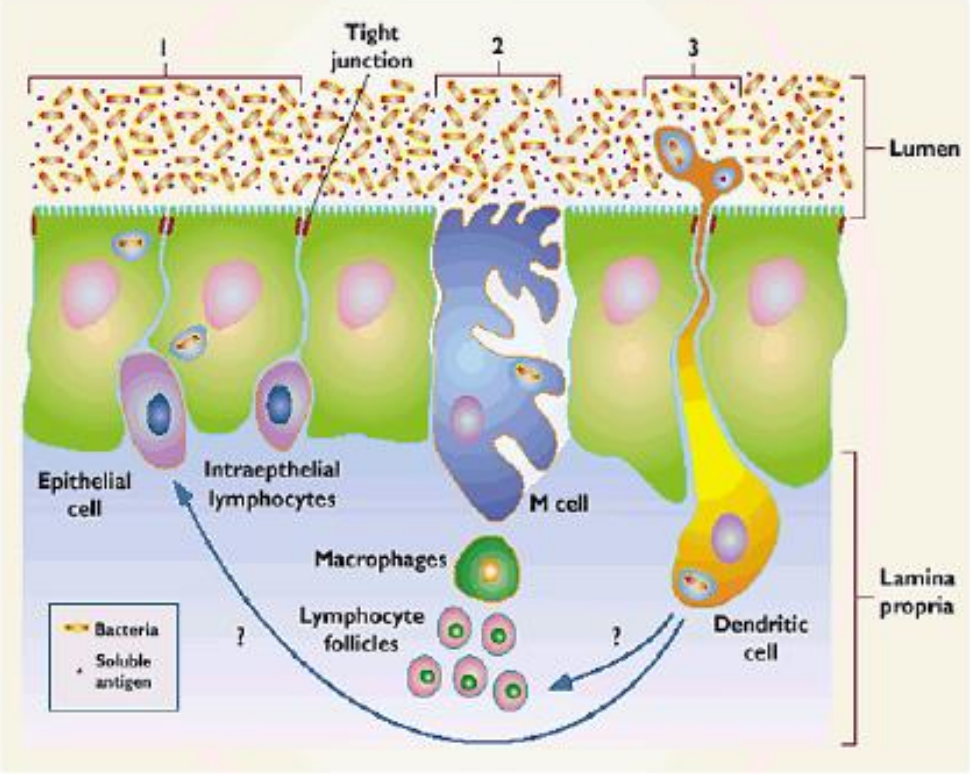
Immunologic features of Inflammation

- Recognition
  - Pattern receptors
  - Complement
- Vasodilation
  - Increase vascular permeability
- Cellular activation
  - Cytokines
  - Complement
- Cellular recruitment
  - Neutrophils



