Chapter 1

Basic concepts in immunology
免疫學的基本觀念

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Learning objectives

- The components of the immune system
- Principles of innate and adaptive immunity
- How does adaptive immunity recognize and respond to foreign stimuli?

Fig. 1.1 Edward Jenner

Portrait of E. Jenner

- Edward Jenner (1749-1823)
- “Father of immunology”
- Invented vaccination (*vacca*, a cow) against smallpox
- In 1980, as a result of Jenner's discovery, the World Health Assembly officially declared "the world and its people" free from endemic smallpox.

Fig. 1.2
The eradication of smallpox by vaccination

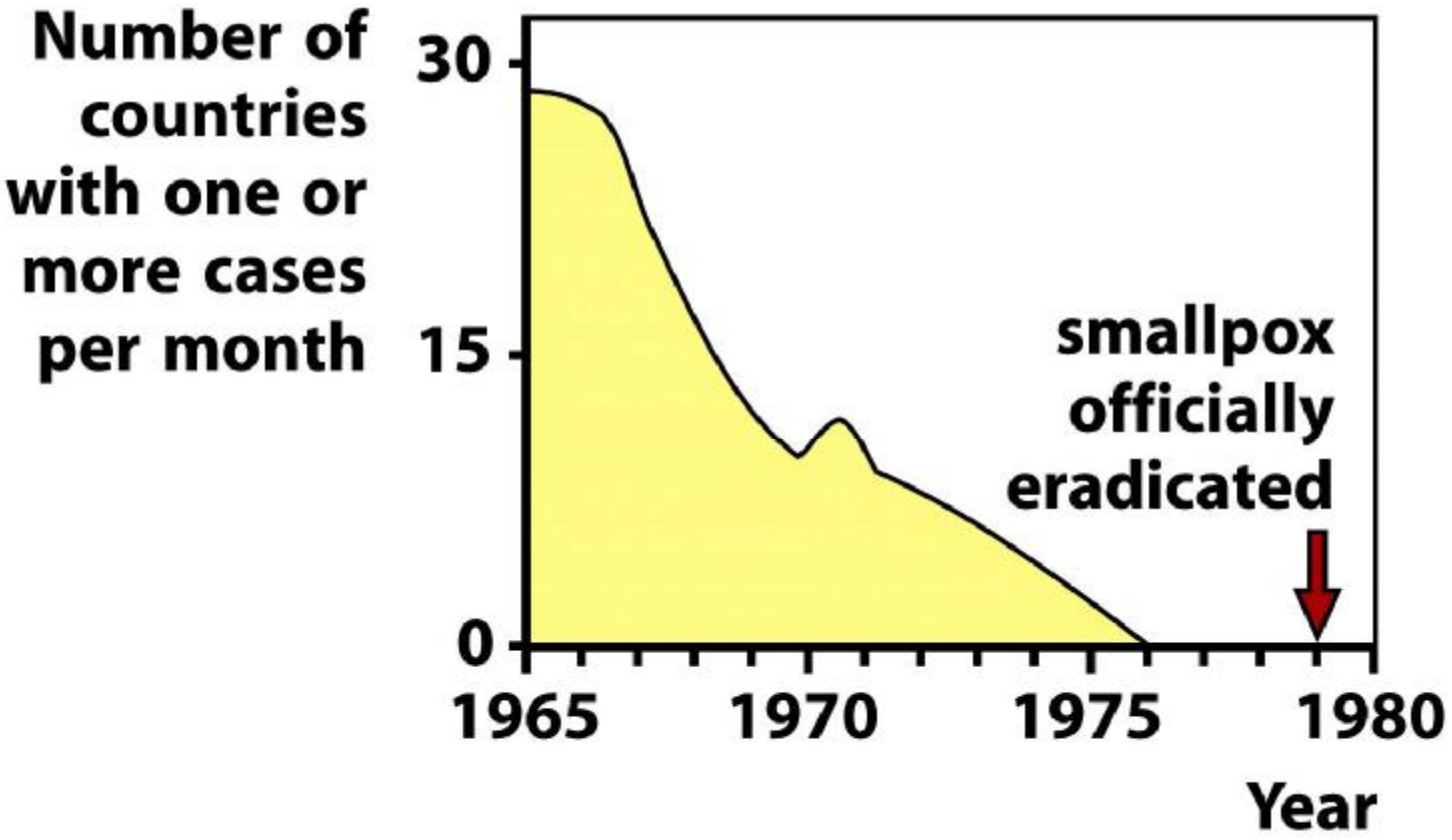


Figure 1-2 Immunobiology, 7ed. (© Garland Science 2008)

Other pioneers in immunology

- Louis Pasteur
  - Elegant 'swan-neck flask' experiments to argue against the doctrine of "spontaneous generation"
  - 'germ theory of disease'
- Robert Koch
  - Infectious diseases are caused by microorganisms
- Behring & Kitasato
  - Found antibodies (Abs) in the serum of vaccinated individuals

Immunity

- Definition:
  - The quality or condition of being immune

Immunity

- Innate immunity
  - Response time: short
    - (e.g. granulocytes and macrophages)
  - Duration: short
- Adaptive immunity
  - Response time: long
    - (e.g. lymphocytes and antibody)
  - Duration: long (protective immunity)
- **Both** innate & adaptive immunity depend upon the activation of white blood cells (WBCs; leukocytes)

Granulocytes = PMNs
多型核白血球

Immunity

- Antibody (Ab)
  - Substances produced against (*anti*) relevant pathogens (*body*)
- Antigen (Ag)
  - Substance capable of stimulating the *gen*eration of *anti*bodies

The components of immune system

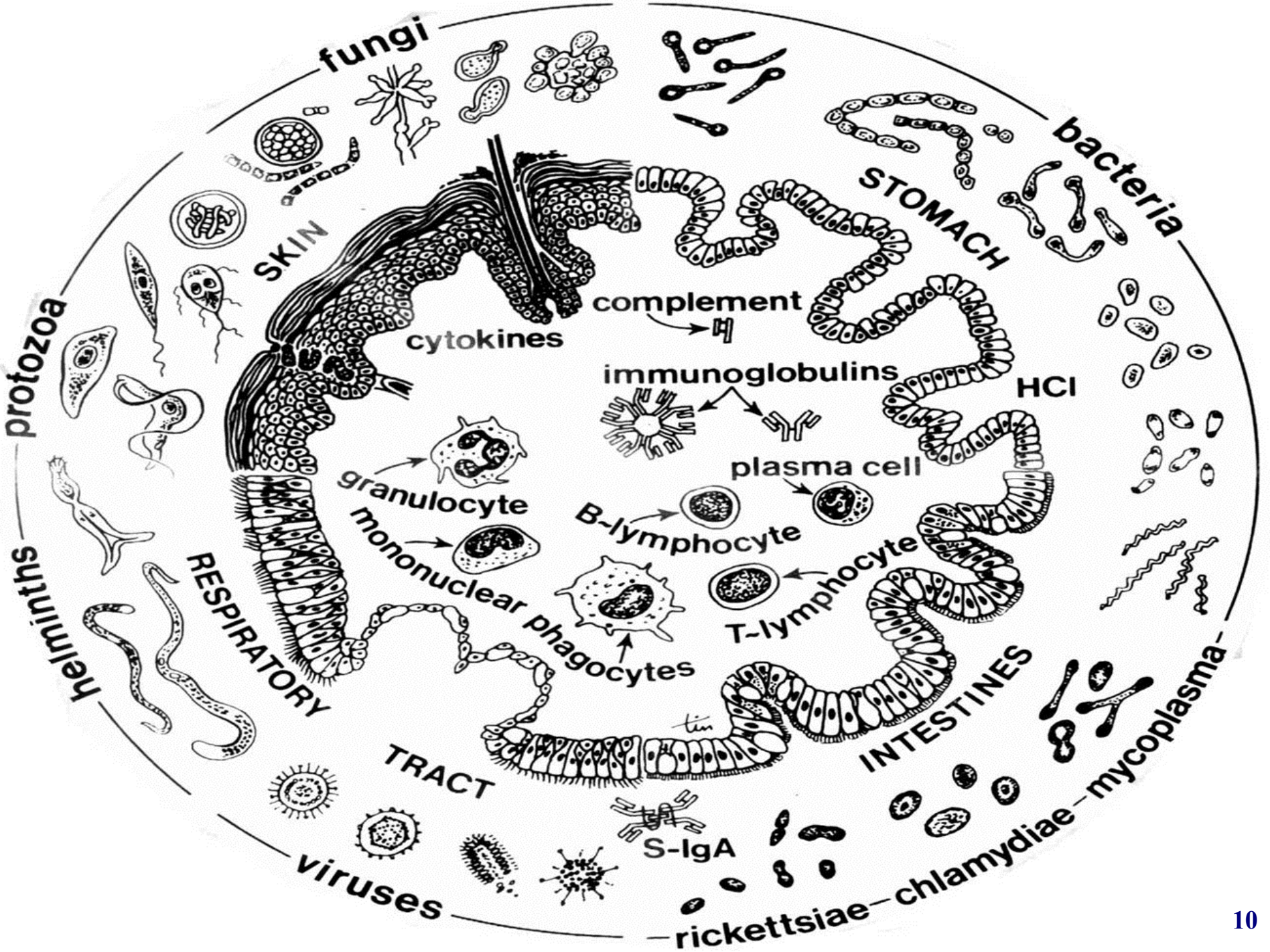

fungi
bacteria
protozoa
helminths
viruses
rickettsiae
chlamydiae
mycoplasma
SKIN
STOMACH
RESPIRATORY
TRACT
INTESTINES
cytokines
complement
immunoglobulins
HCl
granulocyte
plasma cell
B-lymphocyte
mononuclear phagocytes
T-lymphocyte
S-IgA

Fig. 1.3 Cellular components of blood

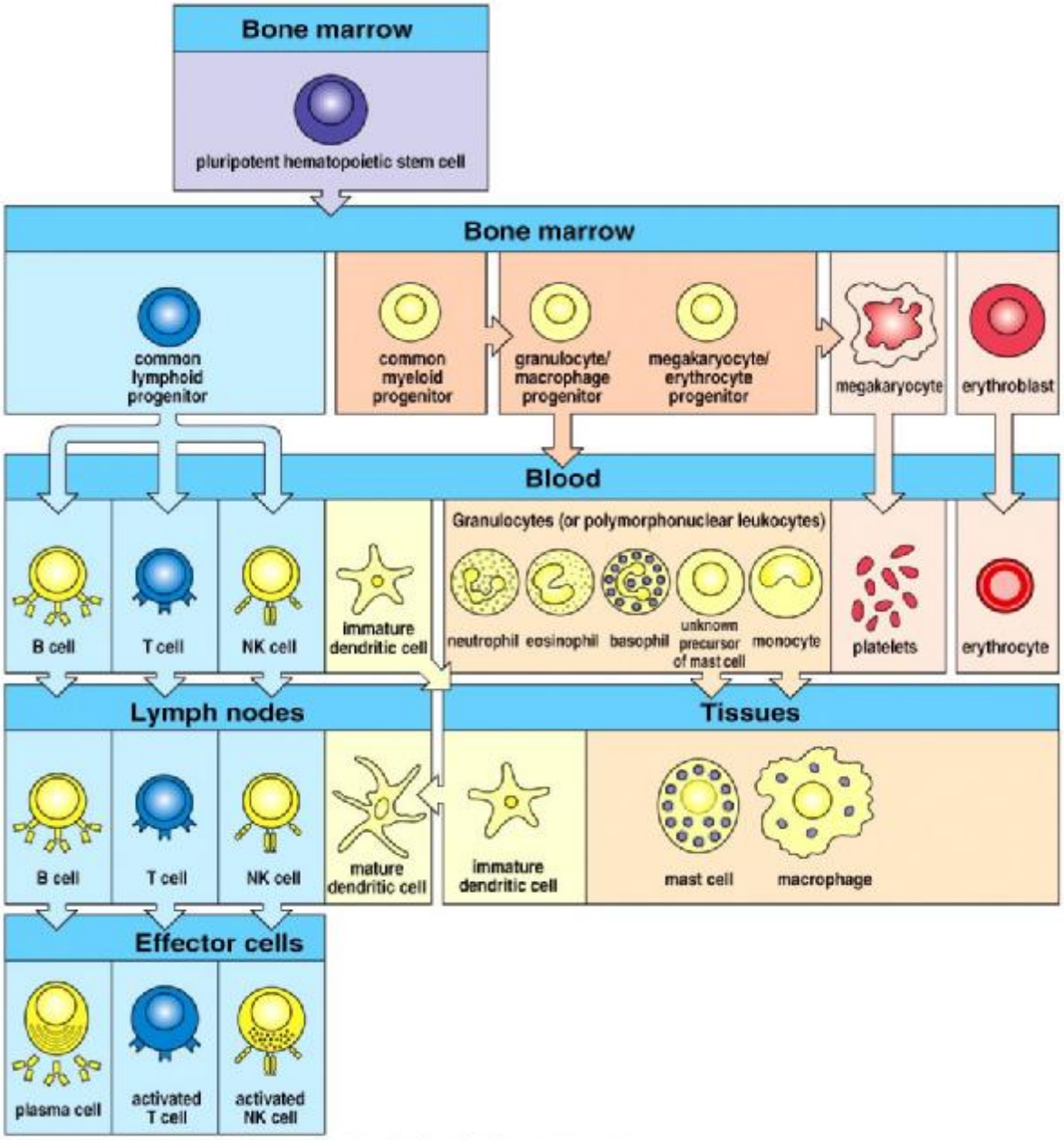
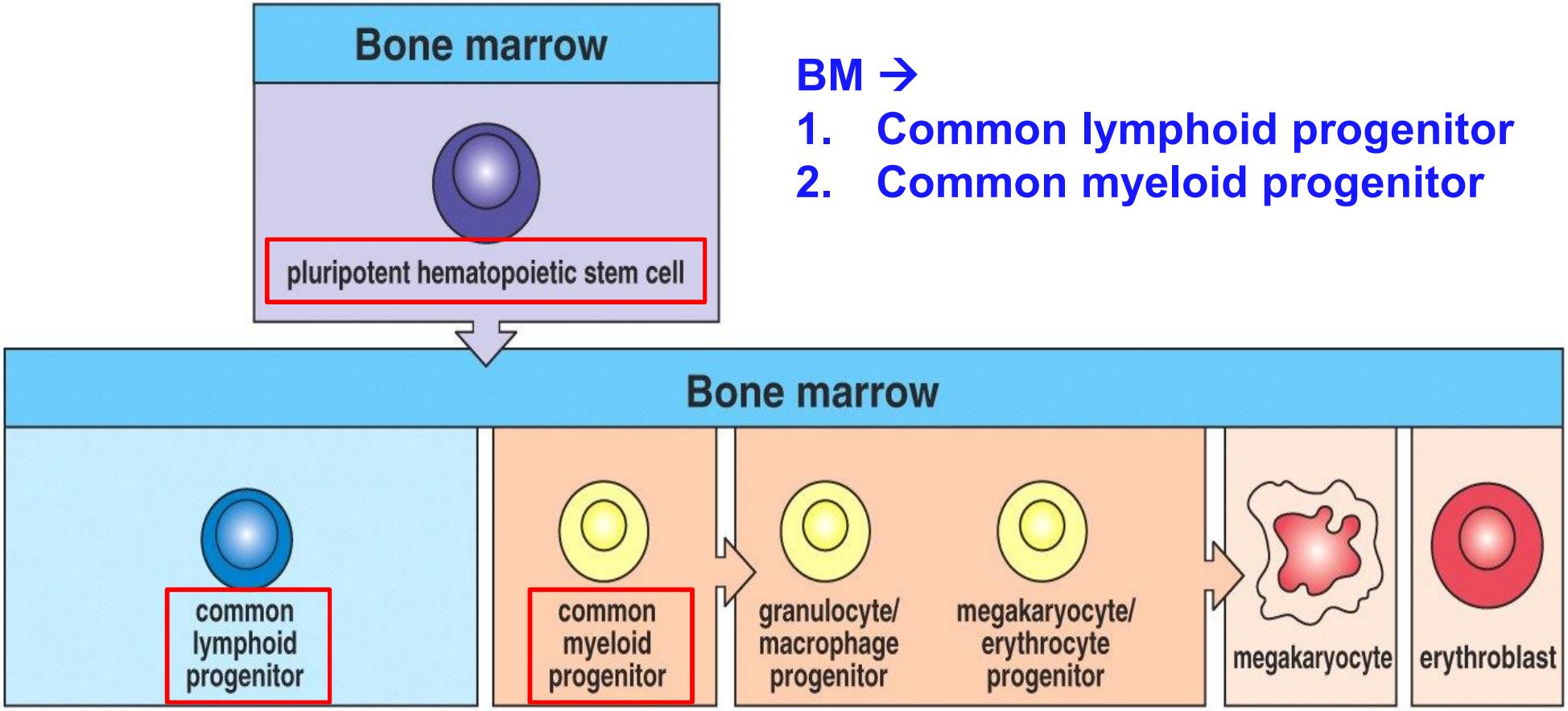


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

- Bone marrow stem cells
- WBC vs RBC
- Differentiated into distinct lineages of blood cells
- Cell lineages of WBCs
  - Lymphoid (B and T lymphocytes)
  - Myeloid (PMNs)

In bone marrow



BM →

1. **Common lymphoid progenitor**
2. **Common myeloid progenitor**

Figure 1-3 part 1 of 4 Immunobiology, 6/e. (© Garland Science 2005)

Bone marrow → peripheral blood

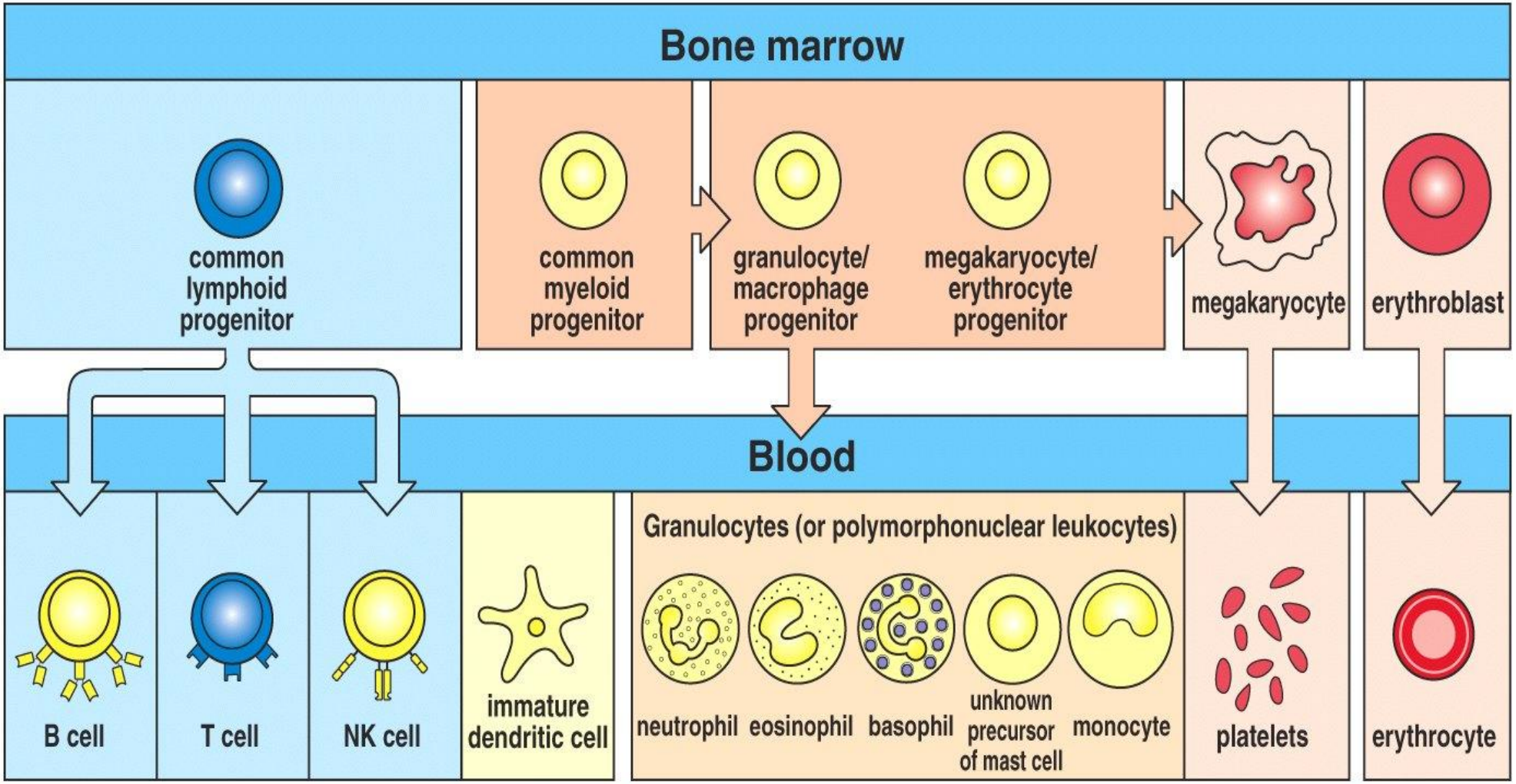
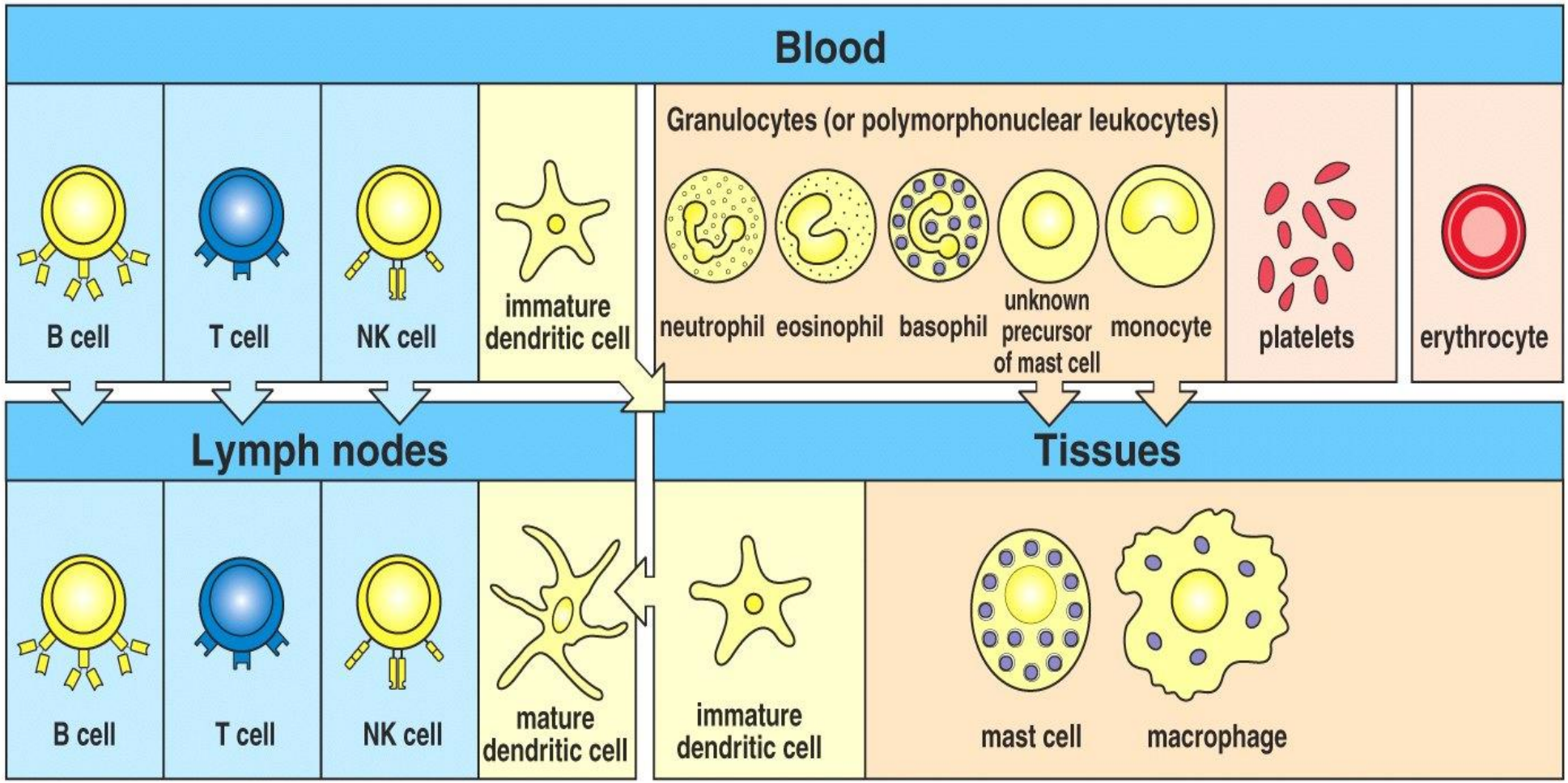


