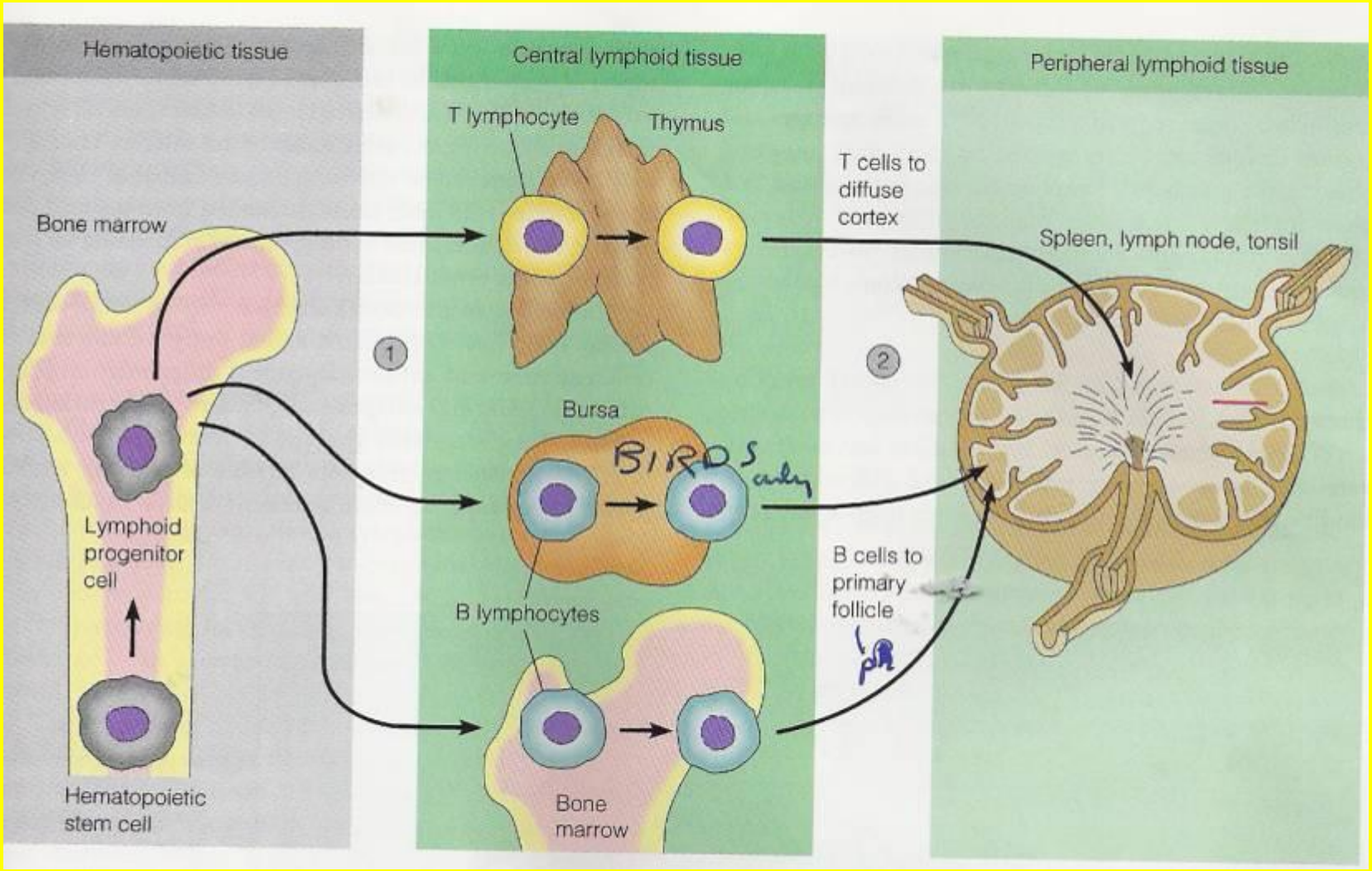
CELLS, TISSUES & ORGANS OF IMMUNE SYSTEM

THE LYMPHATIC SYSTEM

Where Are T Cells And B Cell Made?