Recognition

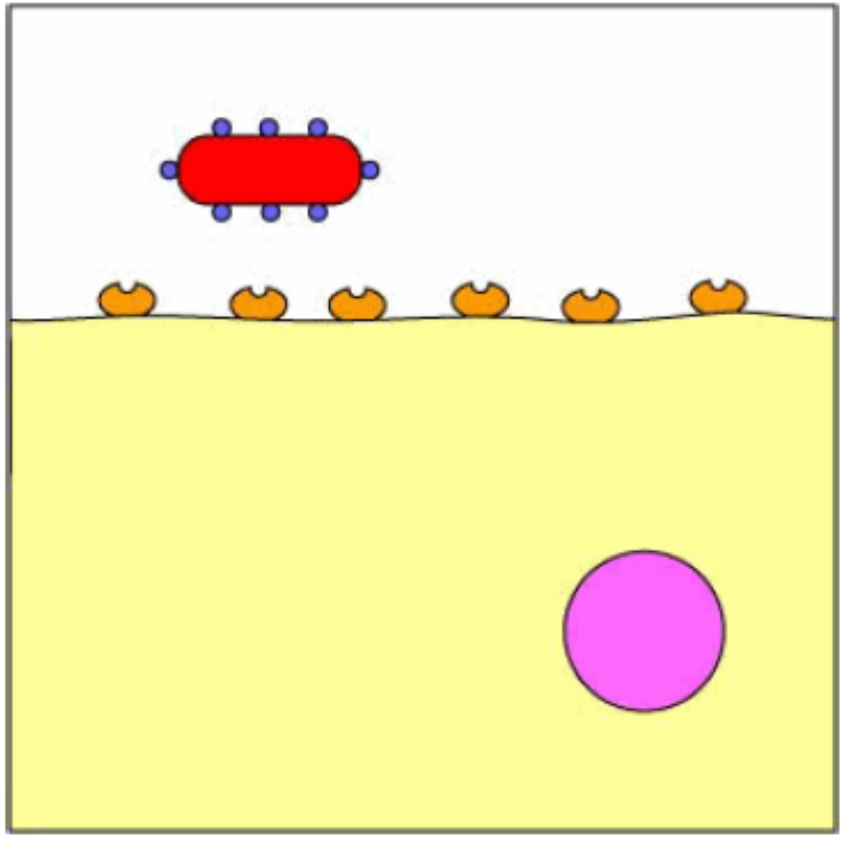
- Invading bacteria (1)
- M-cells (2)
  - Sampling of lumen
- Dendritic cells (3)
  - Also sample lumen



Nature Immunology **2**, 288 - 290 (2001)

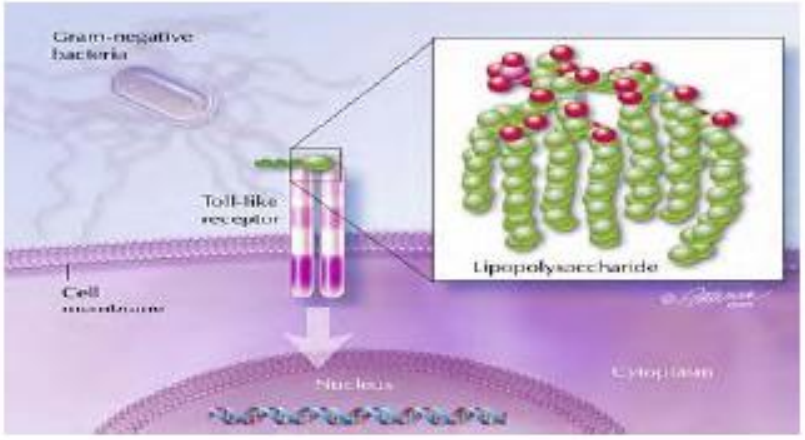
Recognition

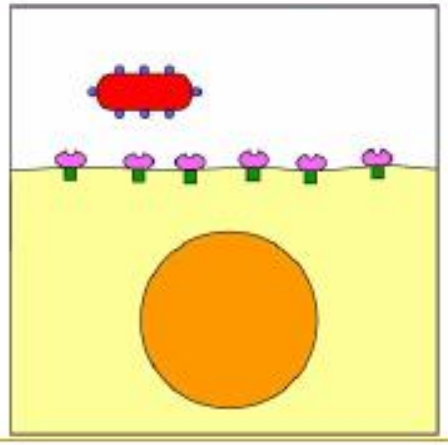
- The receptors of the innate immune system, are specific for structures found exclusively in microbial pathogens **pathogen-associated molecular patterns (PAMPs)**.
  - Bacteria
    - lipopolysaccharide,
    - lipoteichoic acid
    - peptidoglycan,
  - Fungi
    - β-1,3-glucan