Figure 1-3 part 2 of 4 Immunobiology, 6/e. (© Garland Science 2005)

Dendritic cell 之歸屬尚未有定論

Peripheral blood → lymphoid organs



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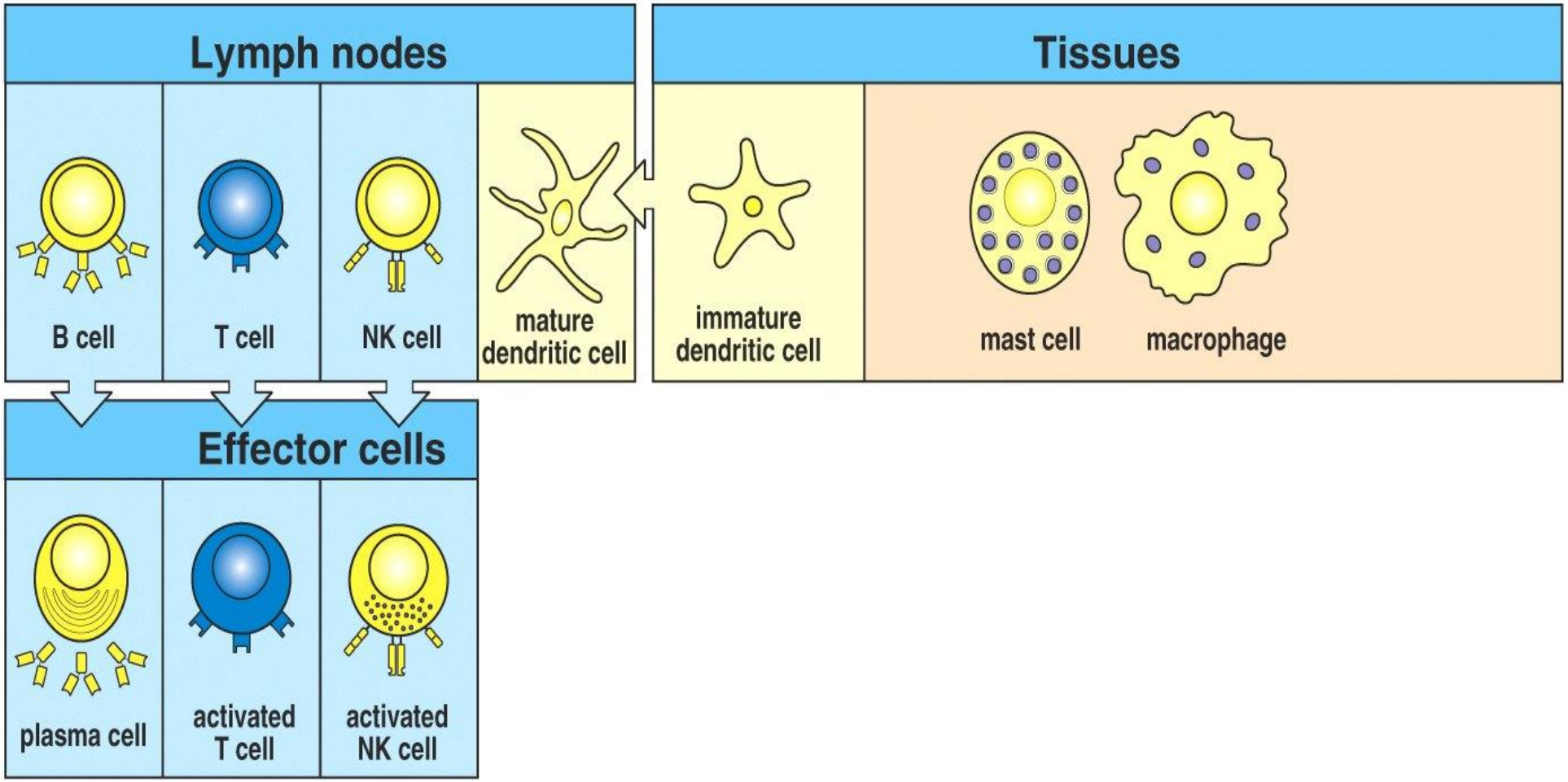


Figure 1-3 part 4 of 4 Immunobiology, 6/e. (© Garland Science 2005)

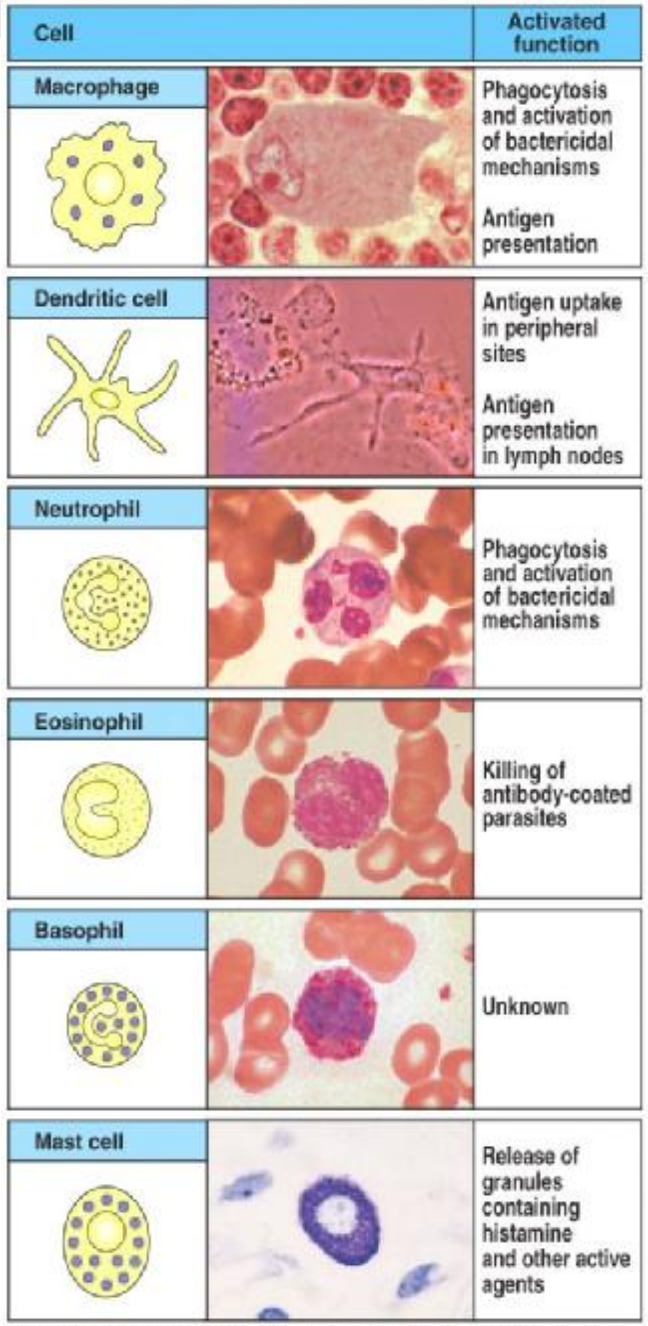


Figure 1-4 Immunobiology, 6/e. (© Garland Science 2005)

Fig. 1.4
Myeloid cells in innate and adaptive immunity

- Myeloid cell lineages
  - Macrophage (Mø)
  - Dendritic cell (DC)
  - Neutrophil (bacterial infection)
  - Eosinophil (parasitic infection)
  - Basophil
  - Mast cell (allergy)

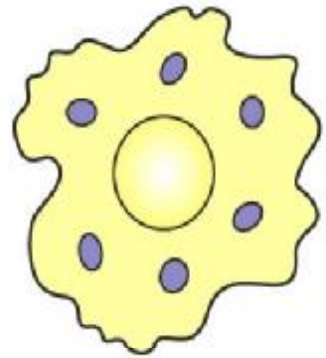
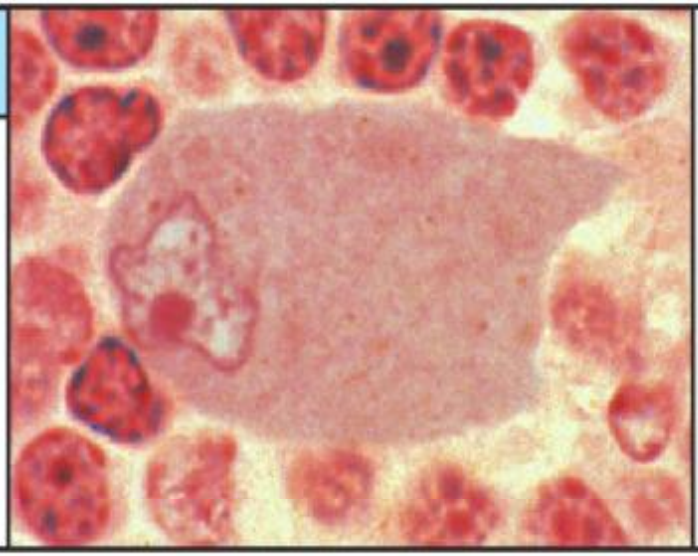
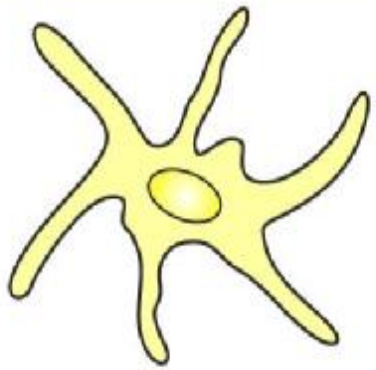
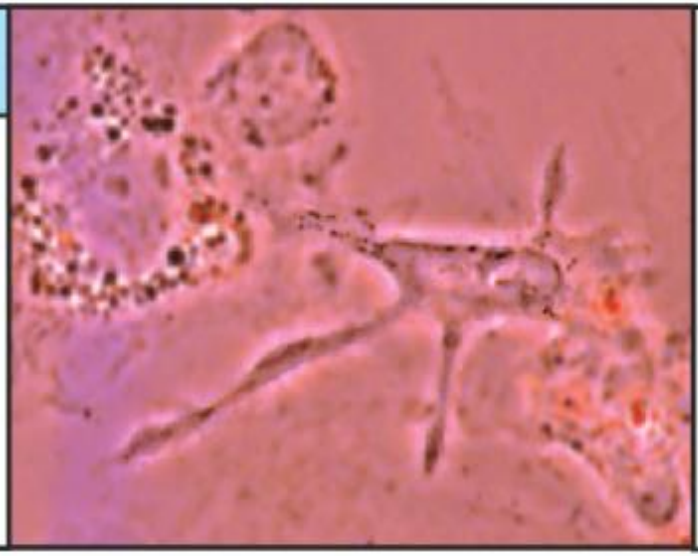
Cell		Activated function
Macrophage 		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell 		Antigen uptake in peripheral sites Antigen presentation in lymph nodes

Figure 1-4 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

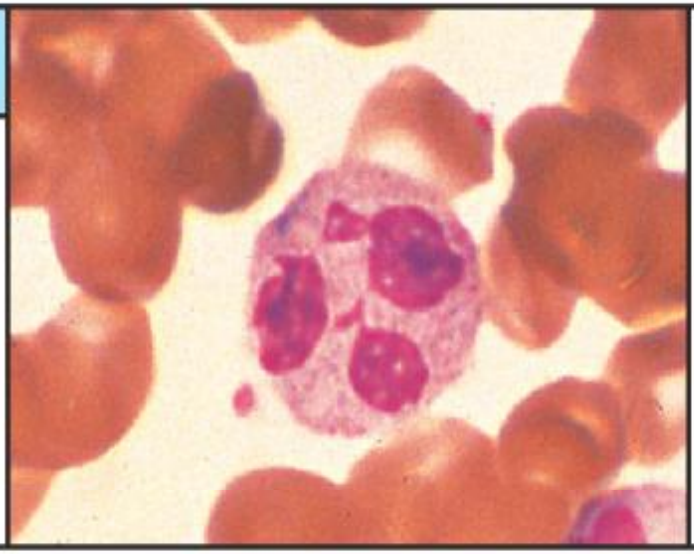
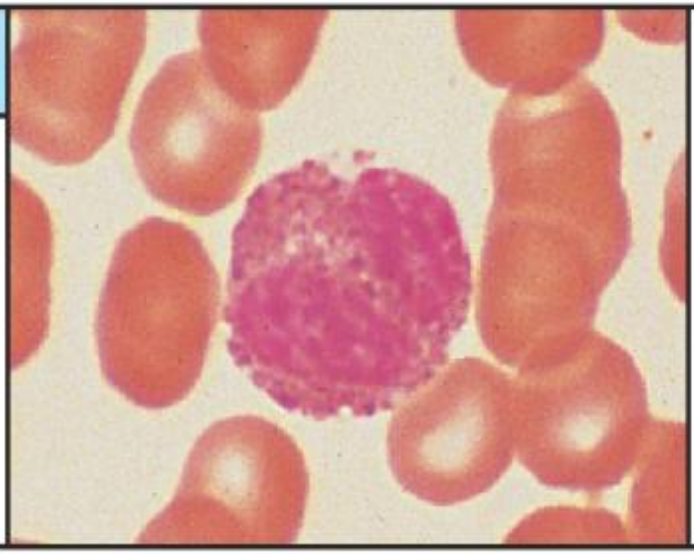
Cell		Activated function
Neutrophil 		Phagocytosis and activation of bactericidal mechanisms
Eosinophil 		Killing of antibody-coated parasites

Figure 1-4 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

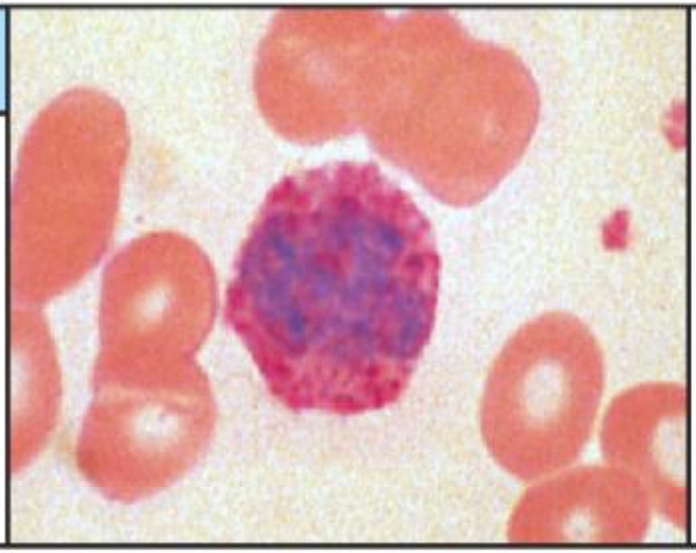
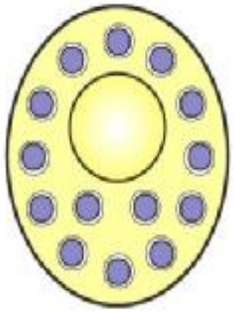
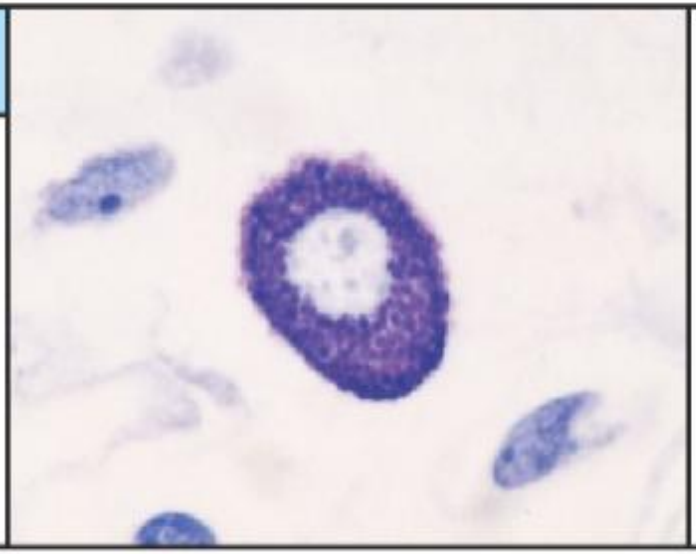
Cell		Activated function
Basophil 		Unknown
Mast cell 		Release of granules containing histamine and other active agents

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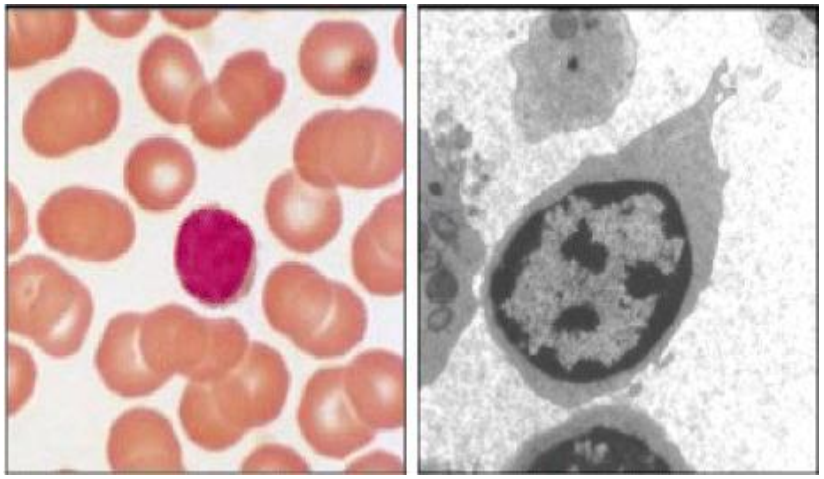
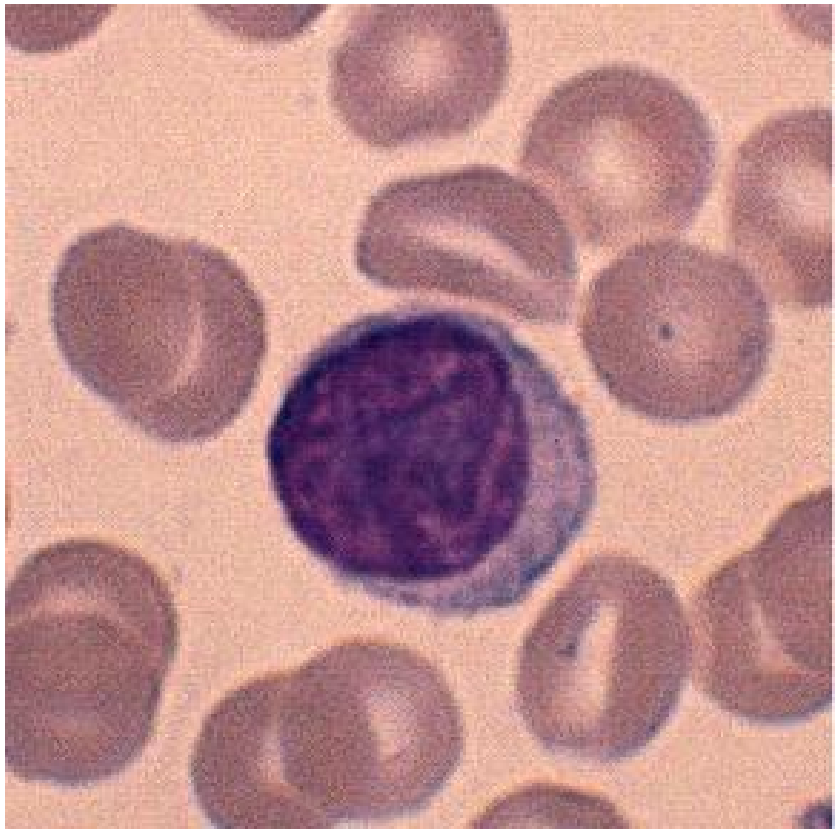
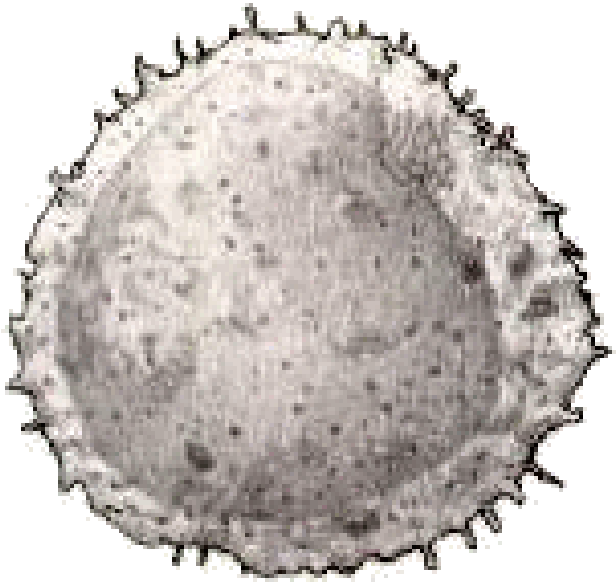
Fig. 1.6 Lymphocyte