Maturation of the immune response

- **Lymphoid organs are separated into primary and secondary organs**
  - **Primary--> bone marrow, thymus**
  - **Secondary or peripheral--> lymphnodes, spleen, mucosal lymphoid tissues (GALT, MALT), provide sites for mature lymphocytes to interact with antigen**

Different organs of the immune system

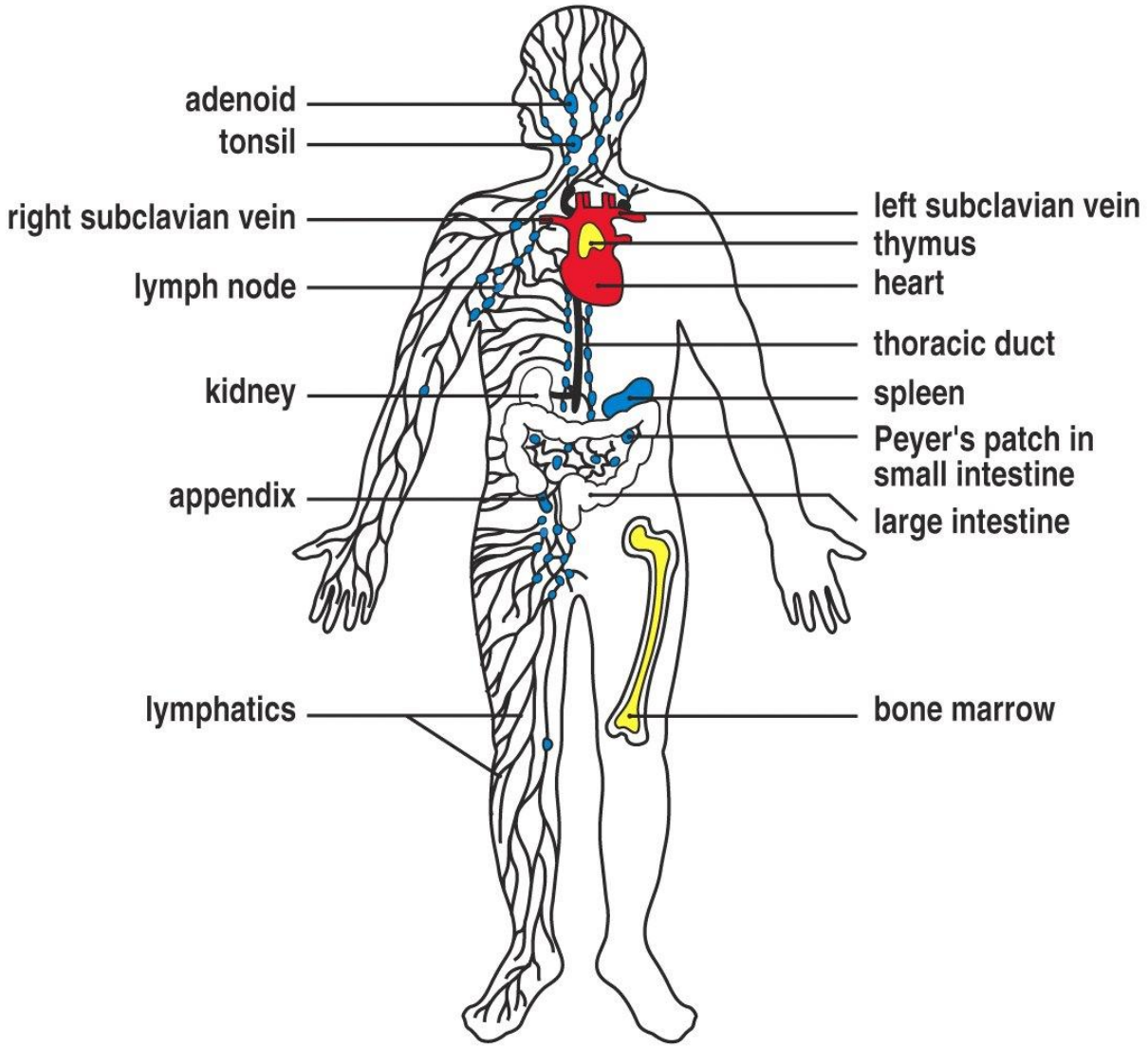


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

The role of bone marrow in immune maturation

- **Microenvironment for differentiation of stem cells**
- **Site of origin of B and T lymphocytes, all other cells of the immune response**
- **“Antigen-independent” maturation of B cells.**
- **Site for mature re-circulating lymphocyte populations**