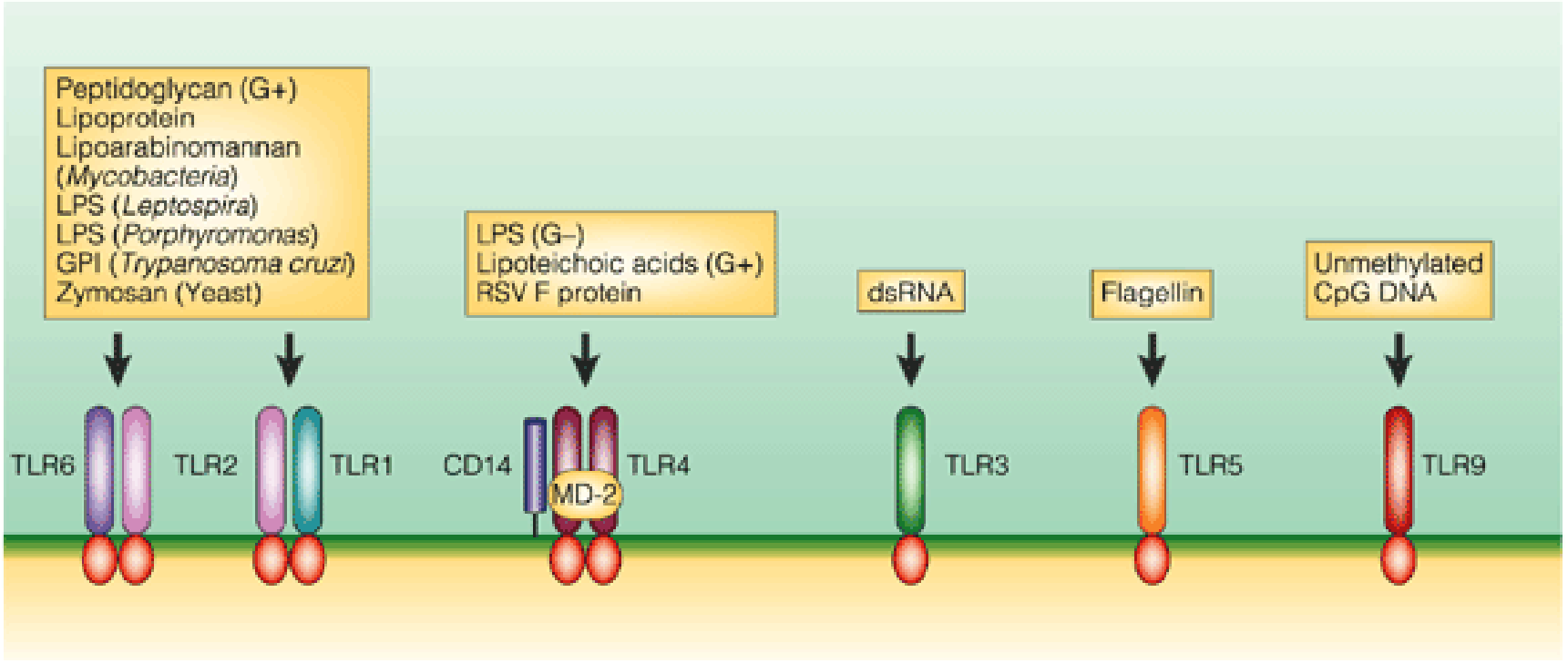
Toll-like Receptors (TLR)

- The TLR family has 10 members, TLR1-10. Each TLR is specific in its expression patterns and PAMP sensitivities.
  - TLR-2 recognizes peptidoglycan and lipoproteins;
  - TLR-4 recognizes lipopolysaccharide and lipoteichoic acid;
  - TLR-5 recognizes bacterial flagellin
- NF-κB binds DNA sequences which transcribe for inflammatory cytokines