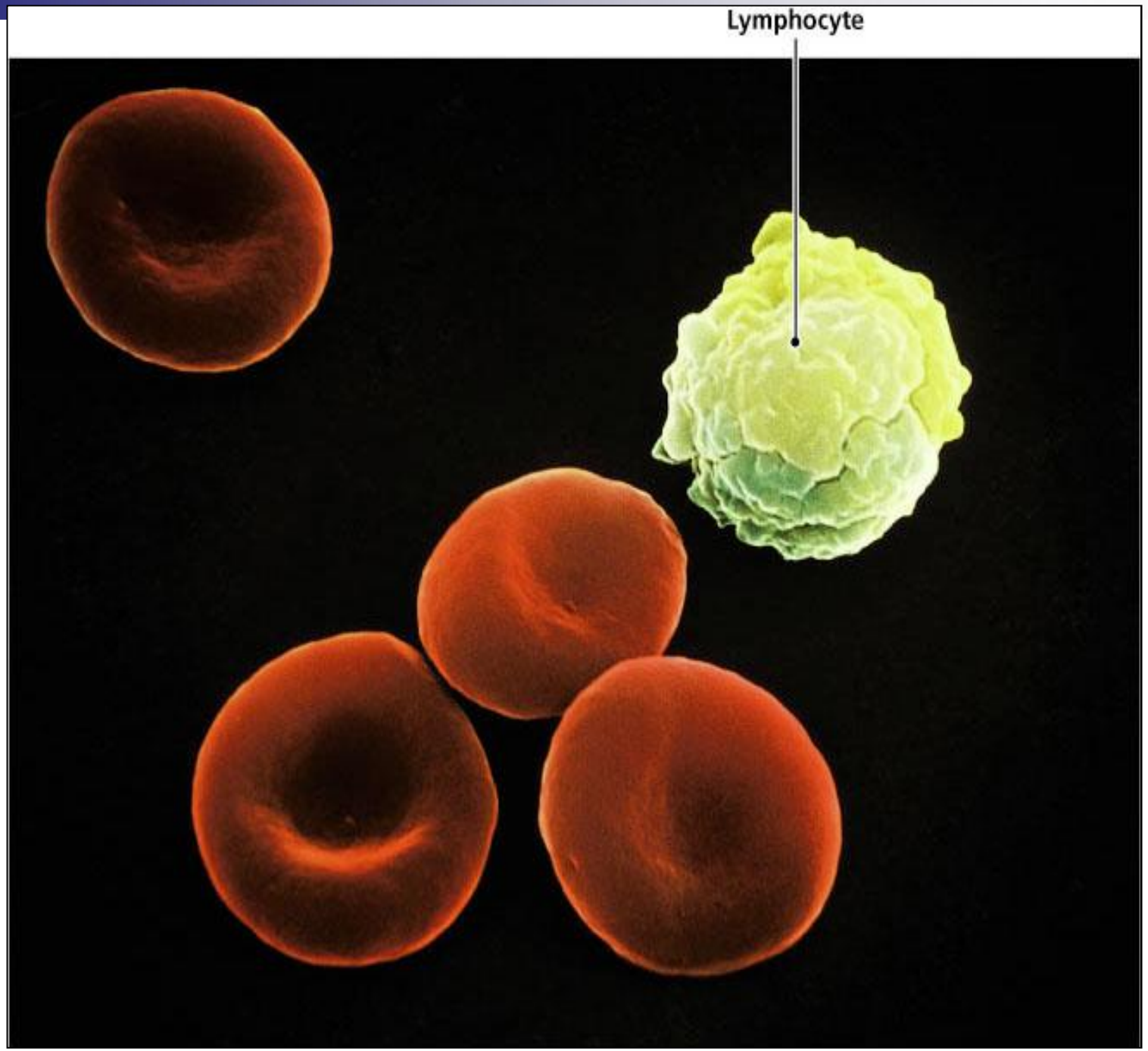


- Lymphocytes
  - Small in size
  - Large nucleus/cytoplasm ratio
  - Adaptive immunity
    - Production of antibodies (B cells)
    - Cytotoxic and helper (T cells)

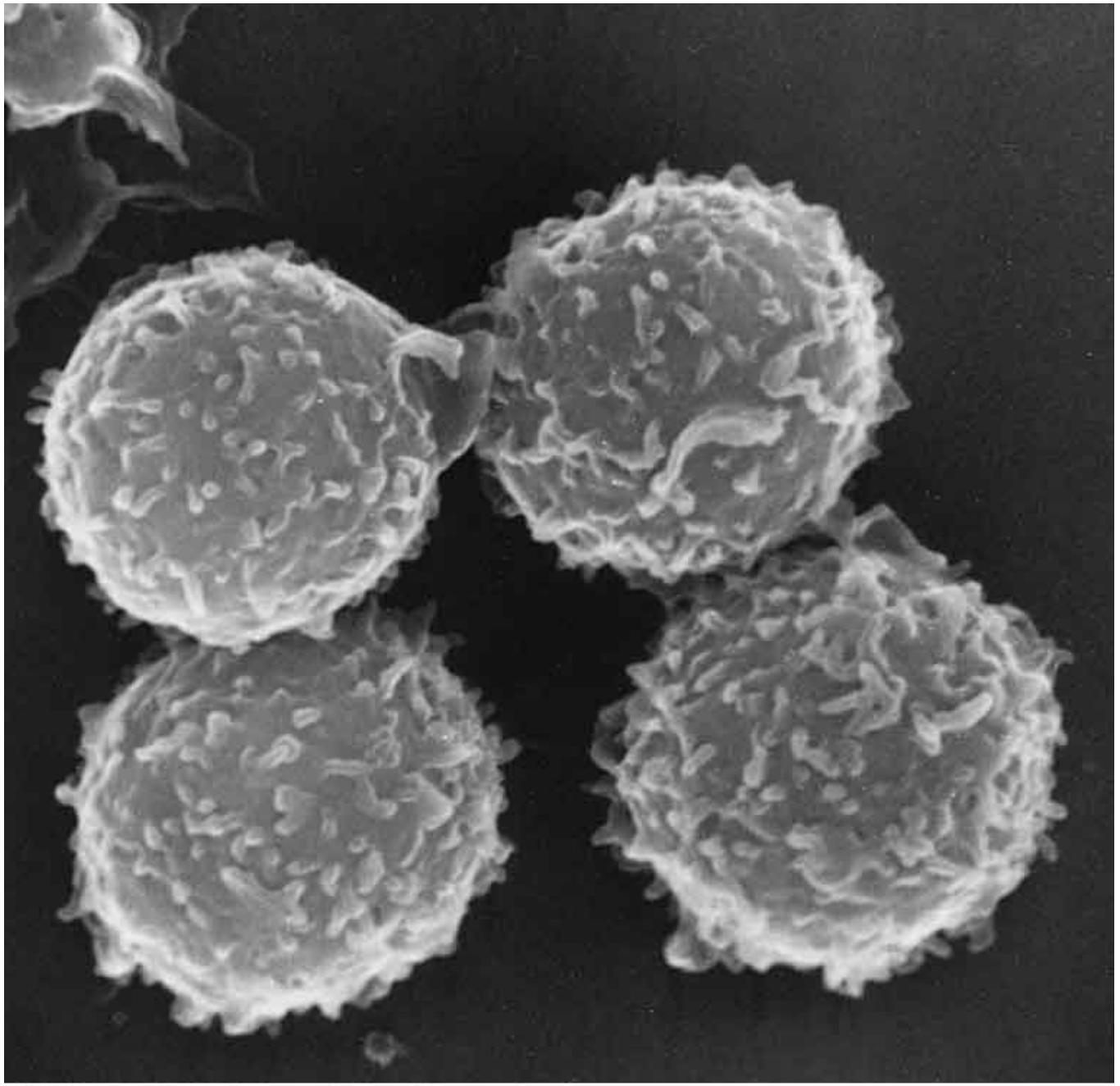




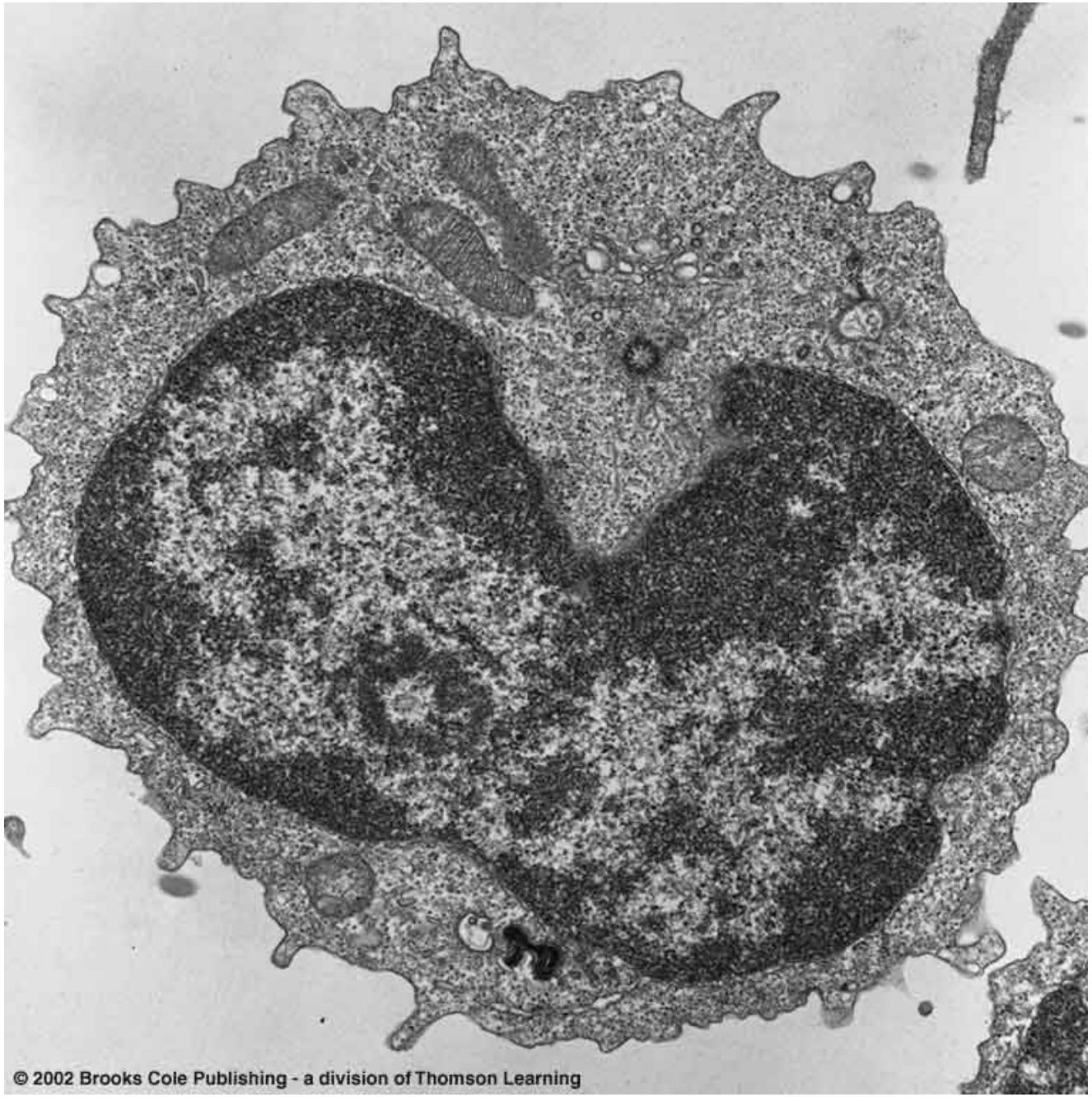
Lymphocyte


Lymphocyte

Lymphocytes (SEM)



Lymphocytes (TEM)



Dendritic cells (DCs) link between the innate and adaptive immune responses

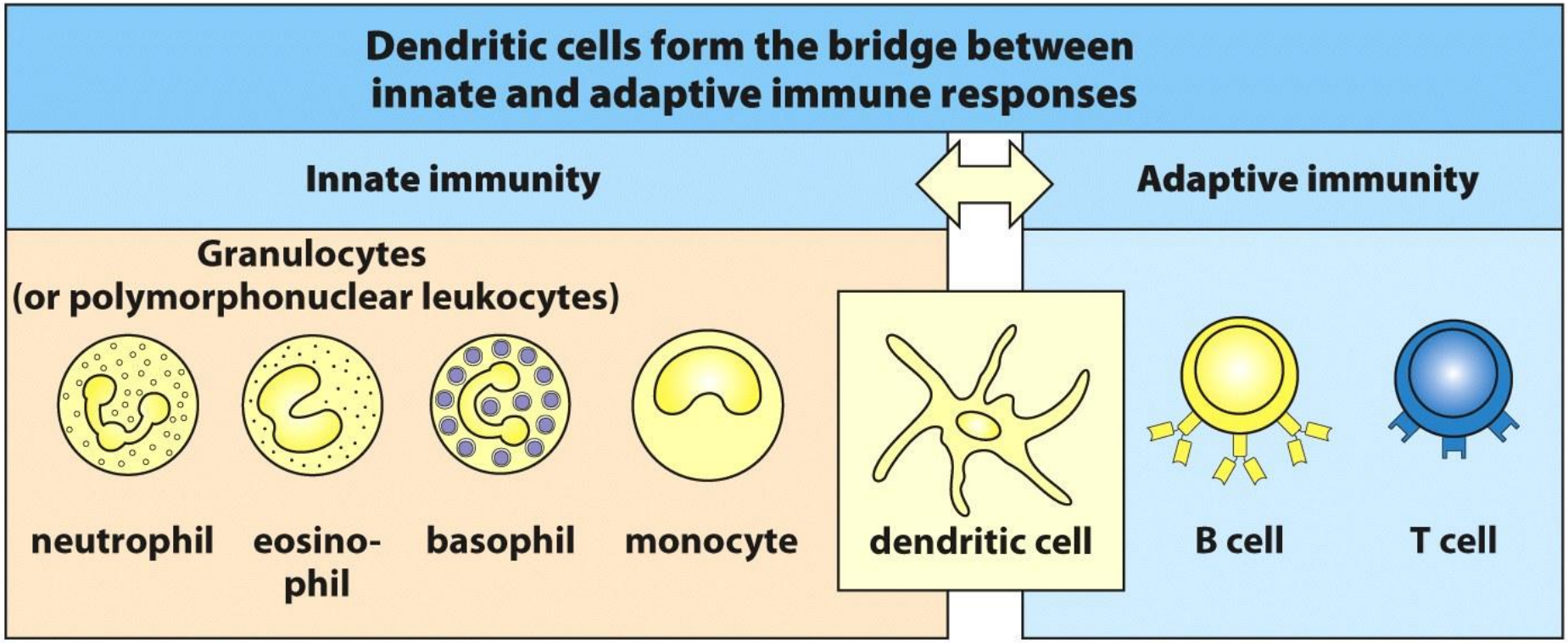
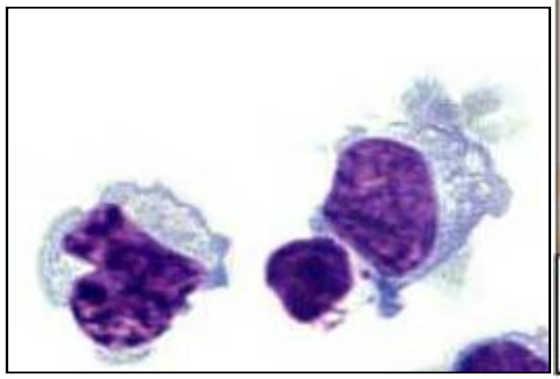
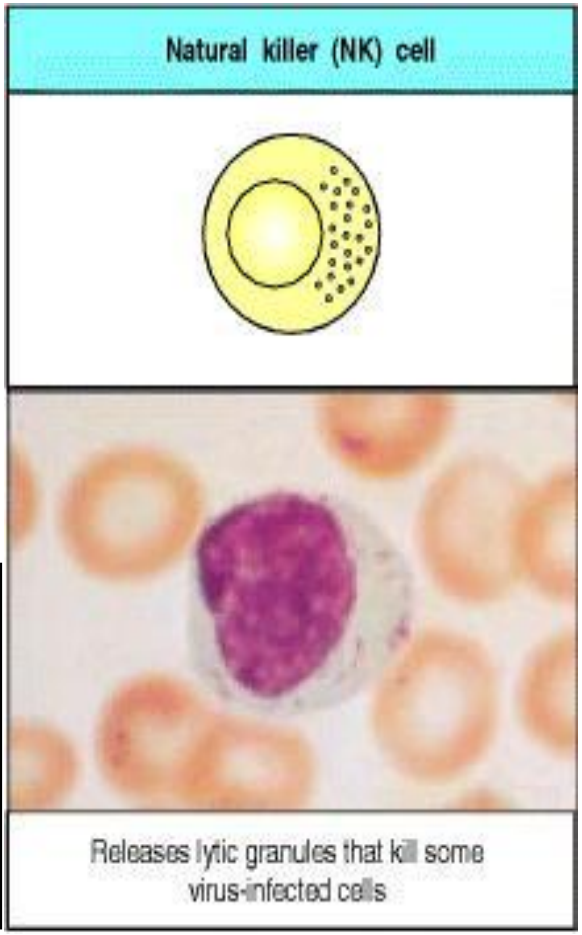


Figure 1.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Fig. 1.5 Natural killer cell

- Natural killer (NK) cell
  - Granular, large in size
  - Innate immunity
  - Has no antigen-specific receptor
  - Eradiate virally infected cells

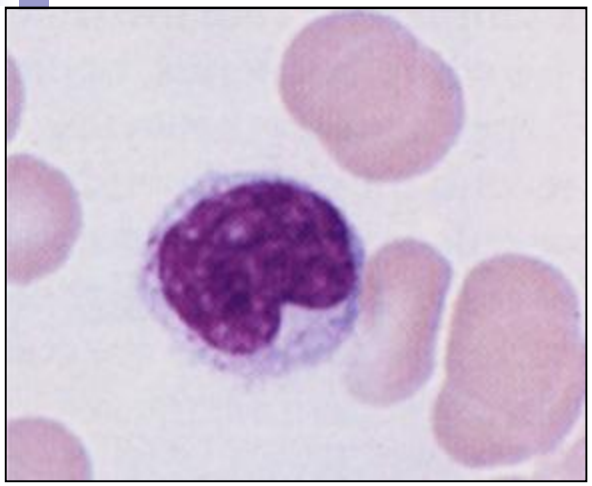


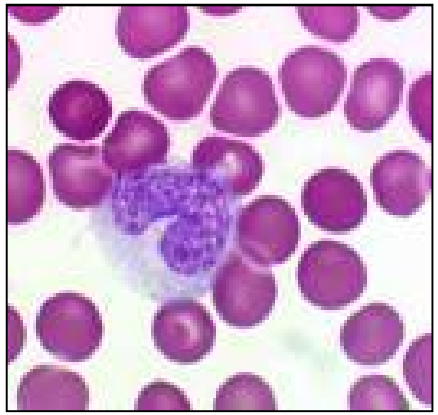


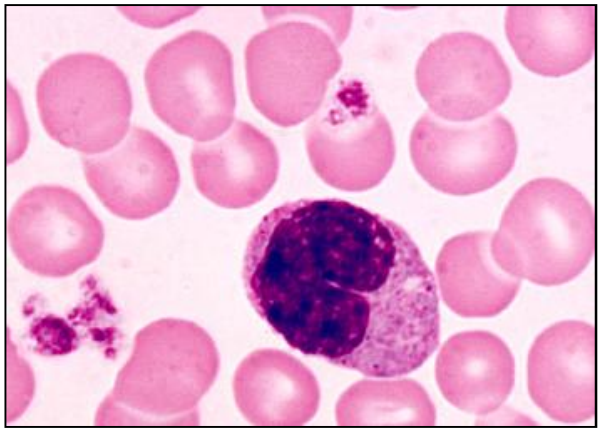
Mononuclear Cells

(monocytes and macrophages)