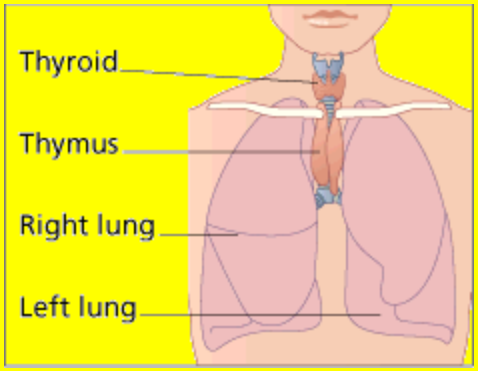
Bone Marrow

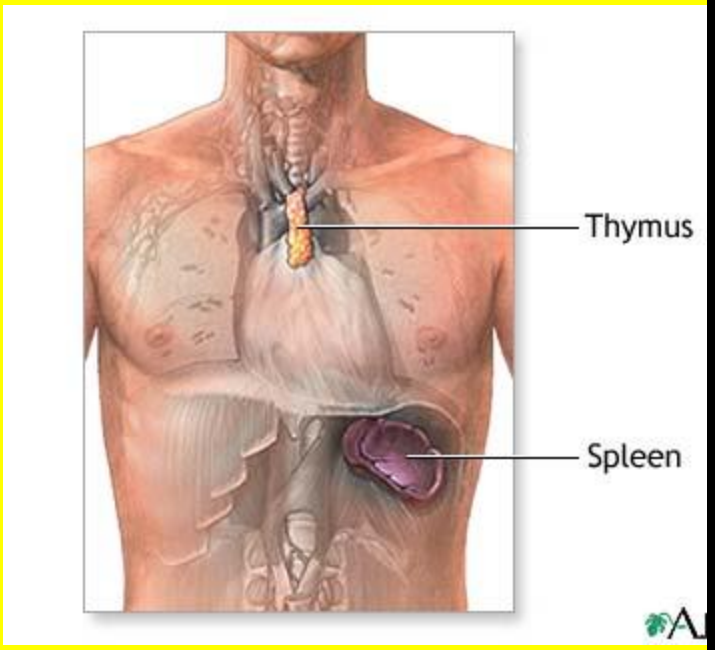
- **Cells move out of Bone Marrow into blood**
- **The bursa in the bird plays the same role for B cell maturation; appendix in rabbit**