Toll-like Receptors and their Ligands



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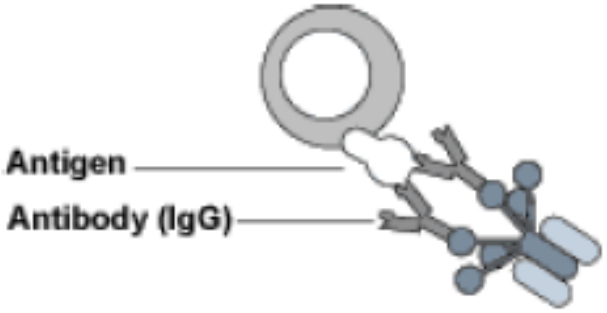
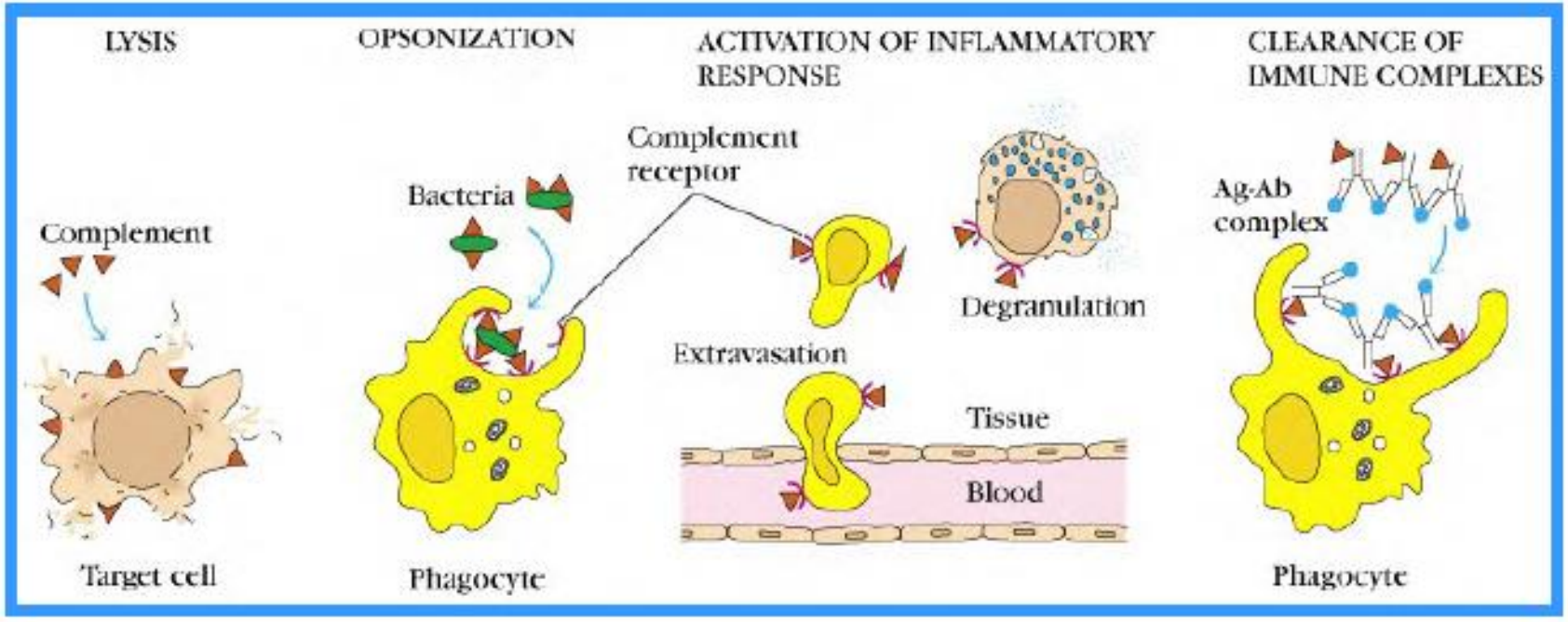
Recognition

- Complement
  - A system consisting of ~ 20 proteins (referred to as **components C1-C9** or as **factors B, D**) that can be nonspecifically activated by polysaccharides or lipopolysaccharides present on bacteria, fungi, etc.