- highly phagocytic cells
- make up monocyte-macrophage system
- monocytes
  - after circulating for ~8 hours, mature into macrophages → stationary in tissues
- Macrophages (M_Φ)
  - reside in specific tissues
  - named according to tissue in which they reside







Monocyte

Monocyte engulfing Streptococci

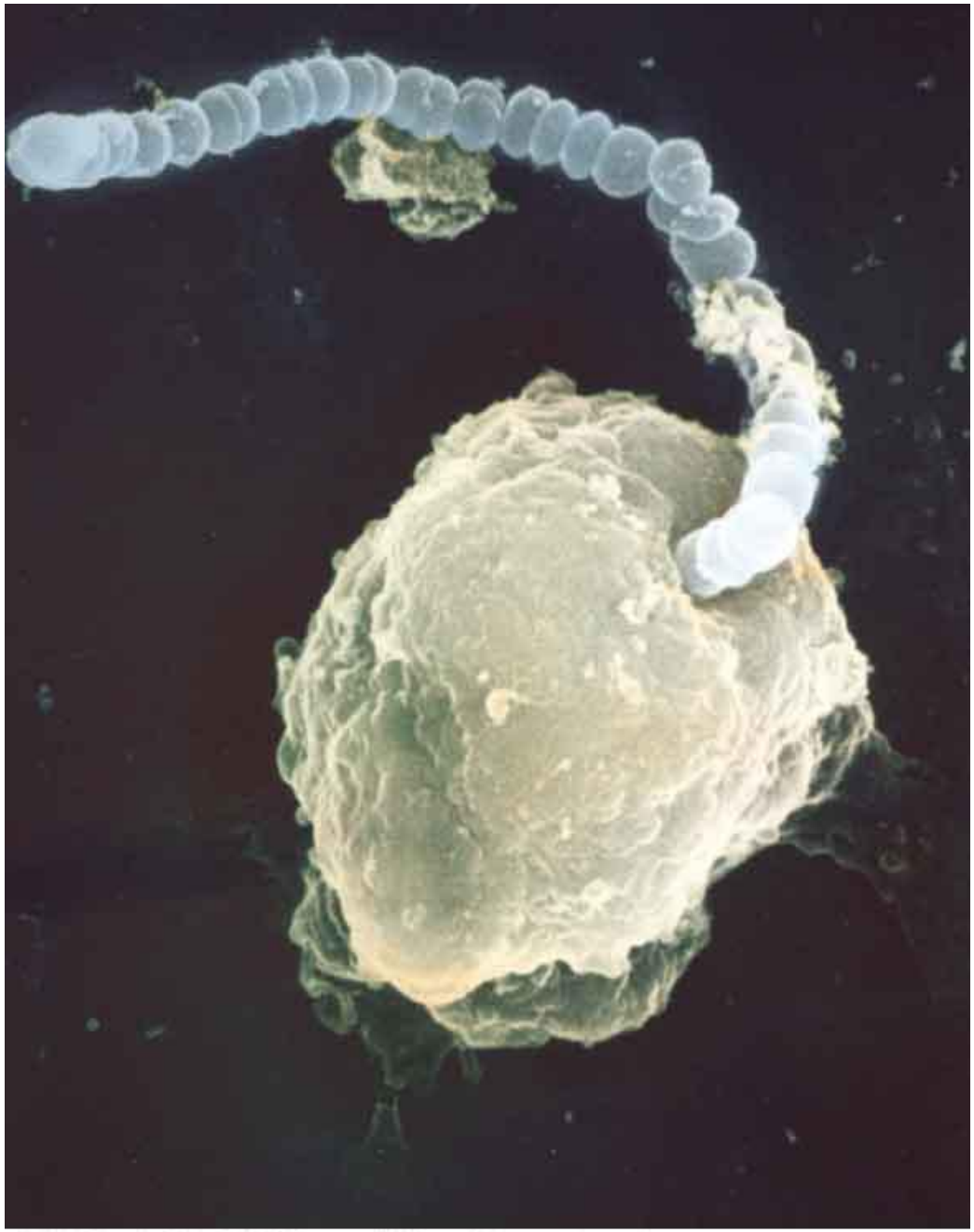


Fig. 1.8
The distribution of lymphoid tissues in the body

- Lymph vs lymphatics
- Afferent ("in") vs efferent ("out") lymphatics
- Primary lymphoid organ
  - Bone marrow (B cells)
  - Thymus (T cells)
- Secondary lymphoid organ
  - Spleen, tonsils, appendix, cervical lymph nodes, lumbar lymph nodes, etc.

淋巴液彙整由胸管(thoracic duct)進入左鎖骨下靜脈(left subclavian vein)回流入心臟

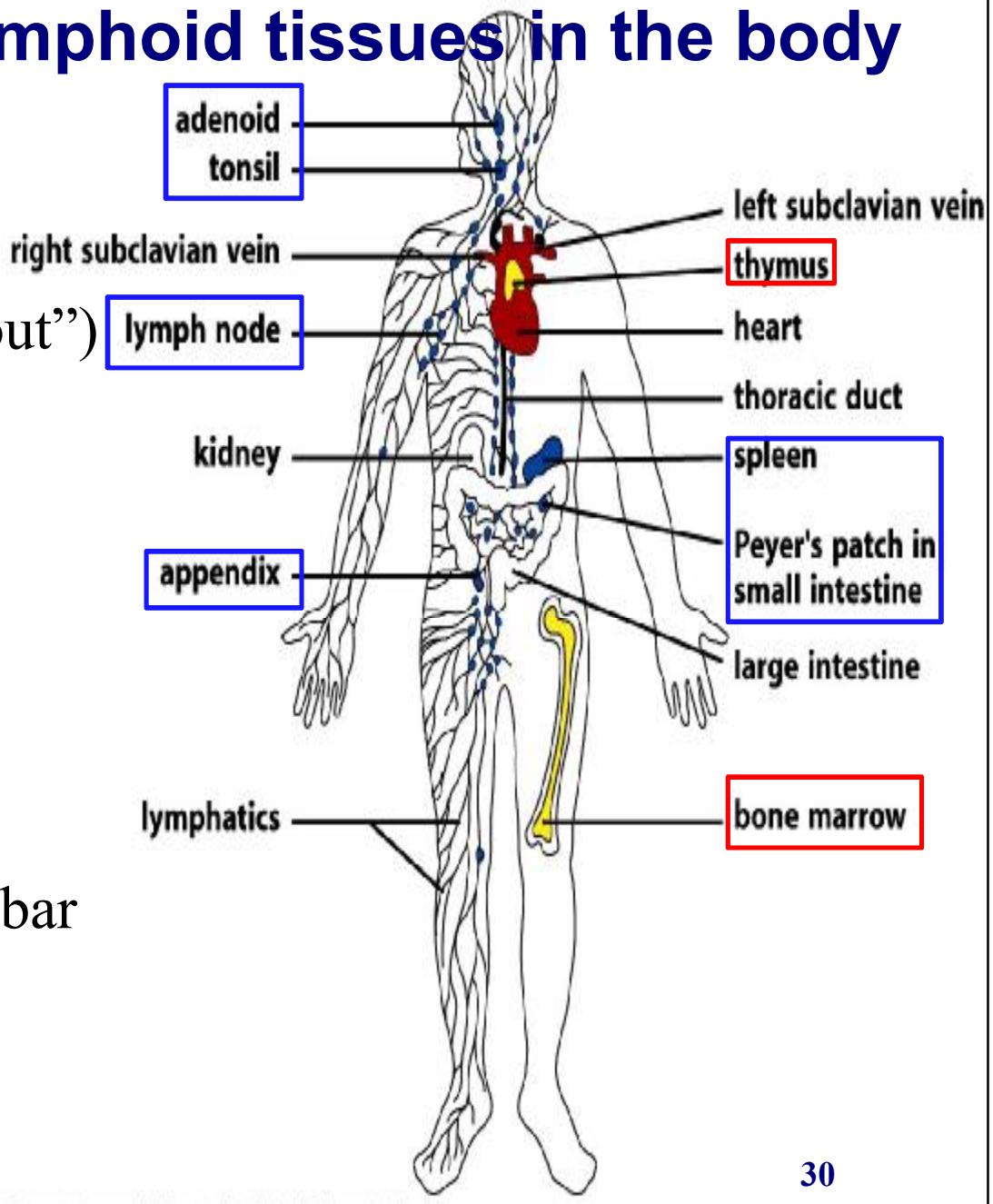


Figure 1-7 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.9 Bacterial infection triggers an inflammatory response

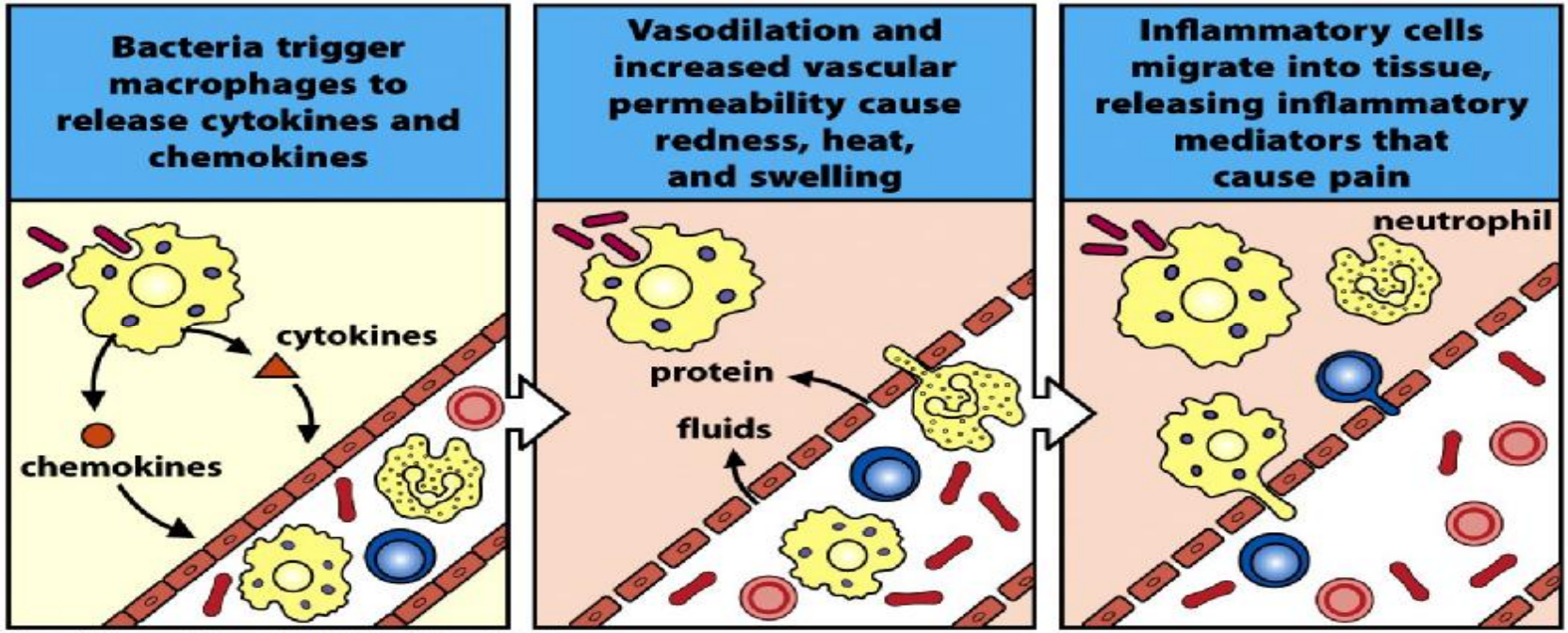


Figure 1-8 Immunobiology, 7ed. (© Garland Science 2008)

- Bacterial infection triggers an inflammatory response
- Cytokine vs chemokine
- Vasodilation and ↑vascular permeability

- 4 elements of inflammation
  - Redness, swelling, heat, pain
- Principal inflammatory cells
  - Neutrophils, macrophages

Changes of the local blood vessel during inflammation

- Signs of inflammation: redness, swelling, heat and pain
- Changes
  1. Increase in diameter of blood vessels, increasing local blood flow (redness, heat).
  2. Blood endothelial cells start to express cell-adhesion molecules (CAMs).
  3. Increase in vascular permeability → edema (swelling, pain)
  4. Clotting in microvessels in the site of infection.

Fig. 3.6 Infections stimulate macrophages to initiate inflammation

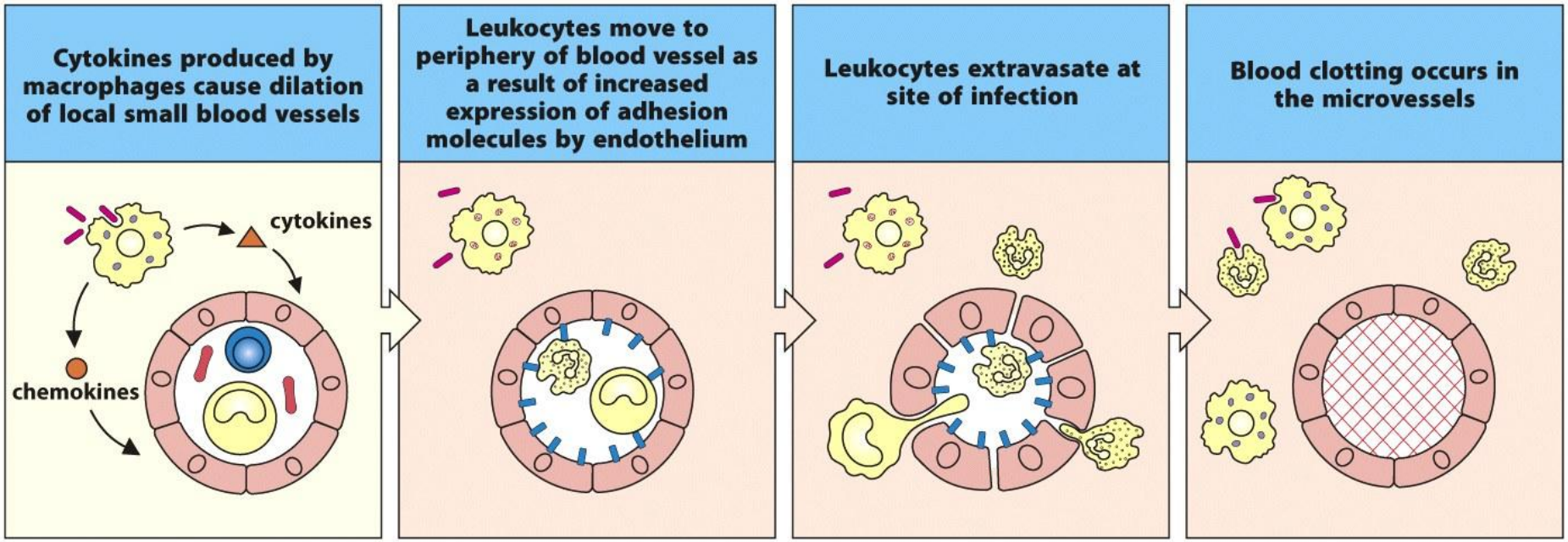


Figure 3.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Essential roles of inflammation (p.82-83)

(1) Deliver effector molecules & cells from blood stream to sites of infections.

(2) Induce local blood clotting, providing physical barrier against spreading of infection.

(3) Promote the repairing process of injured tissues.

Fig. 1.10
Macrophages express receptors to recognize common patterns on pathogens

- Pathogen-associated molecular patterns (PAMPs)
  - Present on most pathogens, but not on our body's cells
  - LPS, lipoteichoic acid (LTA), murein, flagella, …etc.
- Pattern recognition receptors (PRPs)
  - Present on macrophages, DCs, neutrophils, ..etc.
  - Interact with PAMPs to initiate responses

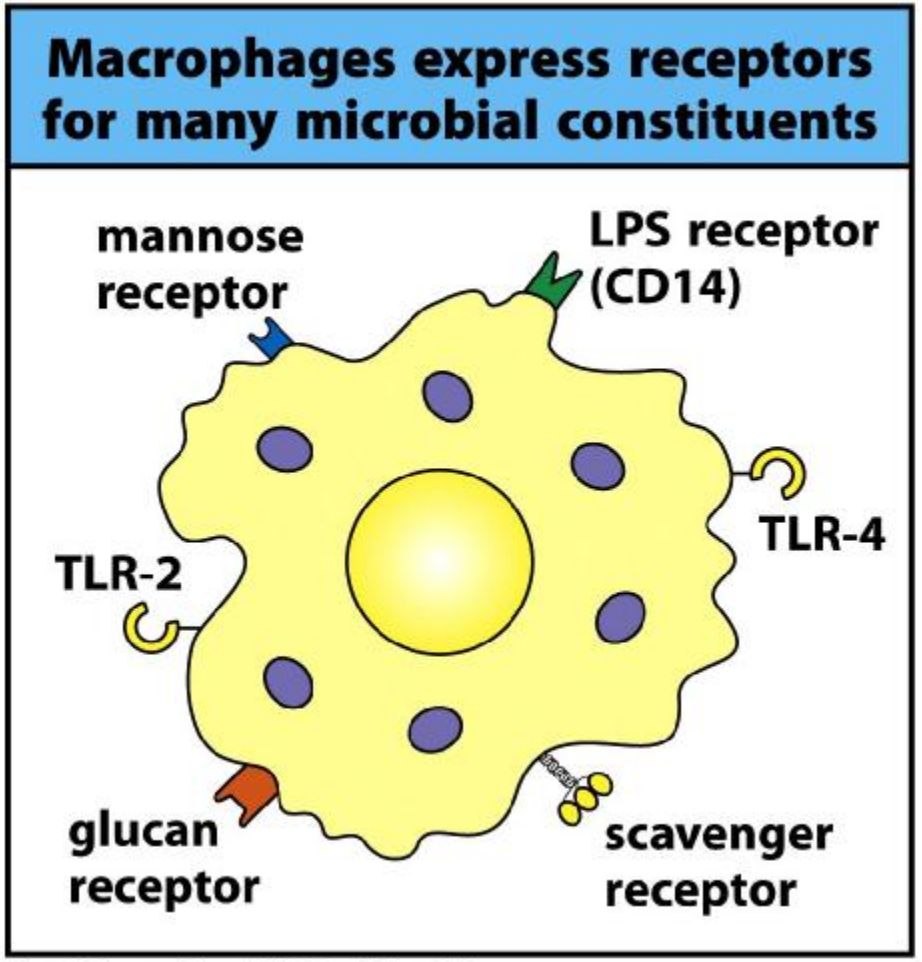


Figure 1-10 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.11 Dendritic cells initiate adaptive immune responses

- Dendritic cells (DCs)
  - Initiator of adaptive immunity
  - Antigen-presenting cell (APC)
  - Immature vs mature DCs
    - Phagocytic vs. non-phagocytic
    - Ag-captureing vs. Ag-presenting
    - Peripheral tissue vs. lymph node

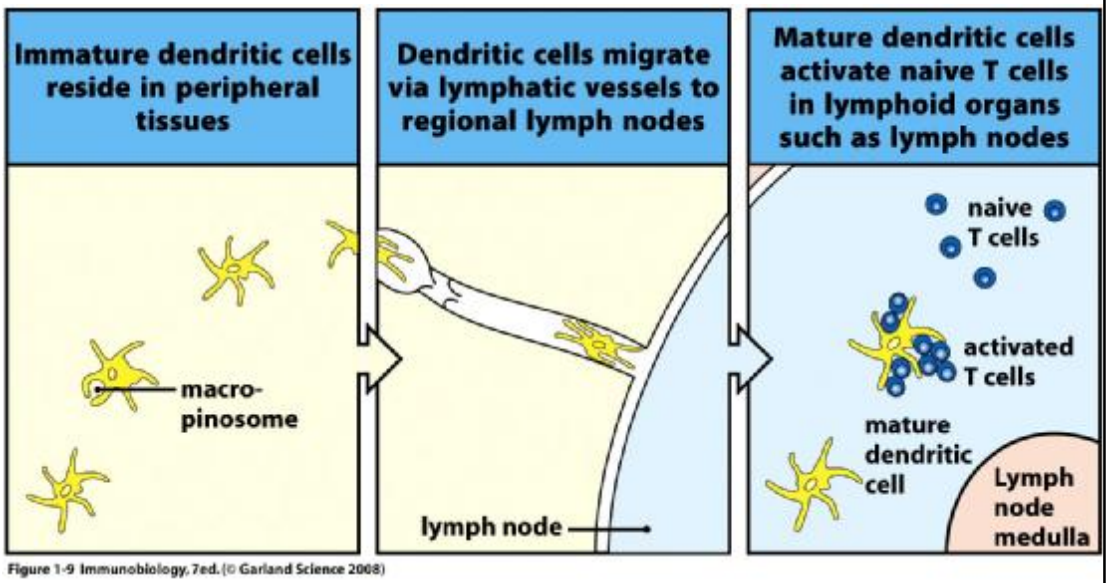


Figure 1-9 Immunobiology, 7ed. (© Garland Science 2008)

  - Carry receptors for common bacterial cell wall component (e.g. proteoglycans)

Principles of innate and adaptive immunity

- Innate immunity
  - Provides first line of defense against numerous m/o
  - Neutrophils and macrophages
    - via inflammation
- Adaptive immunity
  - Provides long-lasting defense
  - B and T cells

Fig. 1.12 Clonal selection

- Clonal selection theory
  - Coined by Macfarlane Burnet (1950s)
  - Central principle of adaptive immunity