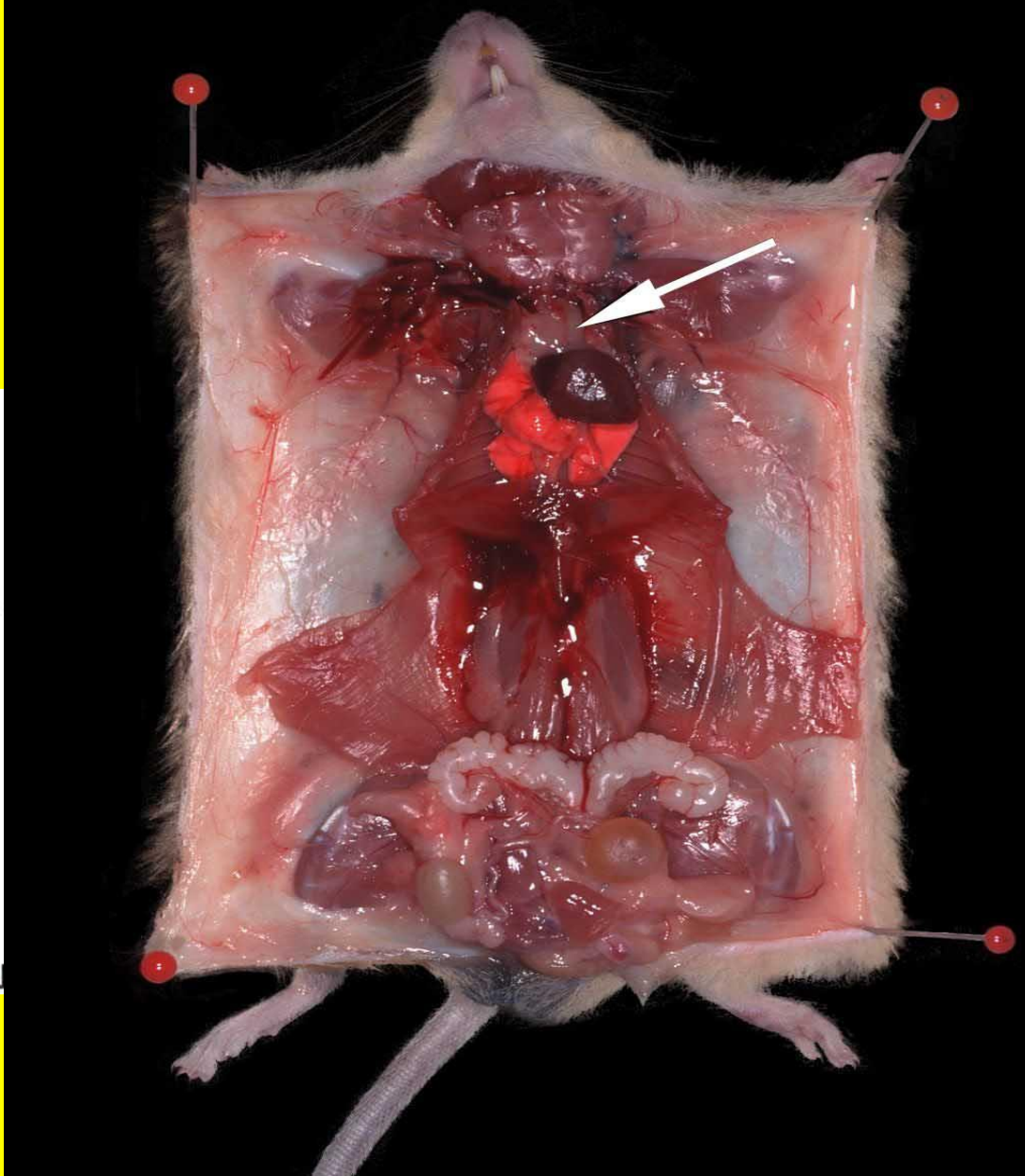
Thymus

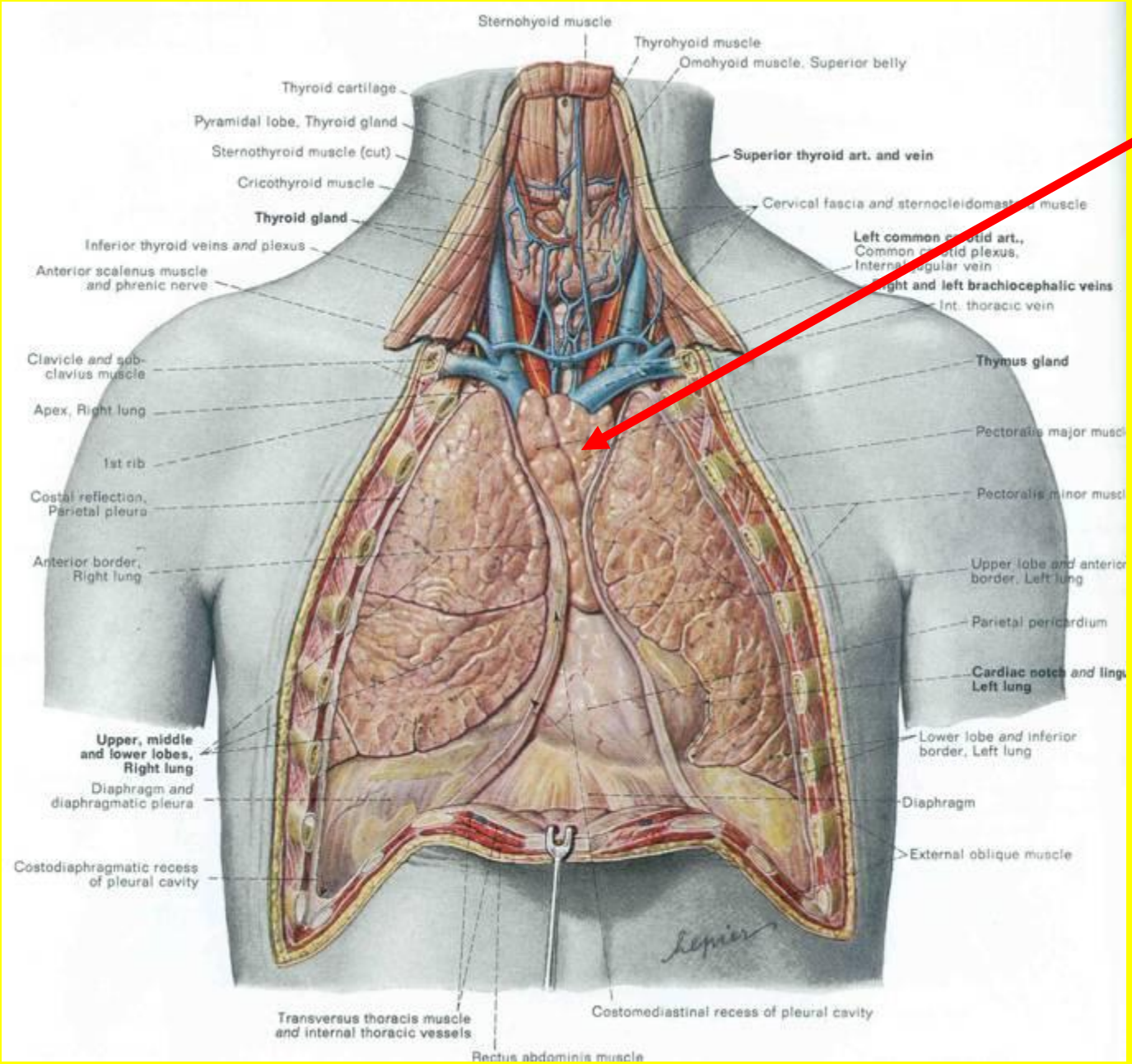
- The thymus is a bi-lobed organ above the heart
- Each lobe is surrounded by a capsule and divided into lobules which are seperated from each other via connective tissue called trabeculae
- Each lobe is organized into 2 compartments
- The outer component is the cortex (packed with immature T cells)
- The inner component is the medulla (sparsely populated with more mature thymocytes)
- Criss-crossing the entire organ is a stromal network of epithelial cells, DCs and macrophages
- These cells participate in positive and negative selection of T cells
- Over 95% of the T cells that enter the thymus die by apoptosis within the thymus without reaching maturity
- The thymus involutes with age