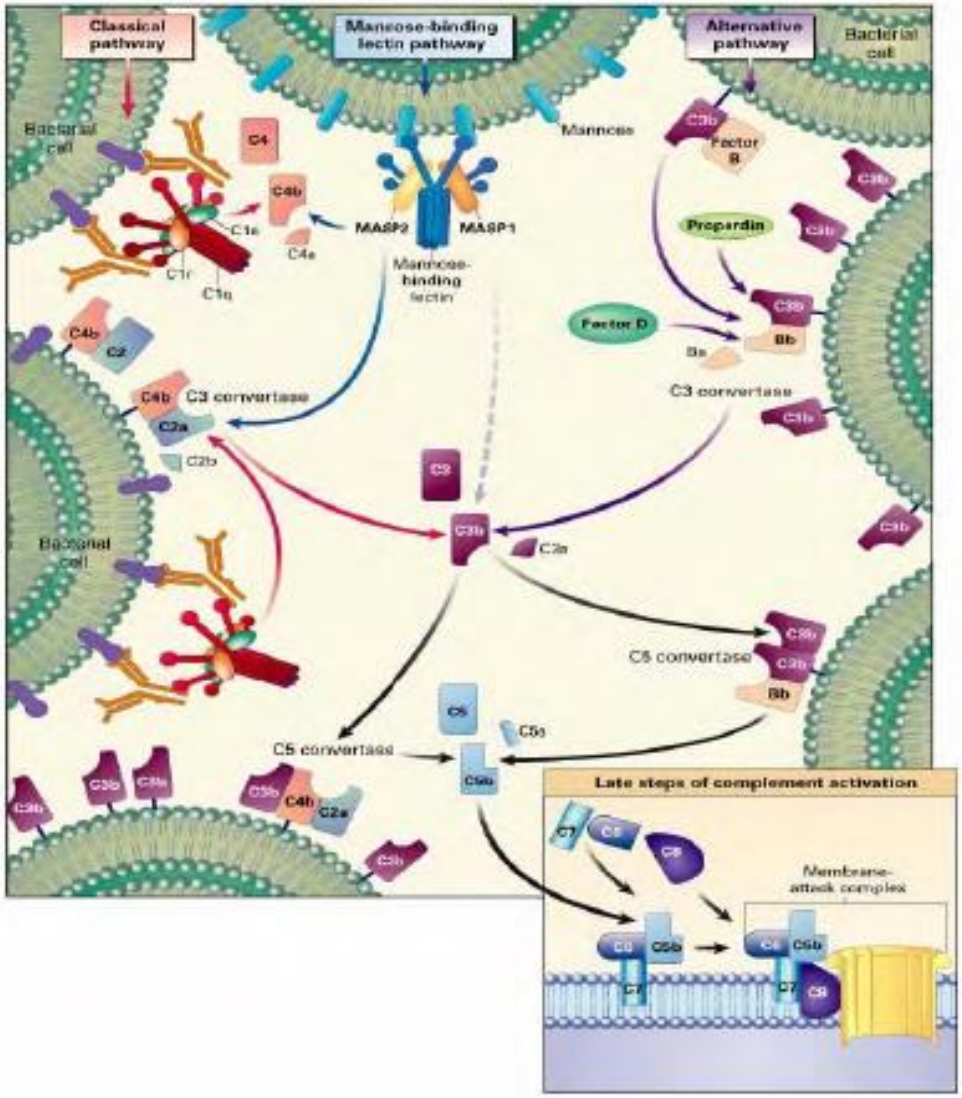


Biological Function of Complement



Complement

- Major pathways of activation
  - Classical – involves Ab
    - Lectin – similar to the classical pathway, but it is initiated by mannose-binding lectin (MBL).
  - Alternative – no Ab
- All pathways can generate a membrane attack complex (MAC)
  - inserts into membranes of cells, susceptible bacteria and enveloped viruses and makes them osmotically unstable, resulting in lysis.