- Lymphocyte receptor
  - A single specificity for each lymphocyte
  - Specificity determined during maturation stage in B.M. (B cells) and thymus (T cells)
  - Different lymphocytes carry receptors of different specificity

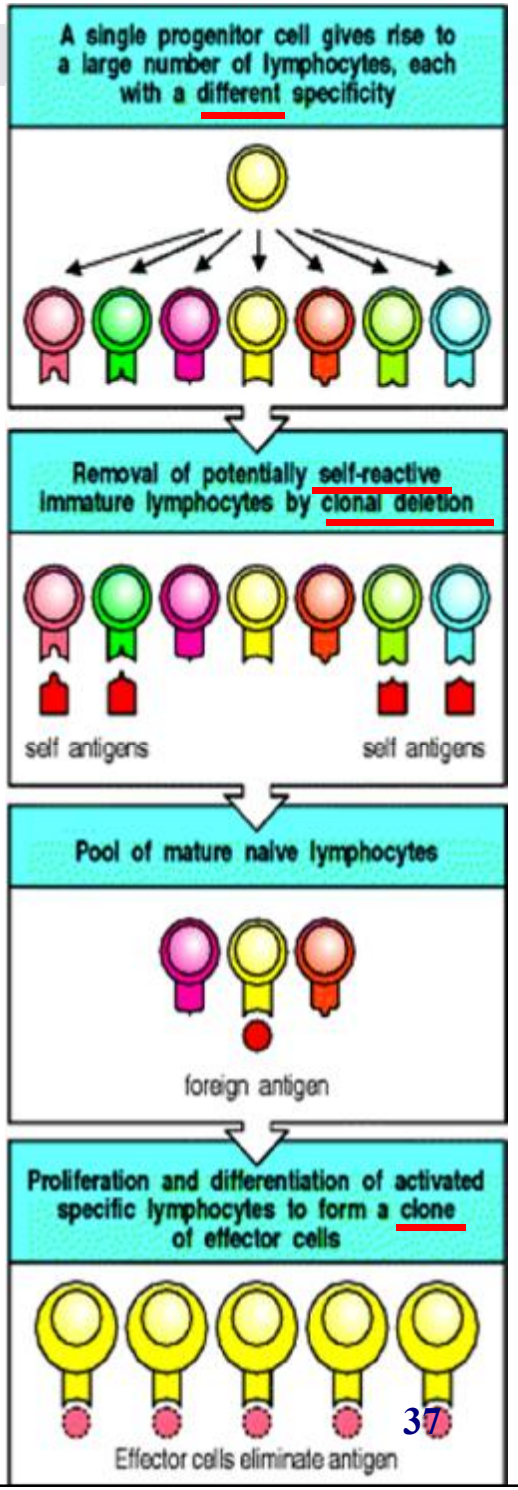


Fig. 1.13

Four basic principles of clonal selection

Postulates of the clonal selection hypothesis

Each lymphocyte bears a single type of receptor with a unique specificity

Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation

The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived

Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes

Figure 1-12 Immunobiology, 7ed. (© Garland Science 2008)

(clonal deletion)

Fig. 3.1 Innate vs. Adaptive Immunity

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Expressed by all cells of a particular type (e.g. macrophages)	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogens	Yes	No
Interacts with a range of molecular structures of a given type	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal distribution	No	Yes
Able to discriminate between even closely related molecular structures	No	Yes

Figure 3.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Fig. 1.14 Ag receptors (BCR vs TCR) are structurally similar

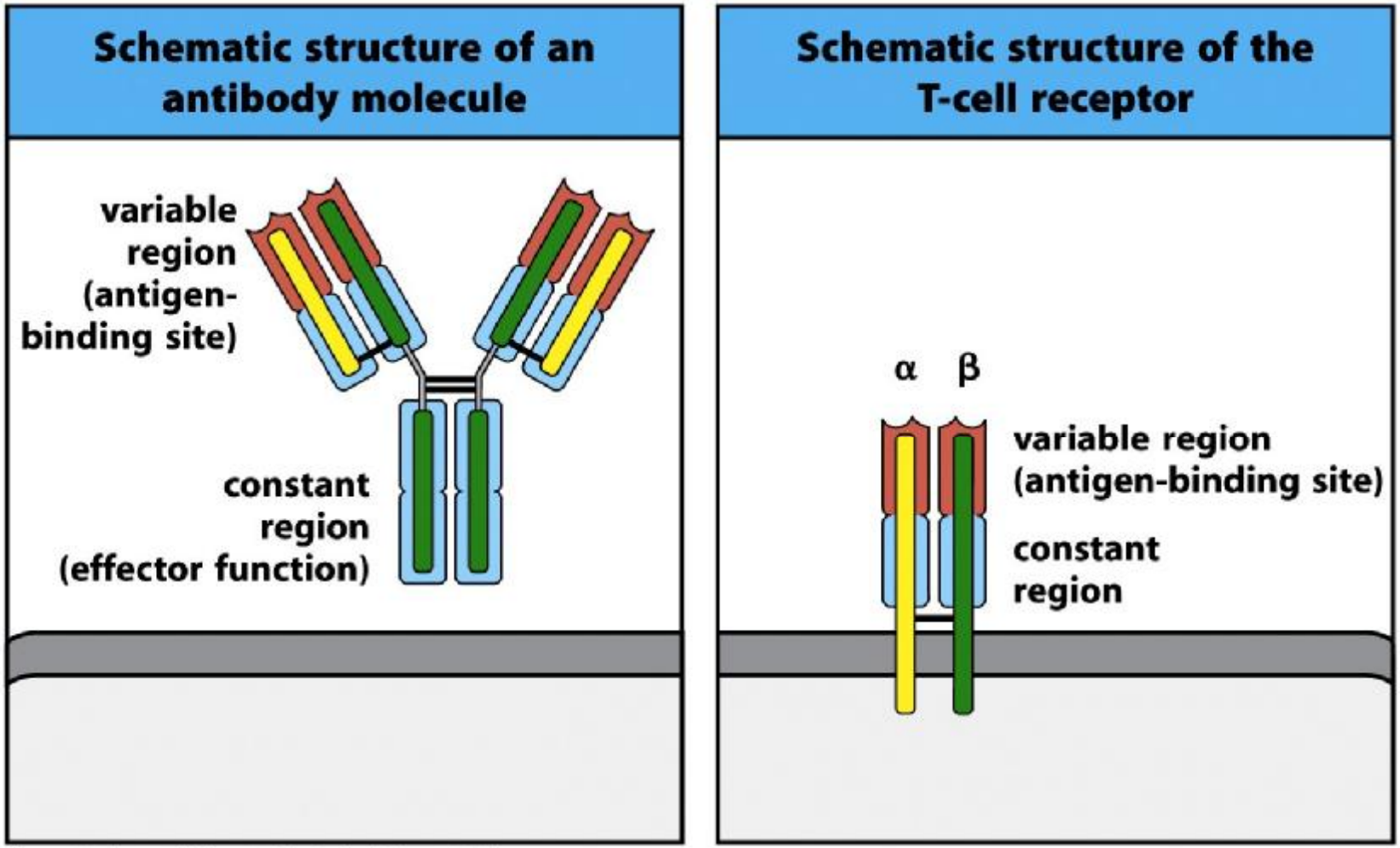
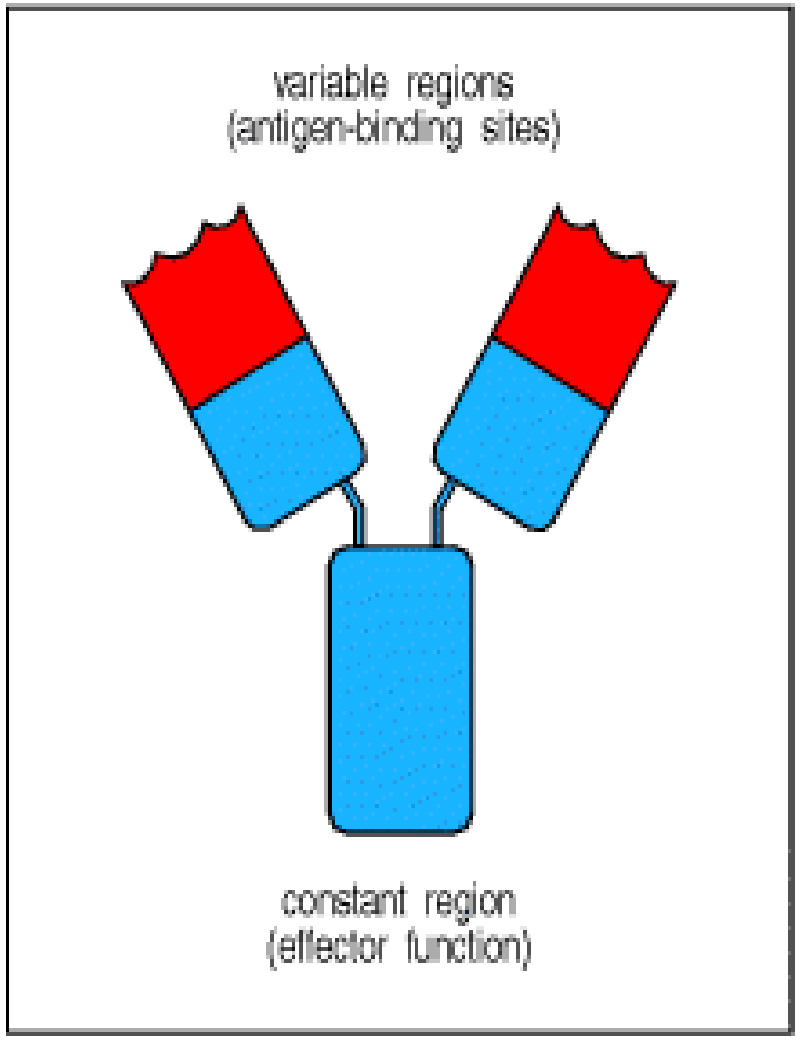


Figure 1-13 Immunobiology, 7ed. (© Garland Science 2008)

Antibody (Ab)

- Secreted vs membrane-bound form
- B cell receptor (BCR)
- 2 heavy (H) & 2 light (L) chains
- Y-shaped
- Variable (V) vs constant (C) region
- Ag-binding vs effector function
- Constant region defines the '**class**' of the Ab

Schematic drawings of Ab



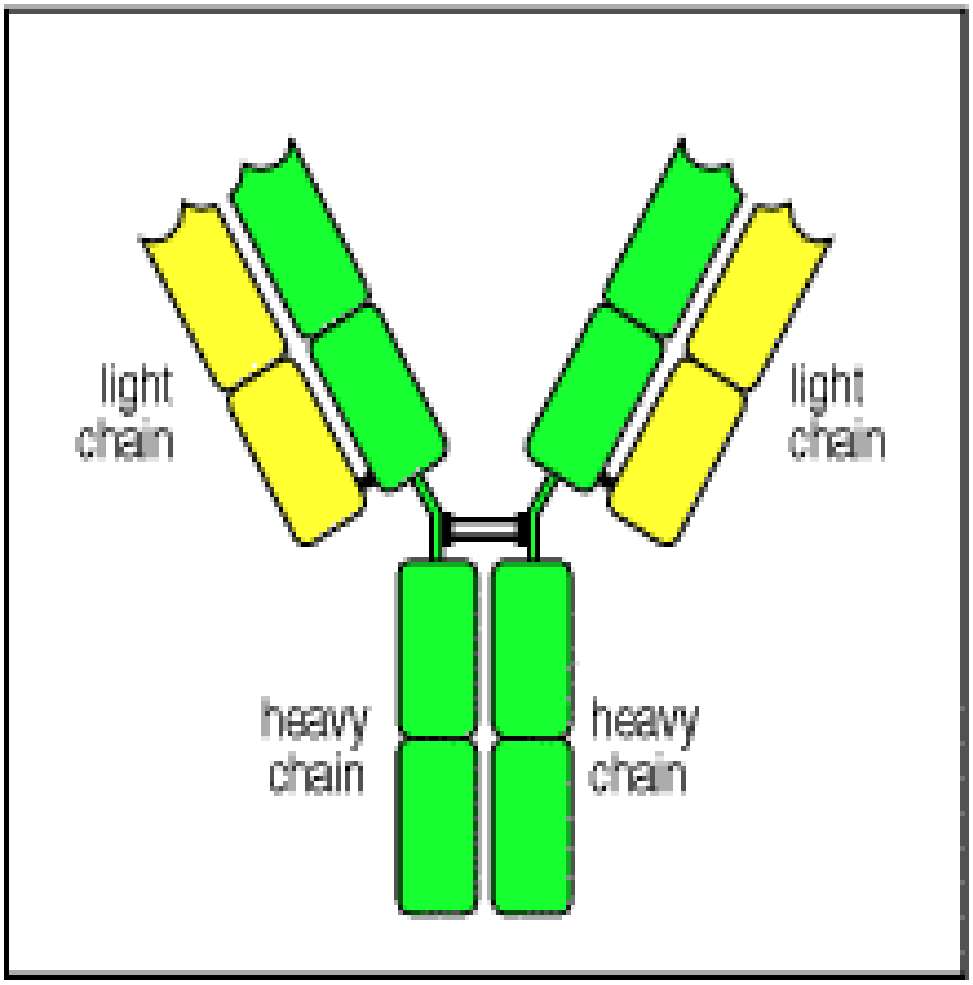


Fig. 1.15 Epitope

- Also called "antigenic determinant"
  - 3-D dynamic structures on Ag recognized by Ab
  - Could be
    - One single stretch of peptide (less frequently)
    - Sever peptides composing a 3-dimentional structure (more frequently)

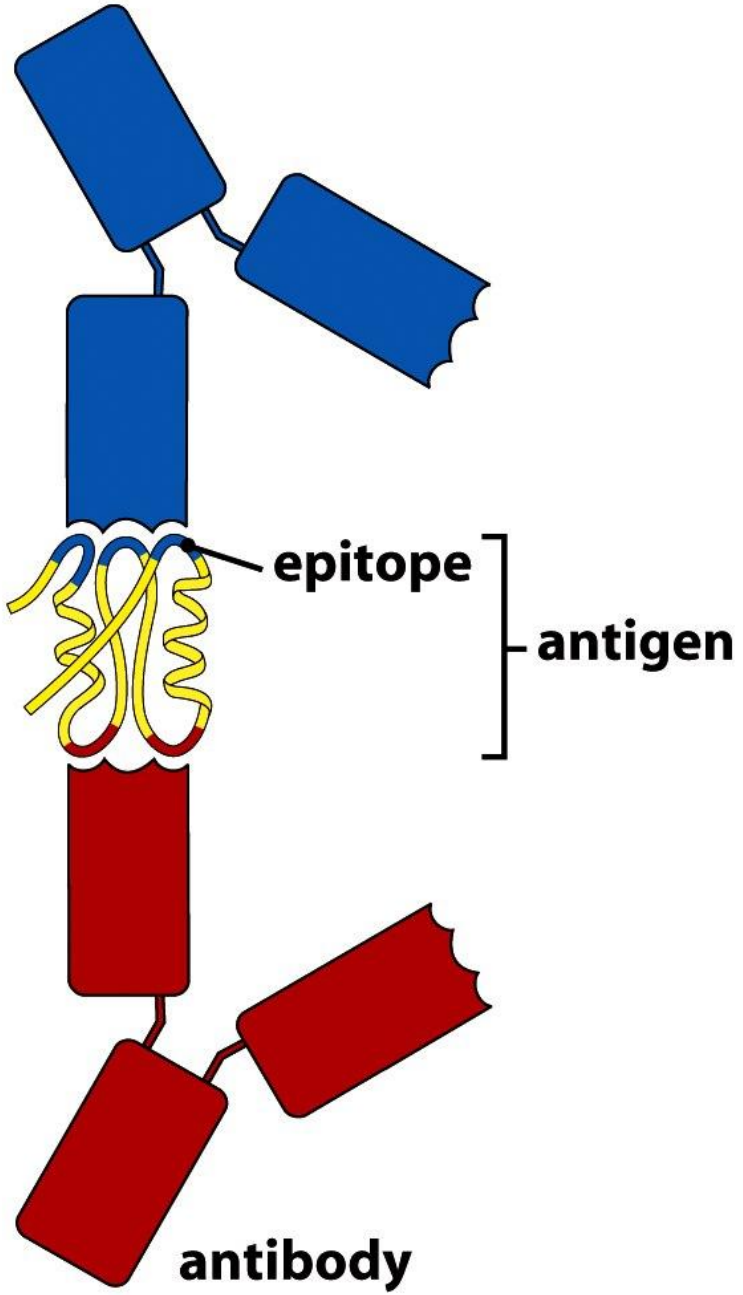
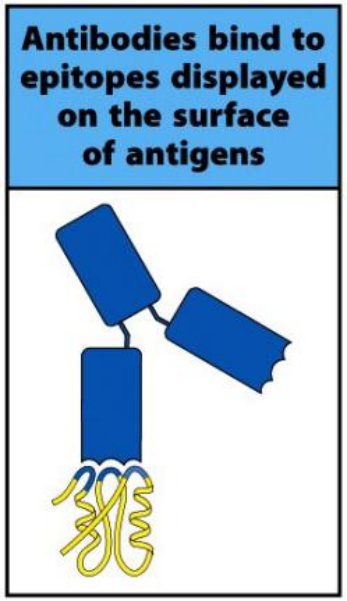


Figure 1-15 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.16 TCR binds a complex of an Ag fragment and a self molecule



- Ab-Ag binding
  - Epitope on Ag
- TCR-Ag binding
  - Ag digested into fragments
  - Epitope(s) exposed
  - Epitope bound to MHC molecule
  - Recognized by TCR

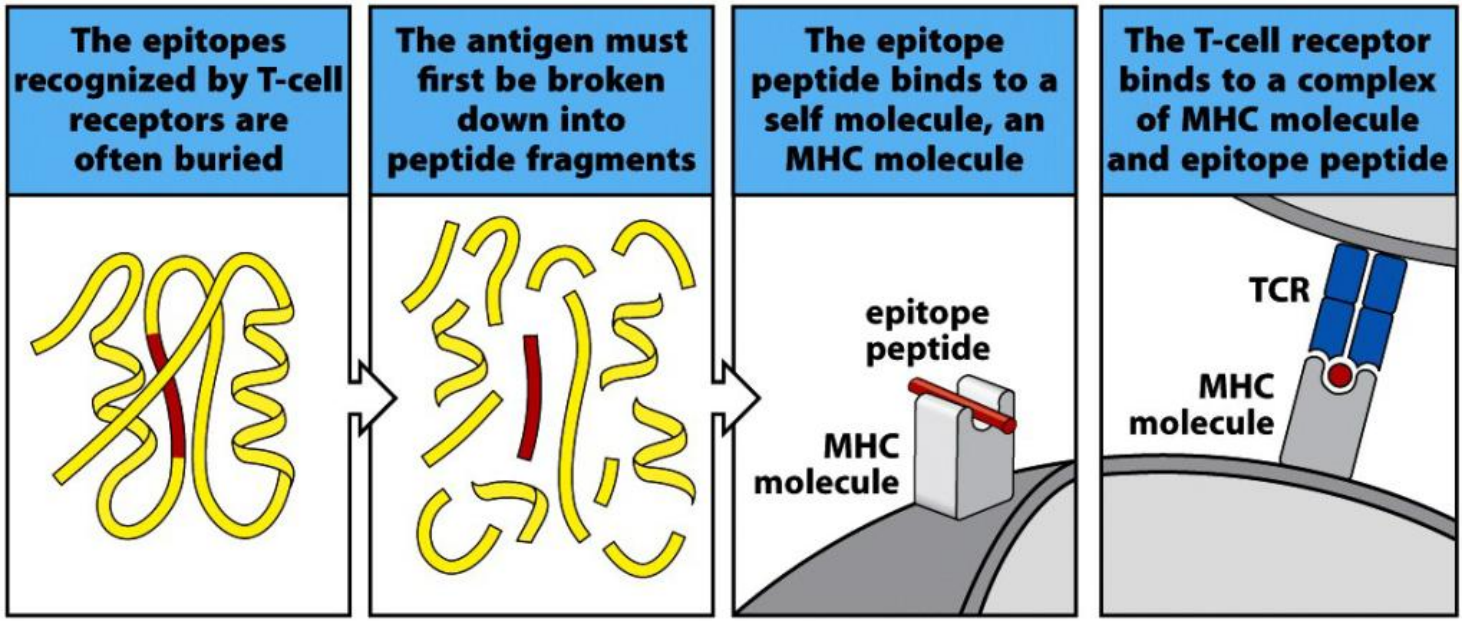


Fig. 1.17 Circulating lymphocytes encounter antigen in peripheral lymphoid organs

- Naïve vs. effector lymphocytes
  - Naïve (lymphocytes that are mature, but have not yet encountered antigens)
- Naïve lymphocytes constantly circulate between blood and lymph.
- Antigens are transported from the infected peripheral tissue to draining lymph node where they are 'captured' by lymphocytes.