Thymus Location

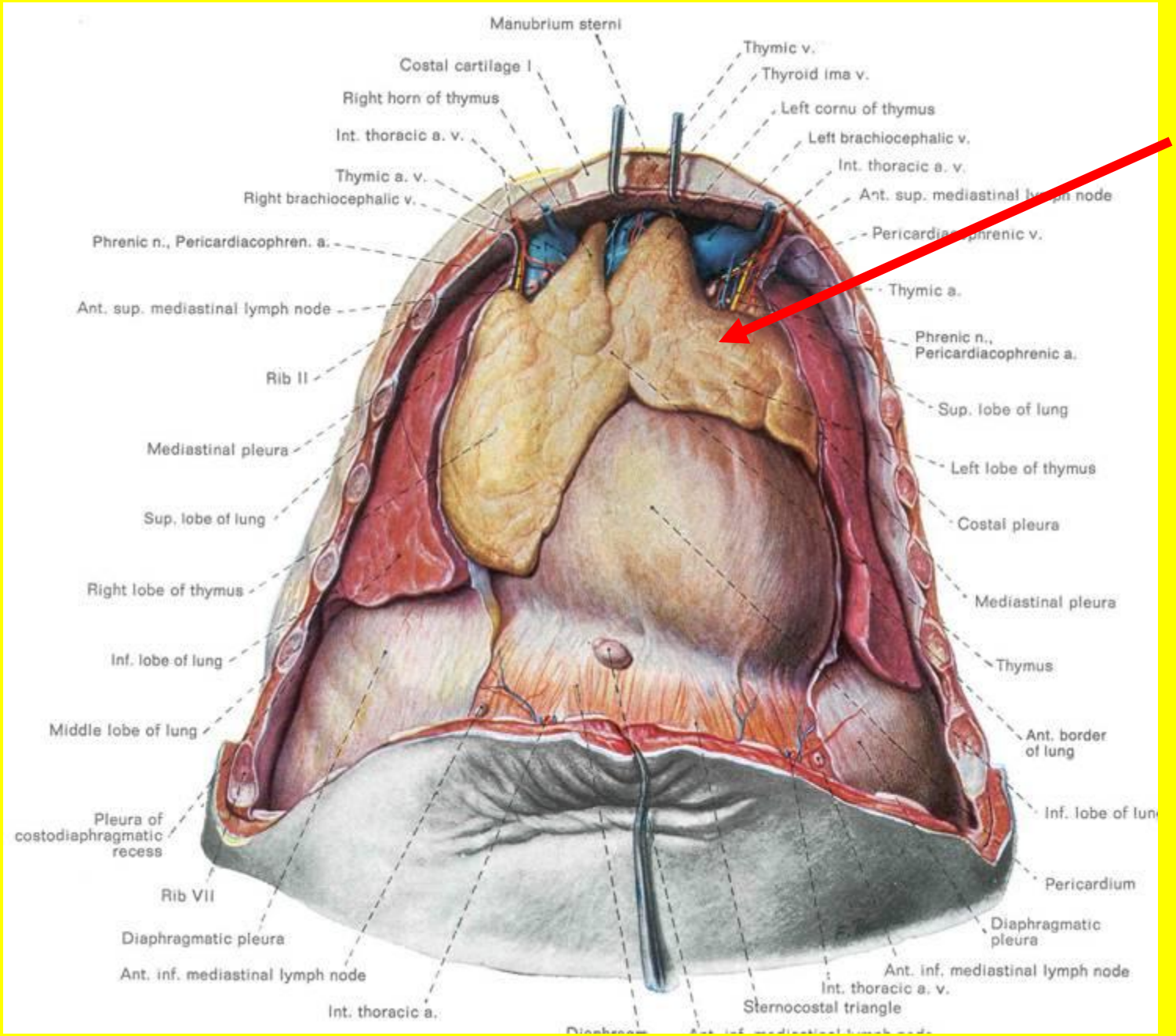








Adult
THYMUS



One-year old THYMUS