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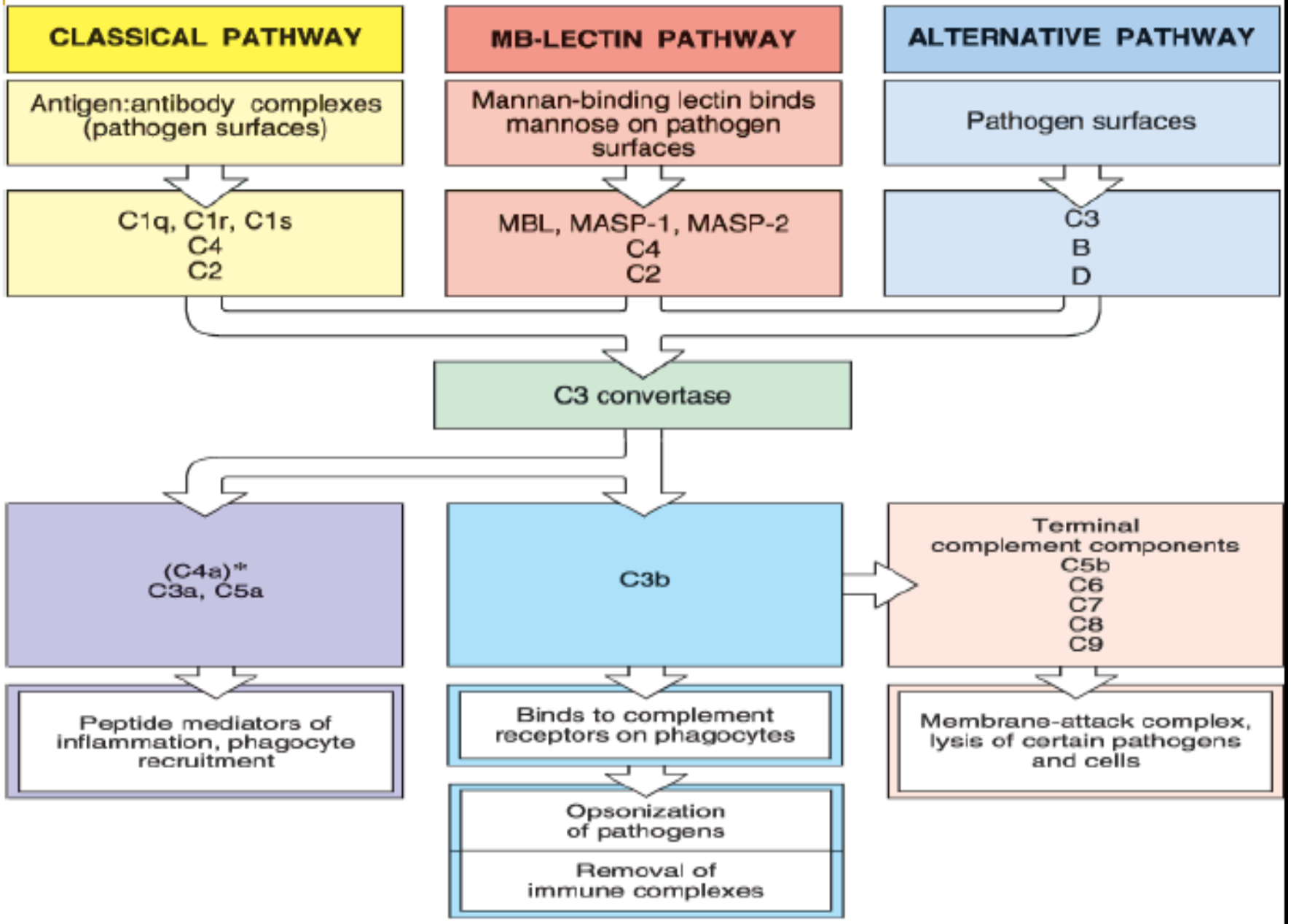
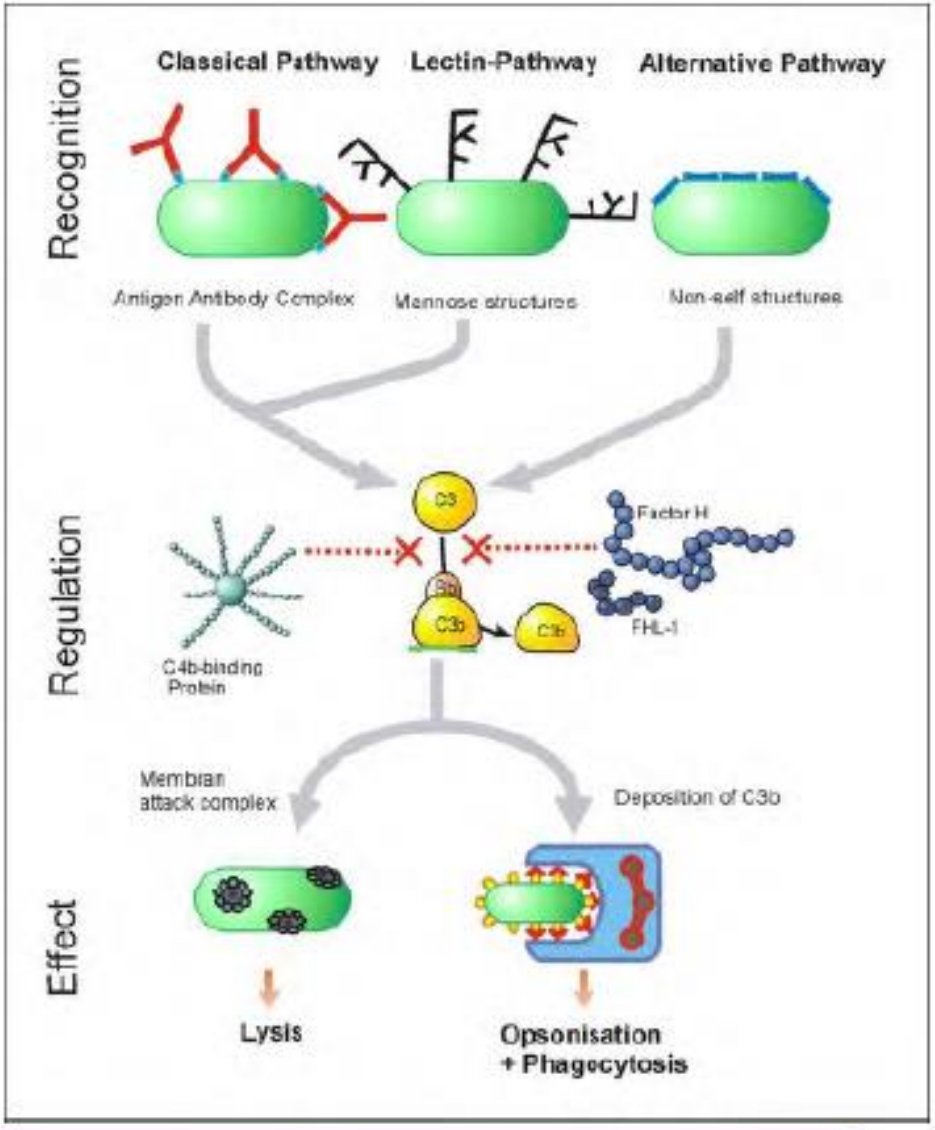