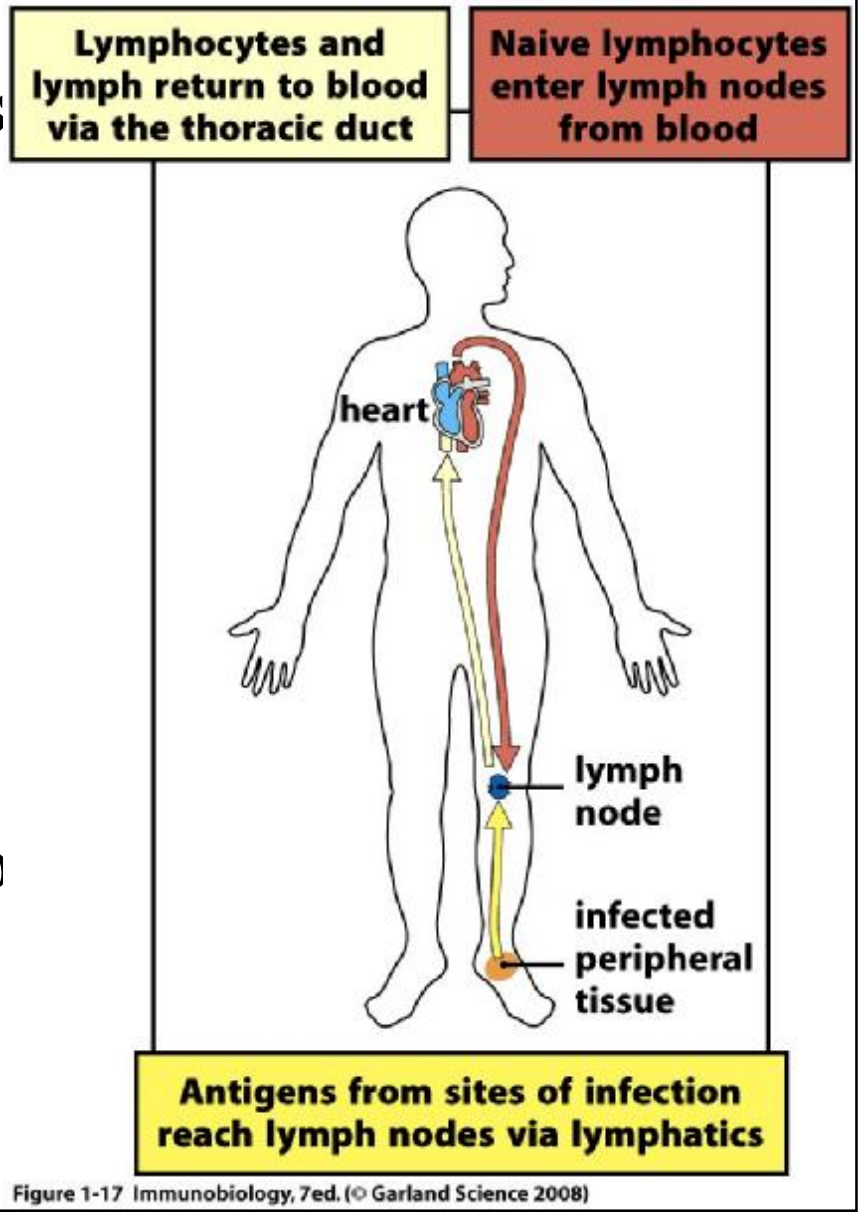
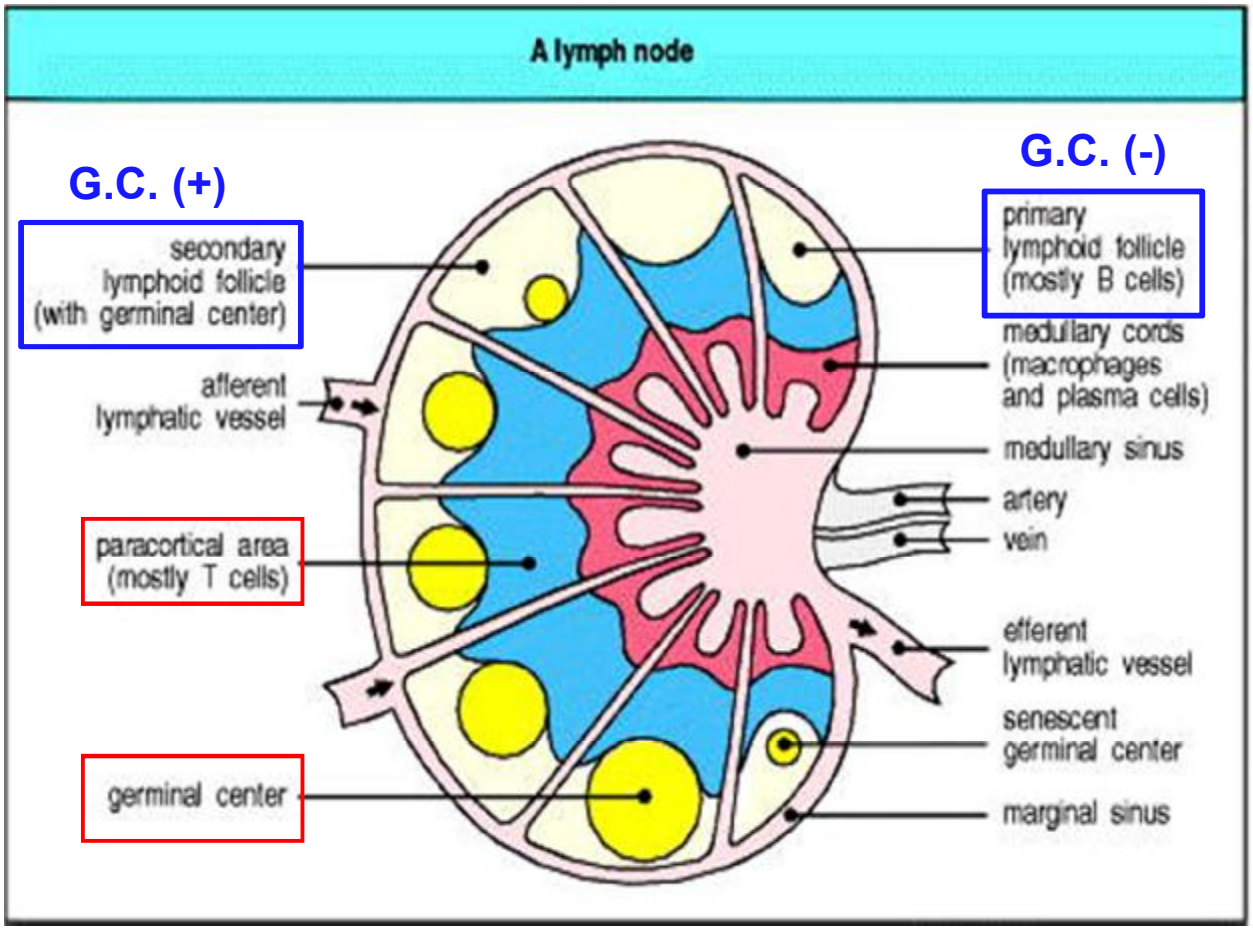
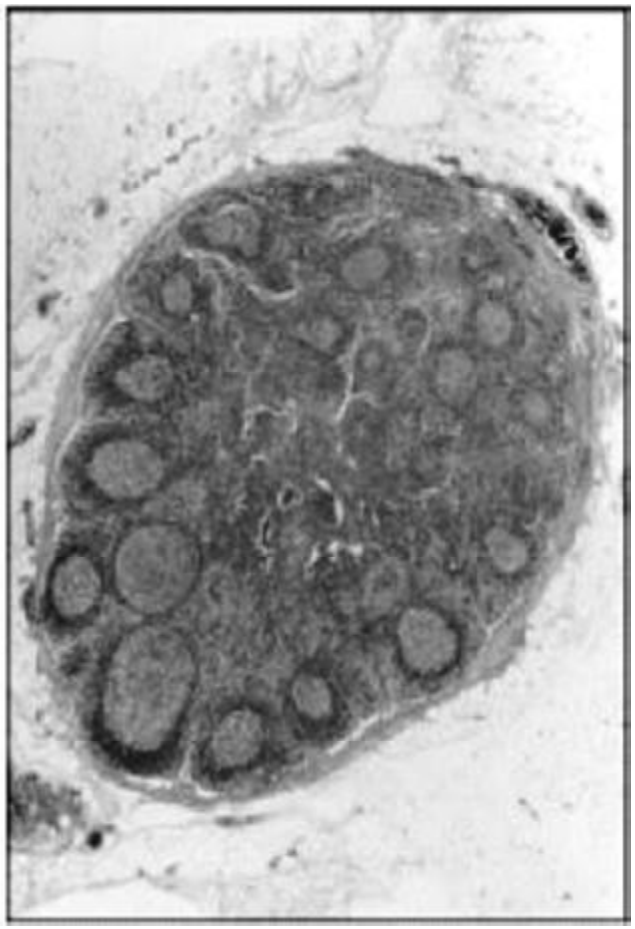


Figure 1-17 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.18
Organization of a lymph node





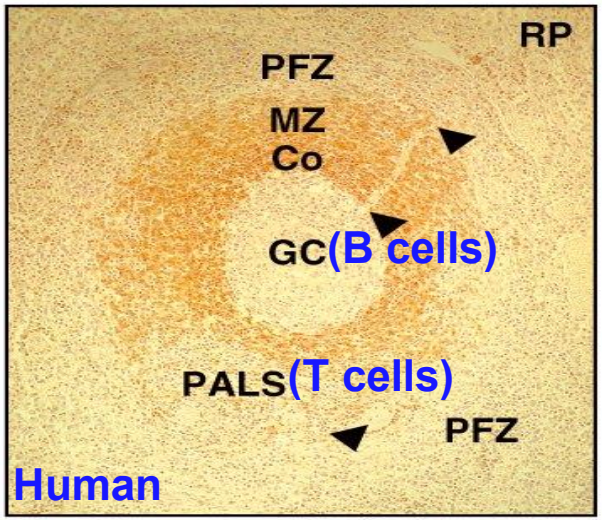
Lymph: continuous filtered extracellular fluid from blood
Follicle: glandular cavity of lymph node where B cells gather and proliferate
Germinal center: dark zone (proliferating B cells) v.s. light zone (mostly FDCs)

Fig. 1.19
Organization of splenic lymphoid tissues

PALS: periarteriolar lymphoid sheath (made up by T cells)

Ag enters the spleen via the **blood**, rather than the lymph!!

Red pulp → RBC destruction



(no marginal sinus!)
(MZ surrounds GC only, but not PALS)

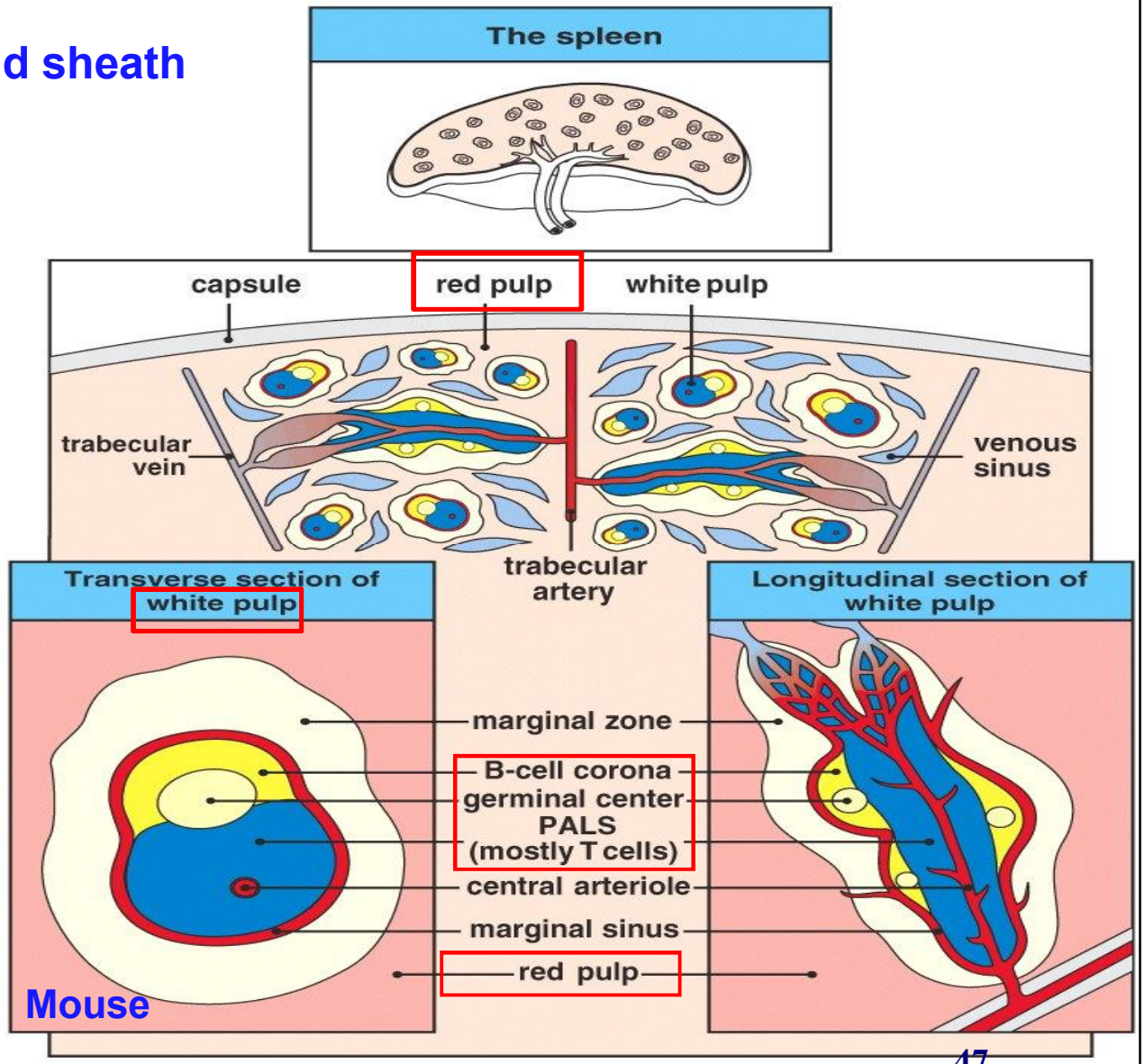


Fig. 1.20 Organization of a typical gut-associated lymphoid tissue

- Gut-associated lymphoid tissue (GALT)
  - Tonsil, adenoids, appendix, Peyer's patches
- Bronchial-associated lymphoid tissue (BALT)
- Mucosal-associated lymphoid tissue (MALT)

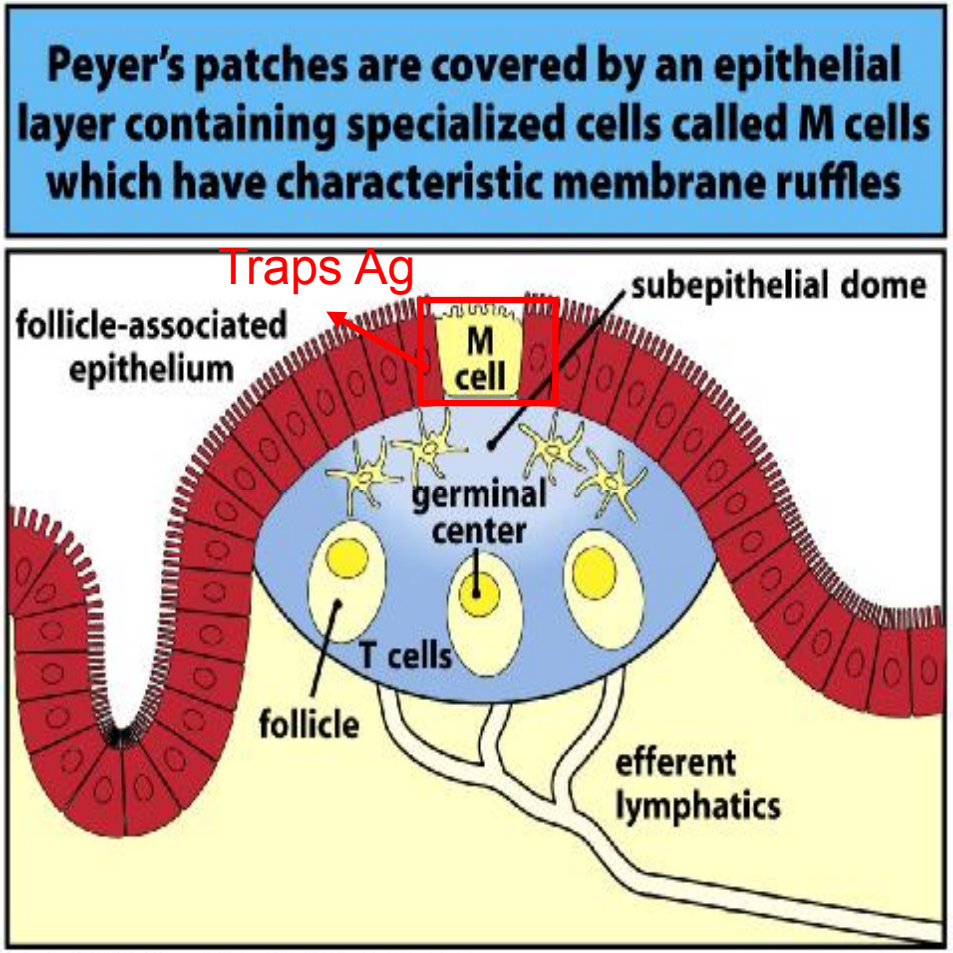


Figure 1-20 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.21 Two signals are required for lymphocyte activation

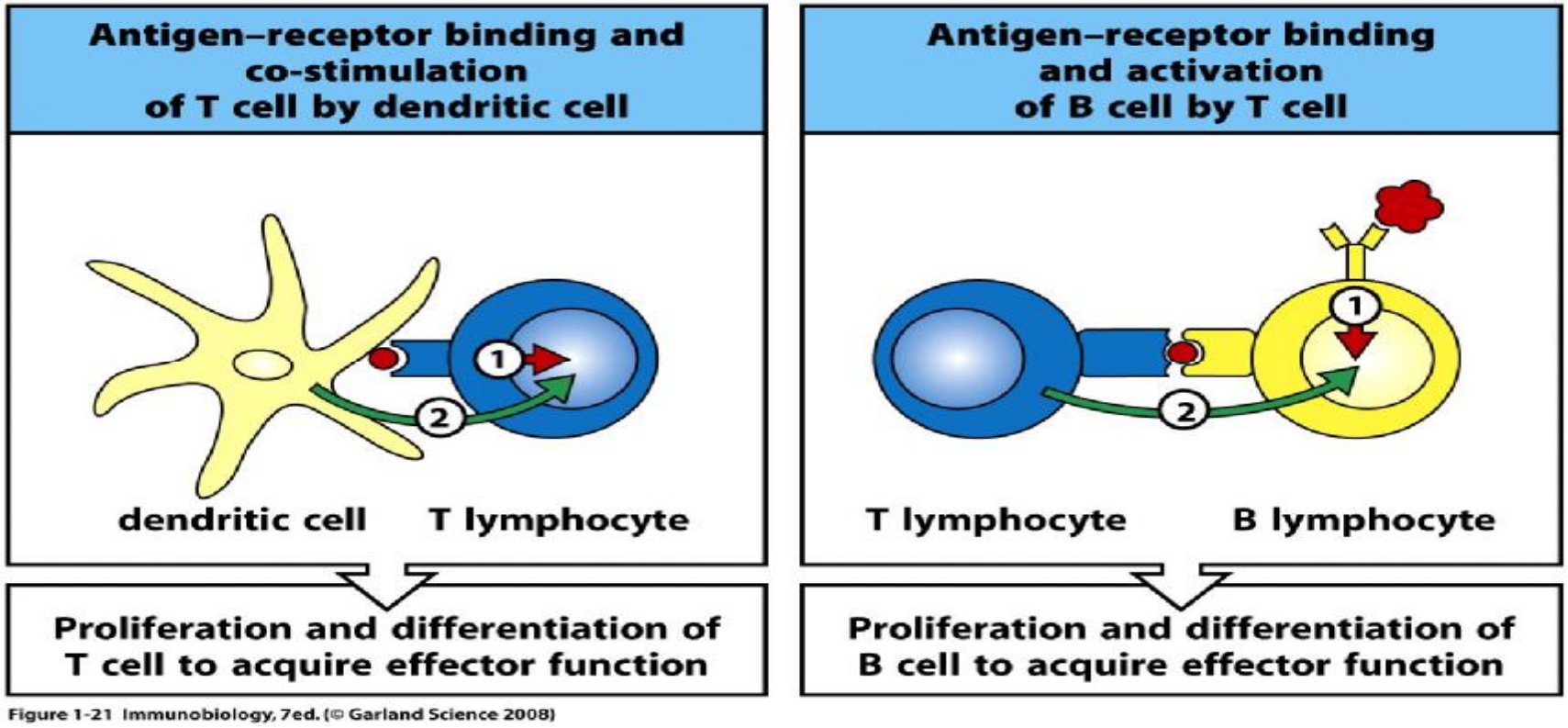


Figure 1-21 Immunobiology, 7ed. (© Garland Science 2008)

- Two-signal model for lymphocyte activation
  1. Ag binding to receptor
  2. Co-stimulatory signal
     - T cell (from dendritic cell); B cell (from T cell)

Fig. 1.22 Antigen-presenting cells

- The professional antigen-presenting cells (APCs)
  - Dendritic cells
  - Macrophages
  - B cells

DCs are the most potent among all APCs!!