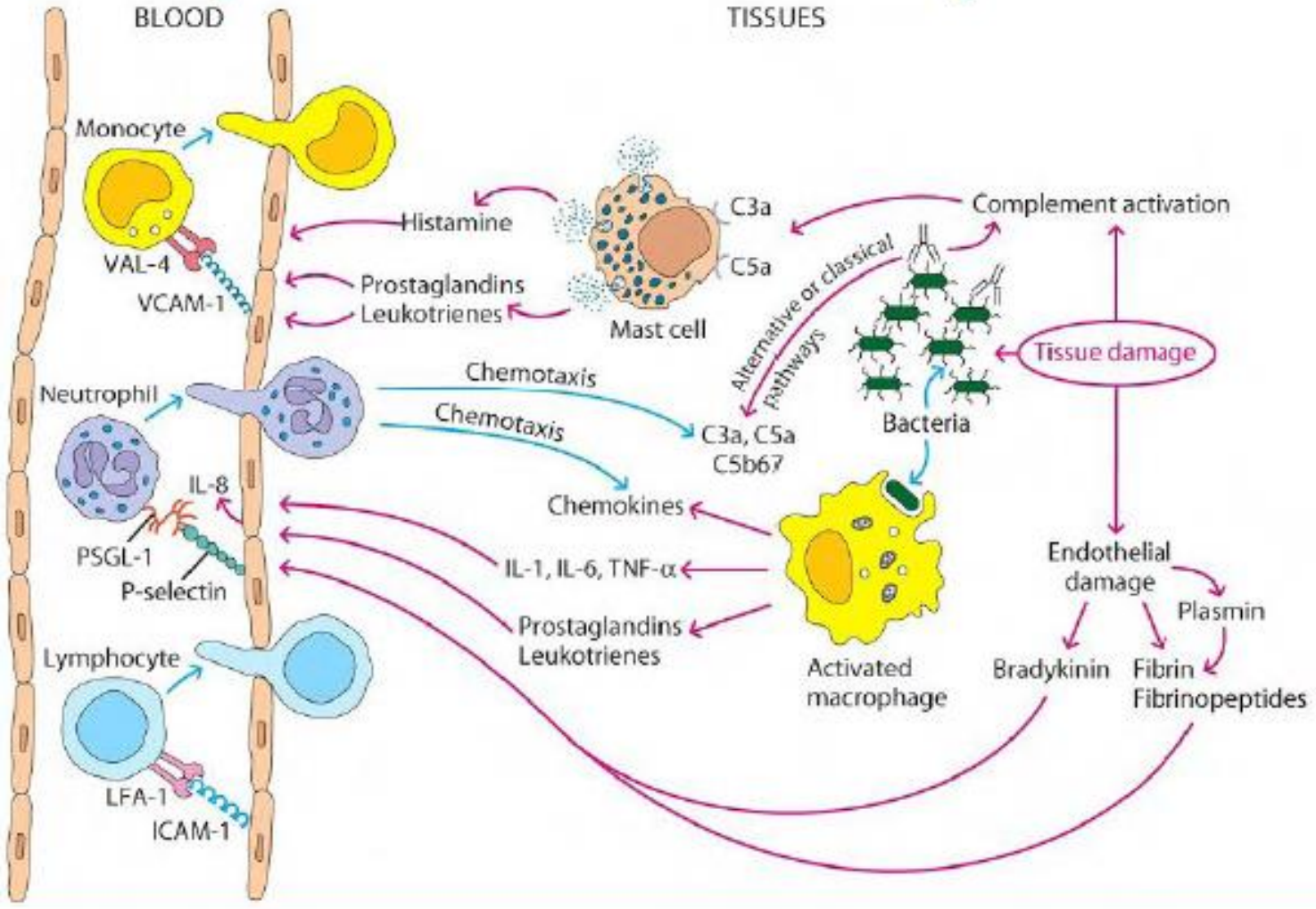
Fig 2.8 part 2 of 2 © 2001 Garland Science

Complement

- Recognition
  - Classical
  - Lectin binding
  - Alternative
- Regulation
  - C1 inhibitor
  - C4b binding protein
- Effector function
  - Lysis
  - Opsonisation
  - Activation of Inflammation



Summary of Innate Immunity



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