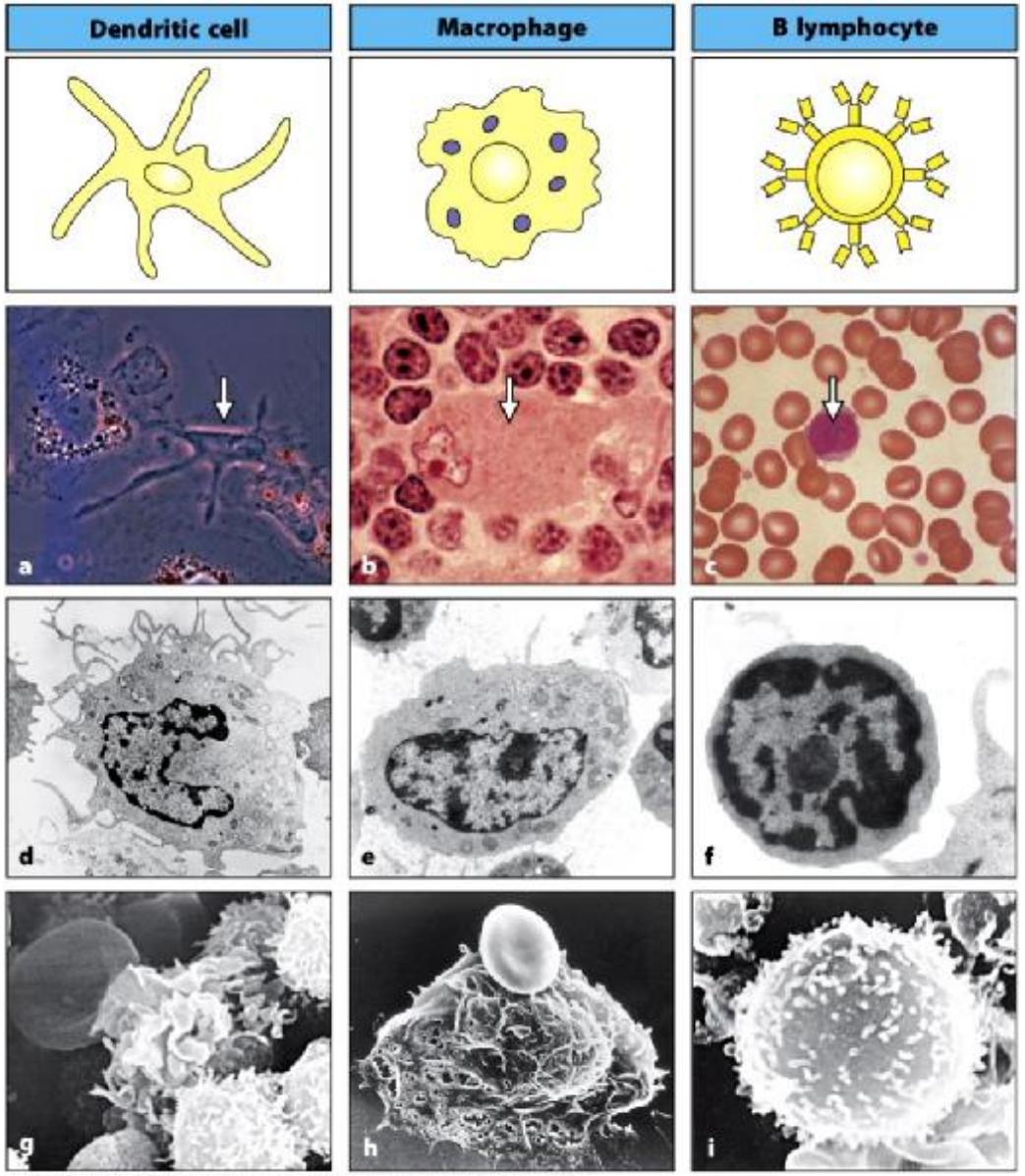


Figure 1-22 Immunobiology, 7ed. (© Garland Science 2008)

Activation of B & T cells

- Resting (Naïve) → lymphoblast → effector
- Activation of lymphocytes into effector cells.
  - High cytoplasm/nucleus ratio
  - Presence of abundant RER (protein synthesis)
    - → Ab production
  - Abundant mitochondria

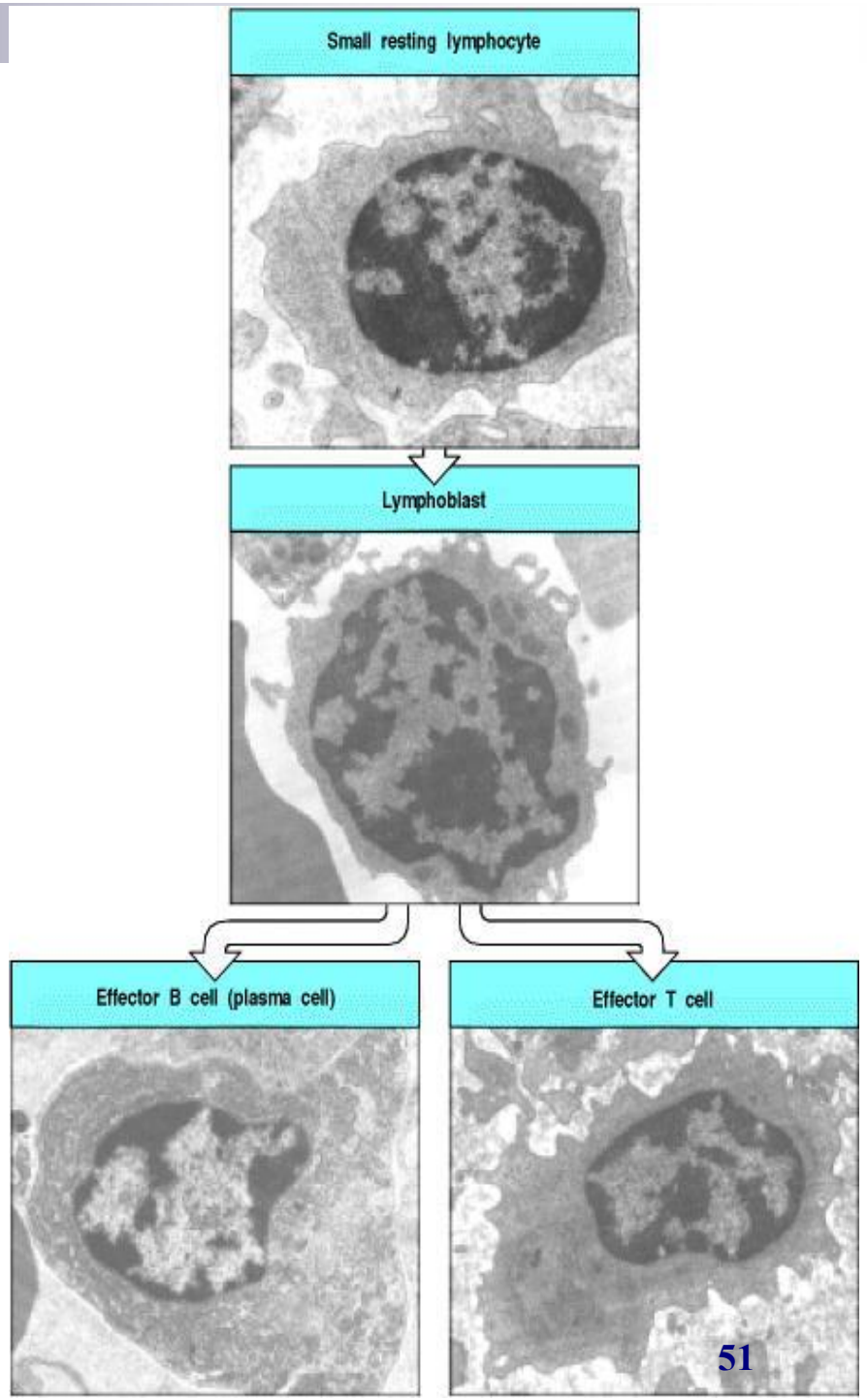


Fig. 1.23 The course of a typical antibody response

- Primary vs secondary Ab responses
  - Lag phase (long vs short)
  - Ab titer (low vs high)
  - Ab affinity (low vs high)
  - Ab plateau time (short vs long)
- Immunological memory is Ag-specific

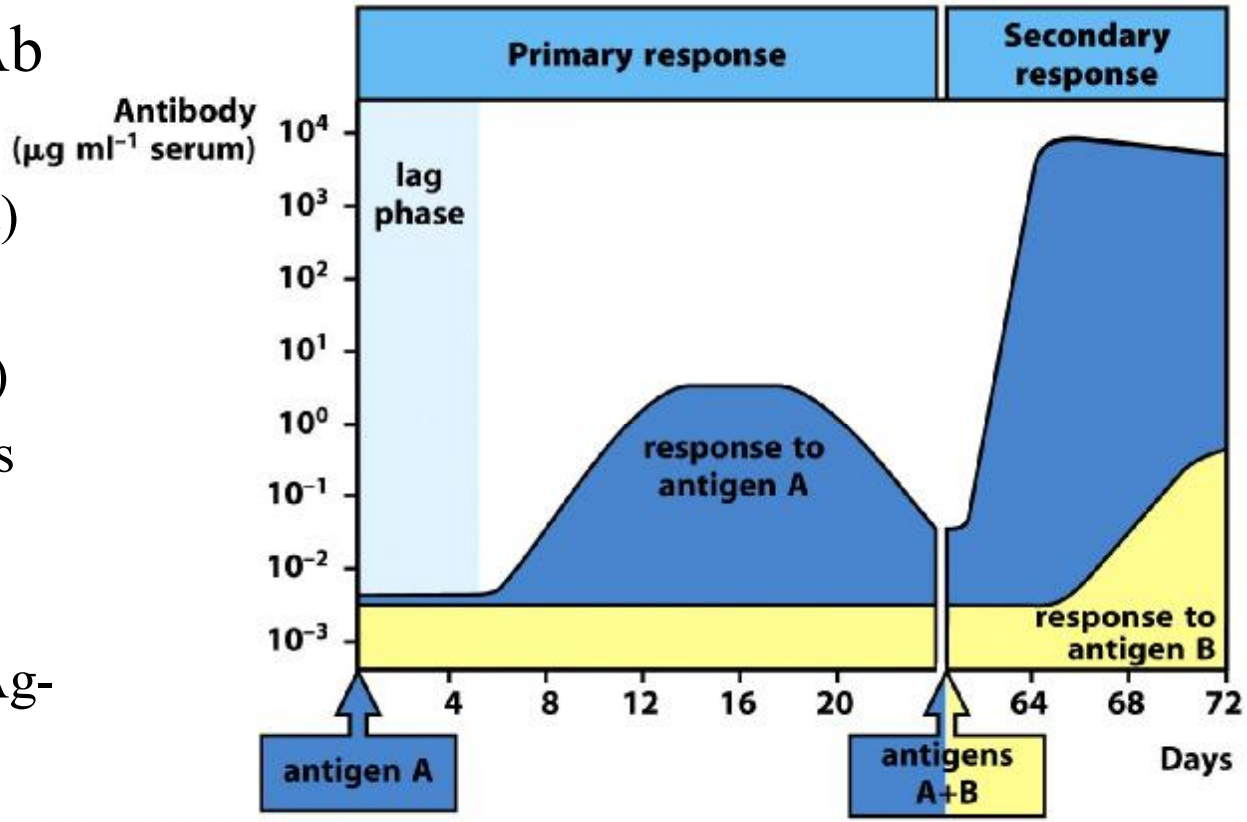


Figure 1-24 Immunobiology, 7ed. (© Garland Science 2008)

The recognition and effector mechanisms of adaptive immunity

Fig. 1.24 The major pathogen types confronting the immune system and some of the diseases that they cause.

The immune system protects against four classes of pathogens		
Type of pathogen	**Examples**	**Diseases**
Extracellular bacteria, parasites, fungi	*Streptococcus pneumoniae* *Clostridium tetani* *Trypanosoma brucei* *Pneumocystis carinii*	Pneumonia Tetanus Sleeping sickness *Pneumocystis* pneumonia
Intracellular bacteria, parasites	*Mycobacterium leprae* *Leishmania donovani* *Plasmodium falciparum*	Leprosy Leishmaniasis Malaria
Viruses (intracellular)	Variola Influenza Varicella	Smallpox Flu Chickenpox
Parasitic worms (extracellular)	*Ascaris* *Schistosoma*	Ascariasis Schistosomiasis

Figure 1-25 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.25 Participation of antibodies in body defense

- Neutralization (中和)
- Opsonization (調理)
- Complement activation (補體活化)

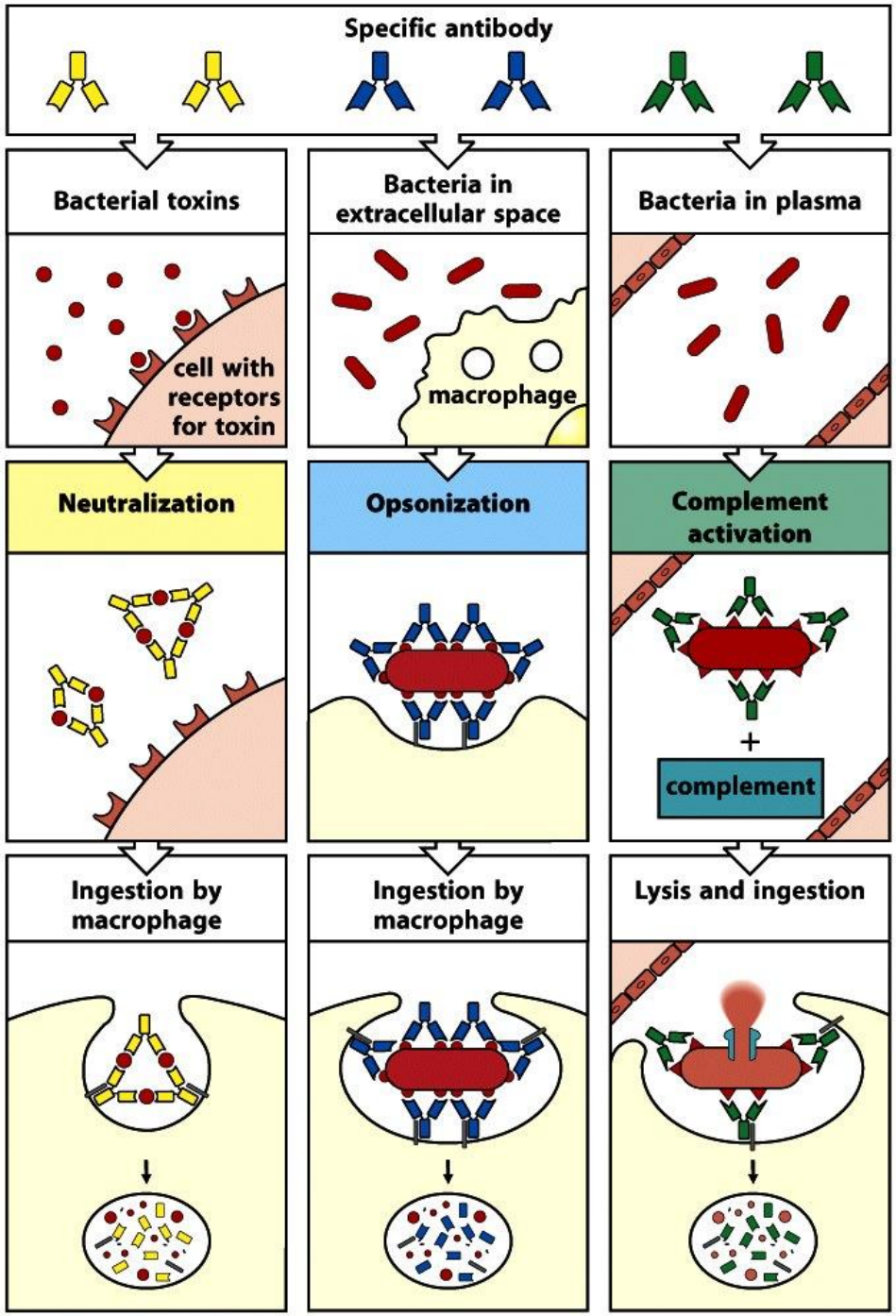


Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.26 Mechanism of host defense against intracellular infection by viruses

- How does our body control intracellular pathogen?
  - Virally-infected cells express viral antigens on their cell surface
  - Cytotoxic T cells (CTLs) execute the killing of infected cells

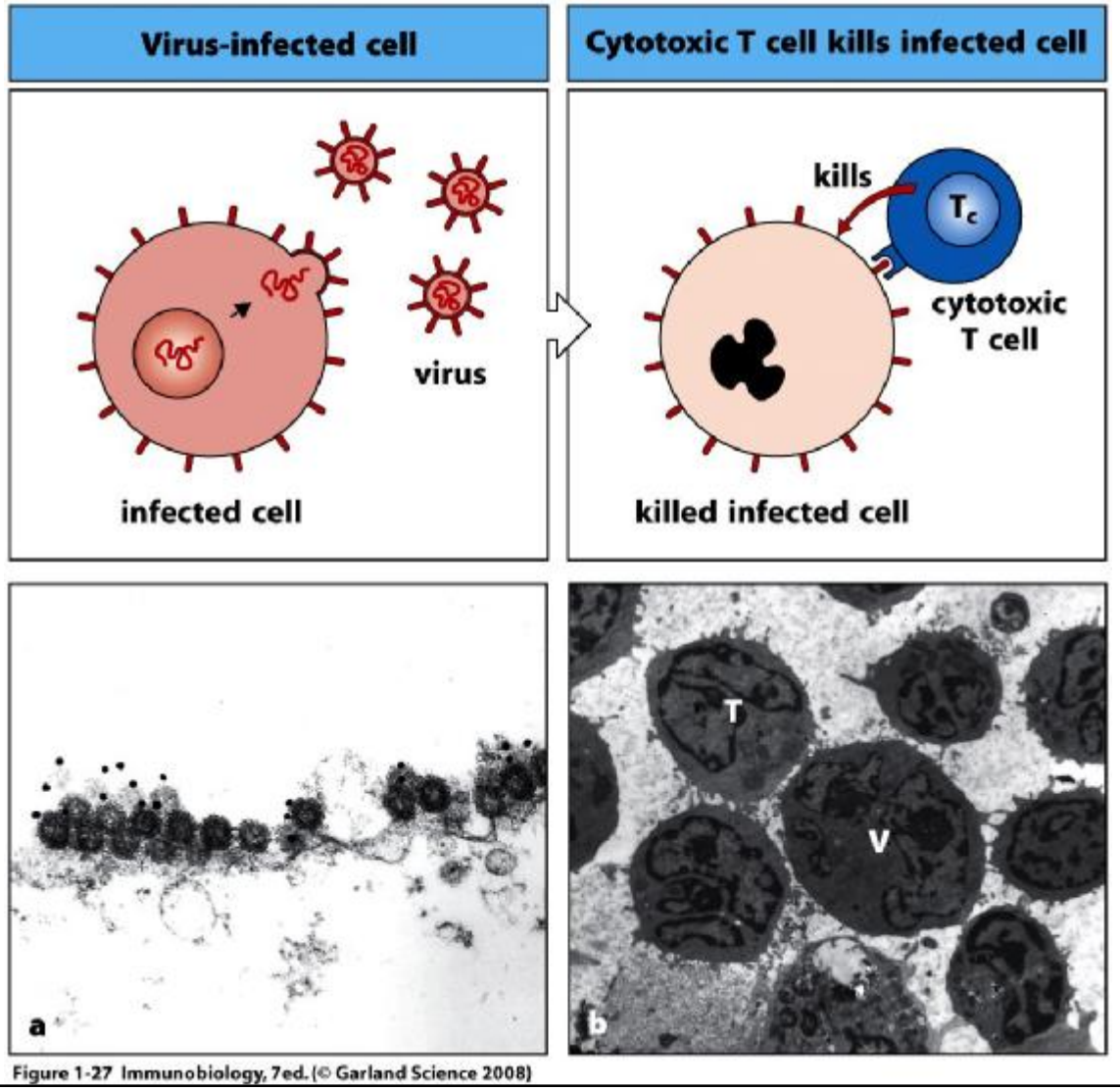


Figure 1-27 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.27 Mechanism of host defense against intracellular infection by mycobacteria

- How does our body control the infection by mycobacteria?
  - T cells
    - CD4+ (helper T, T_H)
      - T_{H1}
      - T_{H2}
    - CD8+ (cytotoxic T, CTL or T_C)
  - T_{H1} promotes the activation of macrophages
  - Fusion of phagosome and lysosome helps the destruction of contained mycobacteria

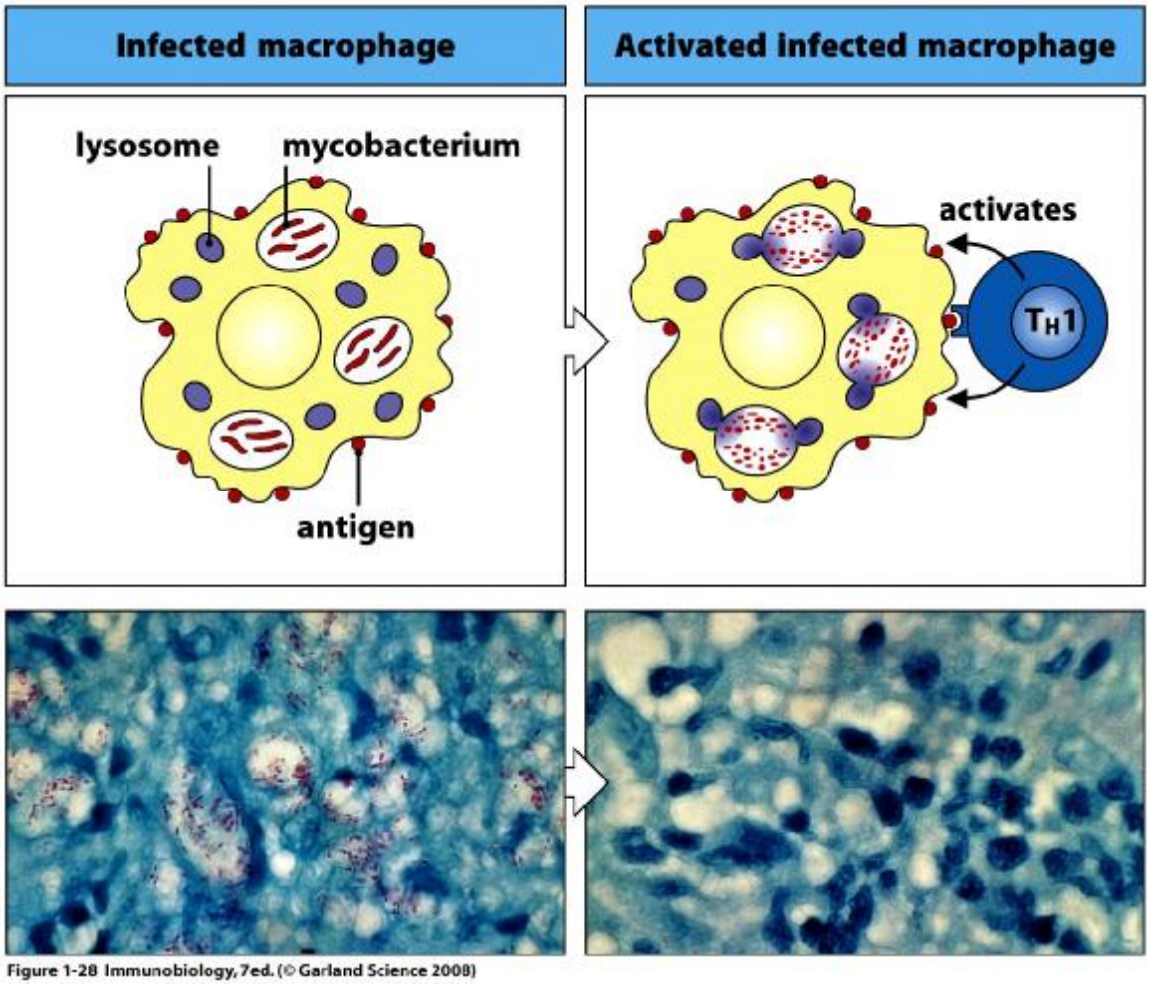


Figure 1-28 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.28 MHC molecules on the cell surface display peptide fragments of antigens

- T cells can **only** recognize foreign Ag as peptide fragment through the help of two different MHC molecules
  - Intracellular Ag → MHC class I
    - Recognized by CD8+ T cells
  - Extracellular Ag → MHC class II
    - Recognized by CD4+ T cells

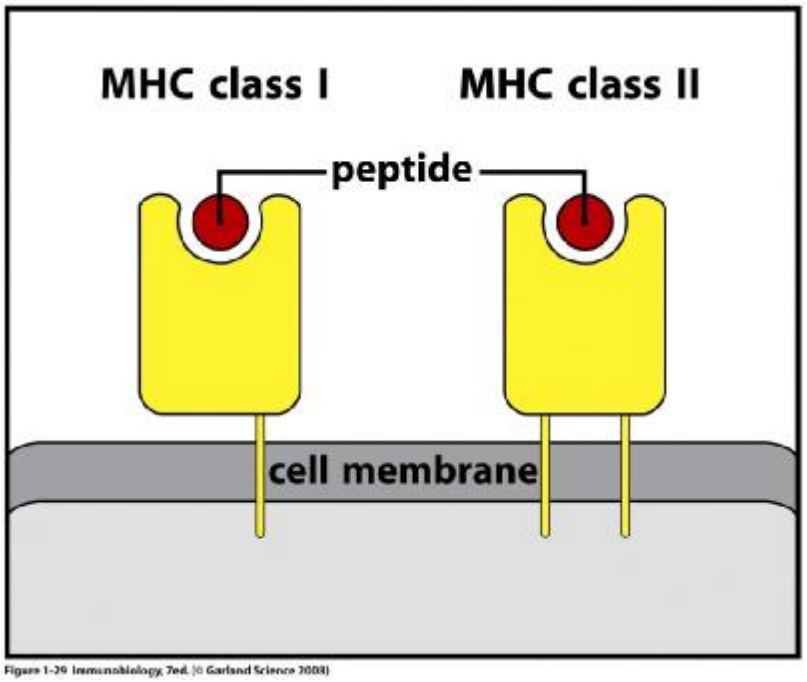


Fig. 1.29 MHC class I molecules present antigen derived from proteins in the *cytosol* (from E.R.)

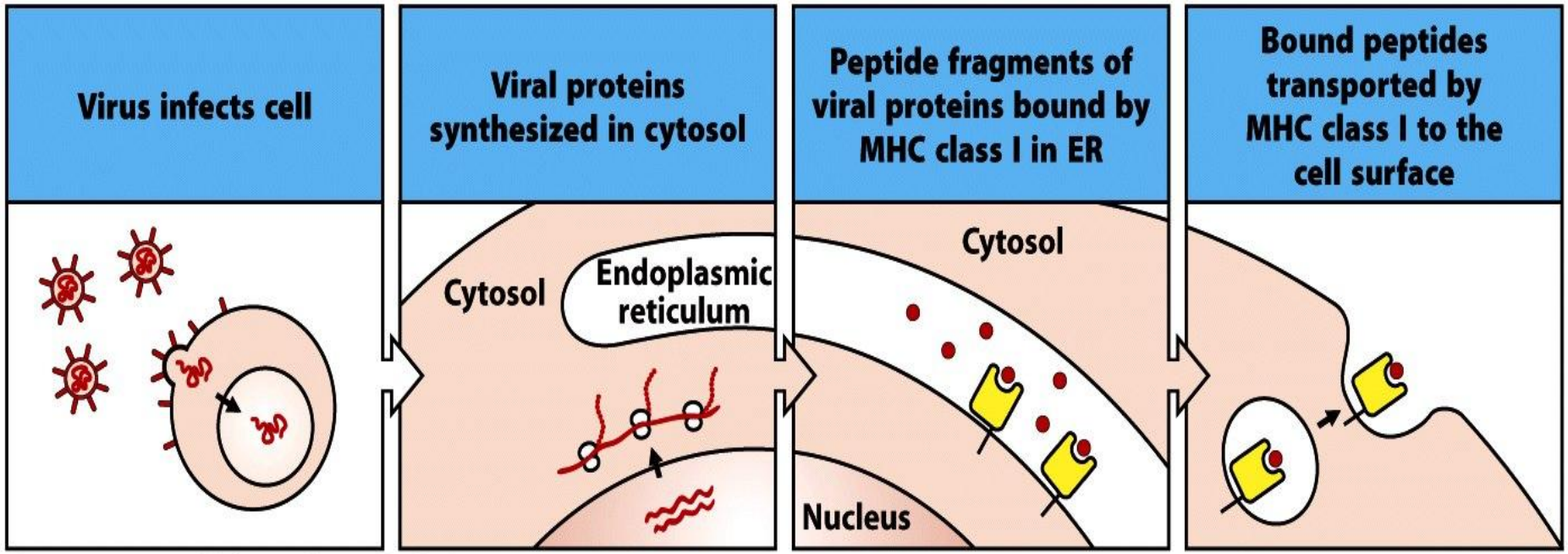


Figure 1-30 Immunobiology, 7ed. (© Garland Science 2008)

See also Fig. 1-27

MHC class II molecules present antigen originating in *intracellular vesicles*

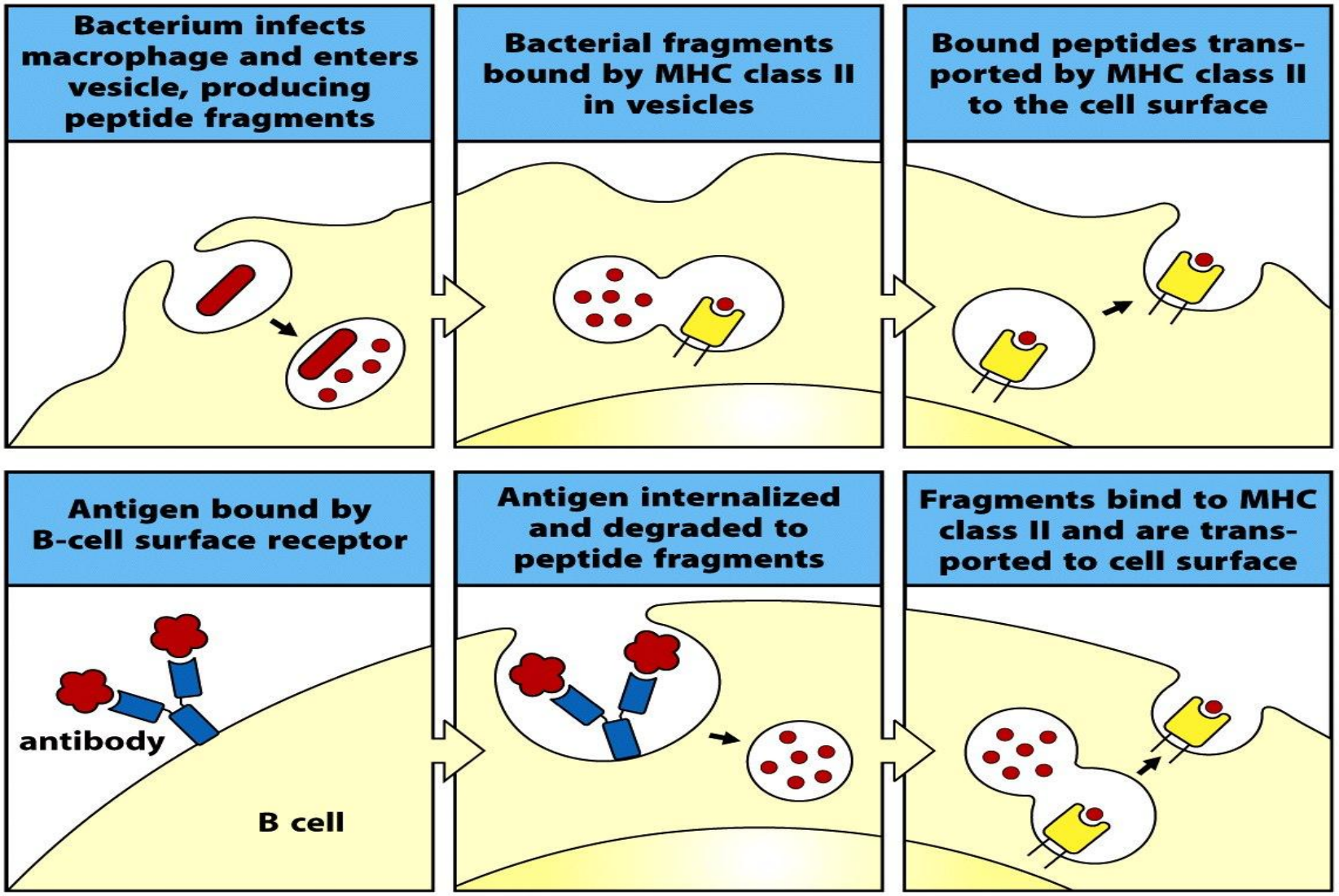


Figure 1-31 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.30 Cytotoxic T cells recognize antigen presented by MHC class I molecules and kill the cell

- Cytotoxic T cells
  - Recognizes Ag peptide complexed with MHC class I
  - $CD8^+$ T cells

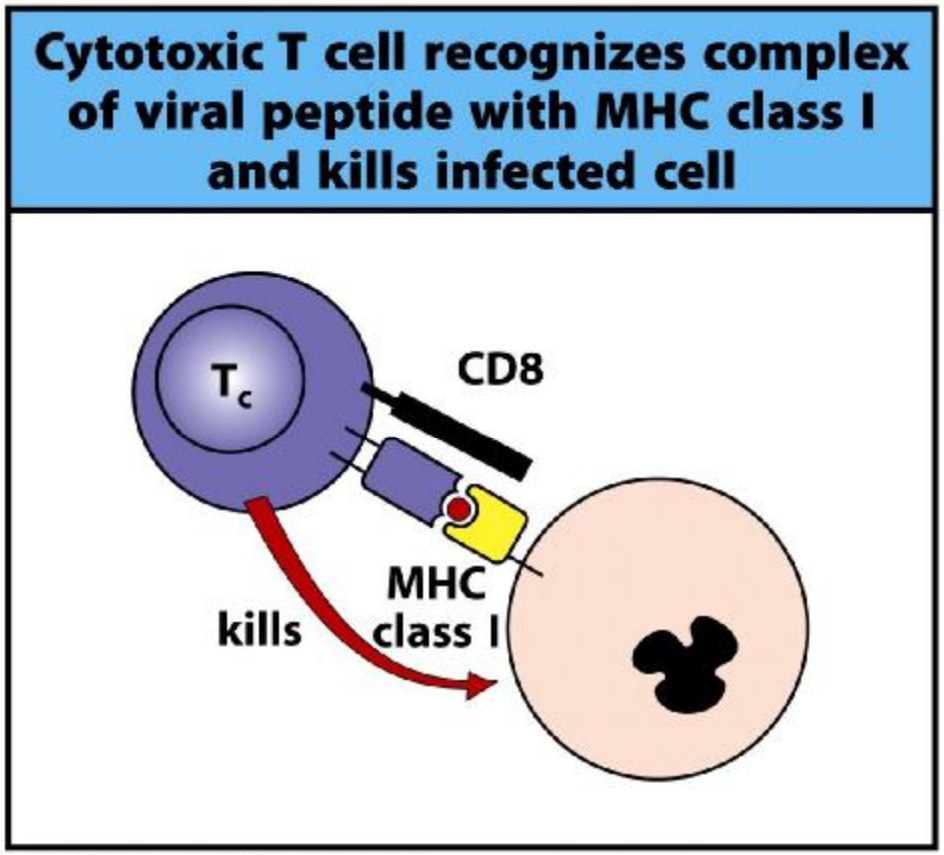


Figure 1-32 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.31 TH1 and helper T cells recognize antigen presented by MHC class II molecules

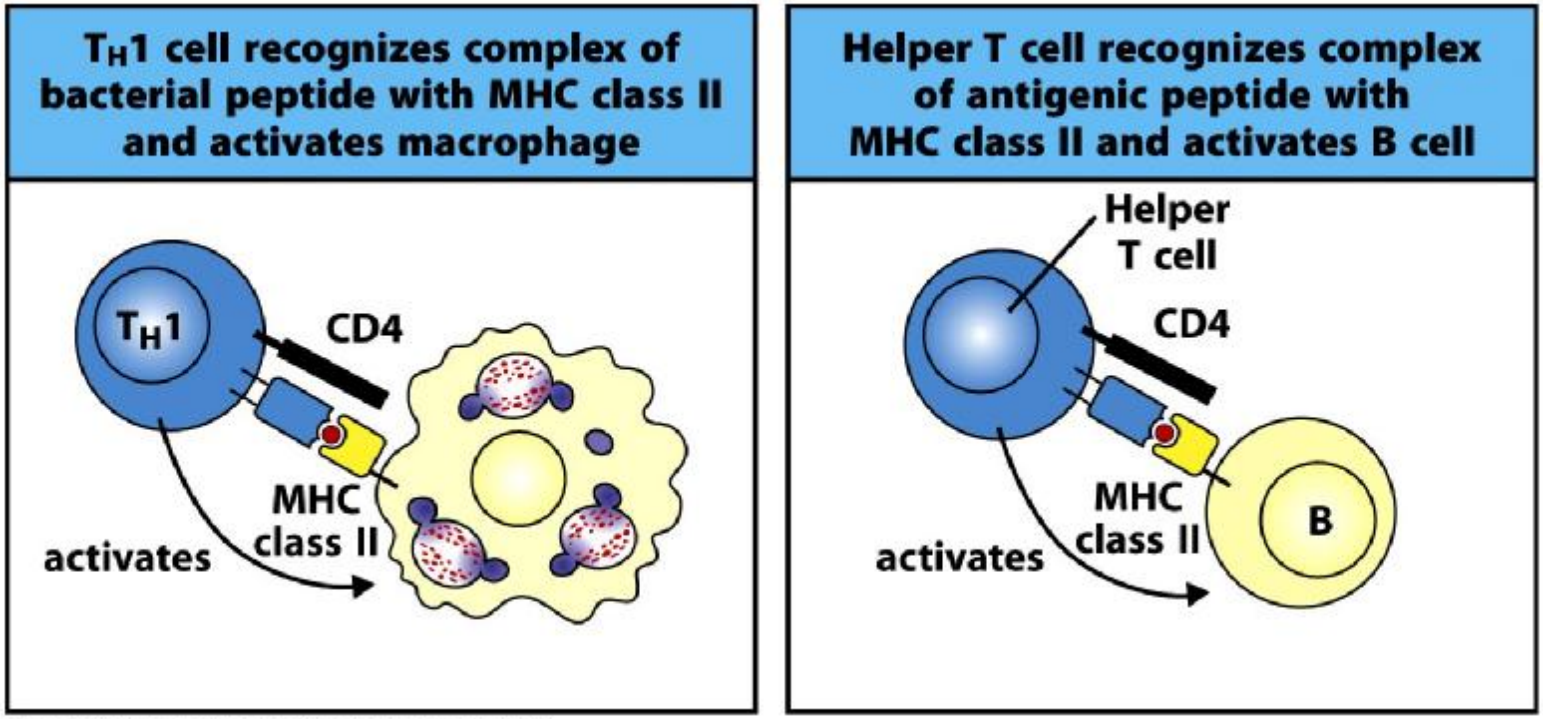


Figure 1-33 Immunobiology, 7ed. (© Garland Science 2008)

- T helper cells
  - Recognizes Ag peptide complexed with MHC class II
  - $CD4^+$ T cells
    - Th1 and Th2 cells

Fig. 1.32 Immune responses can be beneficial or harmful depending on the nature of the antigen

Beneficial or harmful outcomes of various immune responses

Antigen	Effect of response to antigen	
	Normal response	Deficient response
Infectious agent	Protective immunity	Recurrent infection
Innocuous substance	Allergy	No response
Grafted organ	Rejection	Acceptance
Self organ	Autoimmunity	Self tolerance
Tumor	Tumor immunity	Cancer

Figure 1-34 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.33 Successful vaccination campaigns

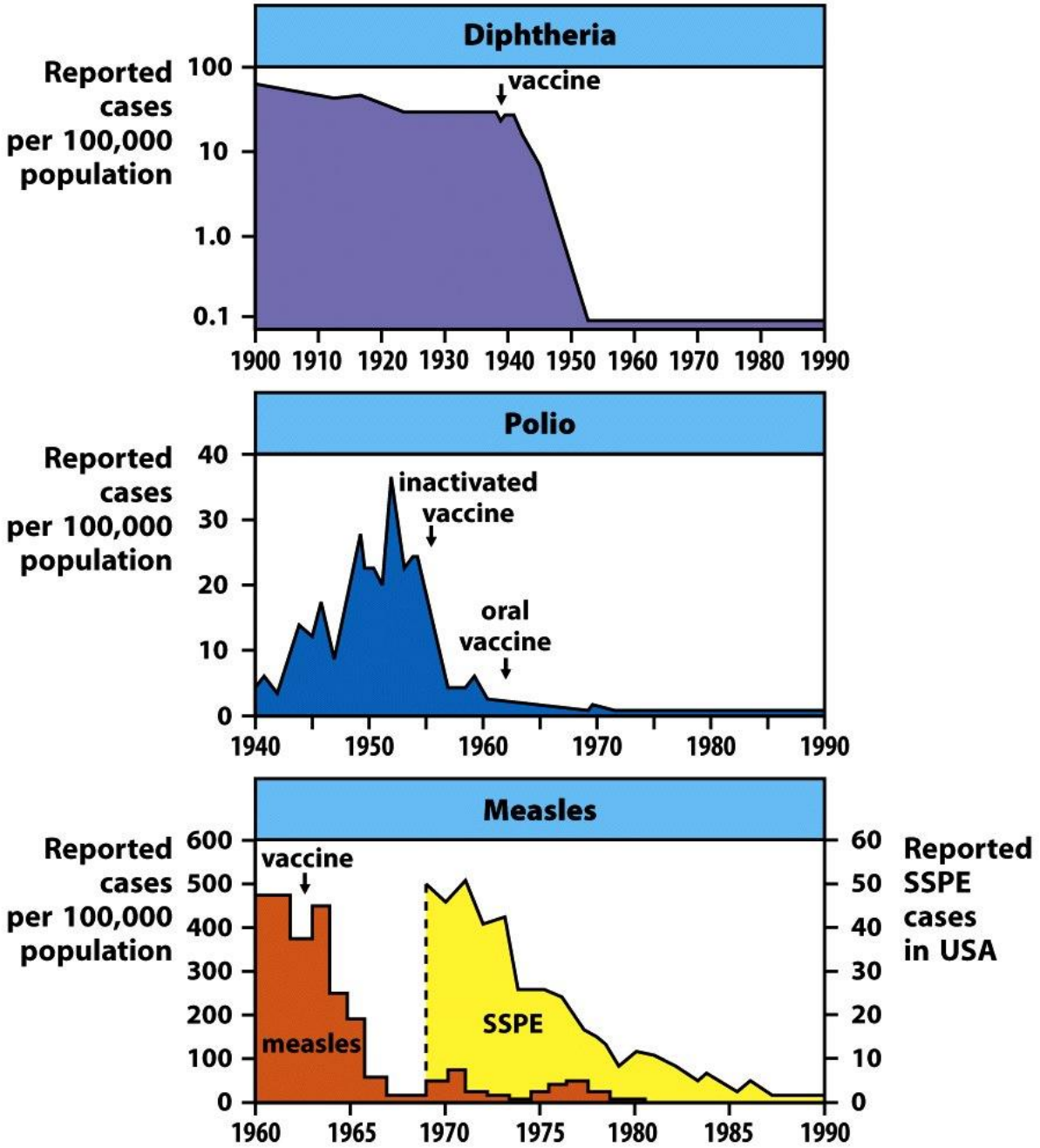


Figure 1-35 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 1.34 Phases of the immune response

Phases of the immune response			
Response		**Typical time after infection to start of response**	**Duration of response**
Innate immune response	Inflammation, complement activation, phagocytosis and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Effector cells and antibodies eliminate the pathogen	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Figure 1.34 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Summary

- The immune system helps the host defend against infections.
- The immune systems is composed of innate and adaptive systems, both hosting different protective functions, yet cooperating with each other.
- Host defense requires different recognition systems and a wide variety of effector mechanisms to seek out and destroy various external/internal pathogens.

End of Chapter