The Thymus

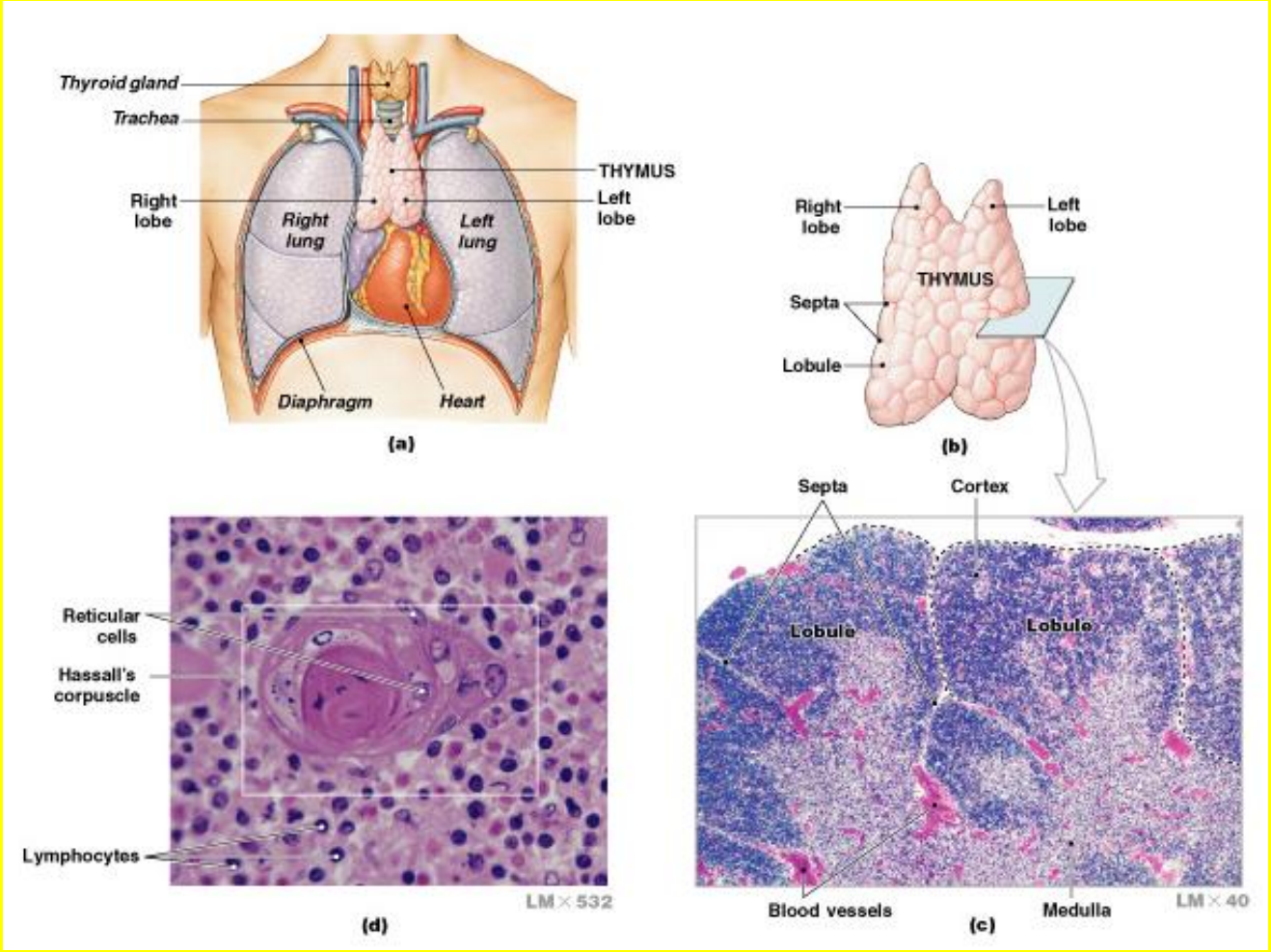
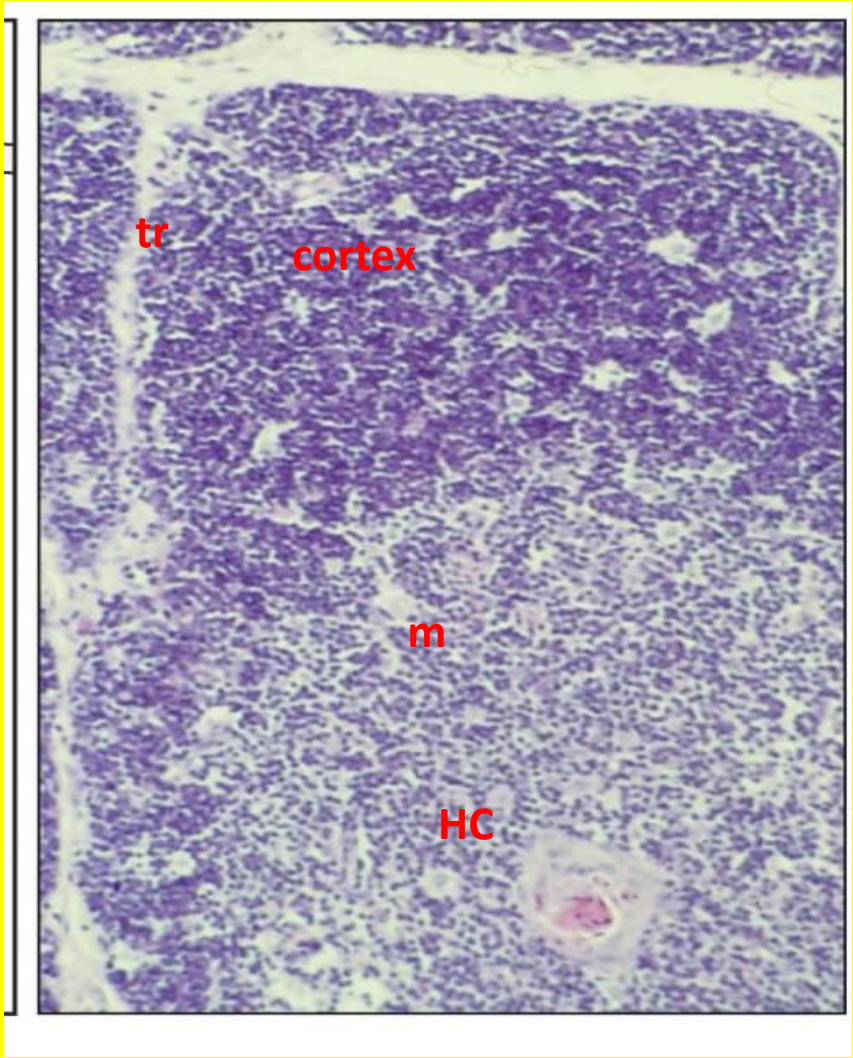
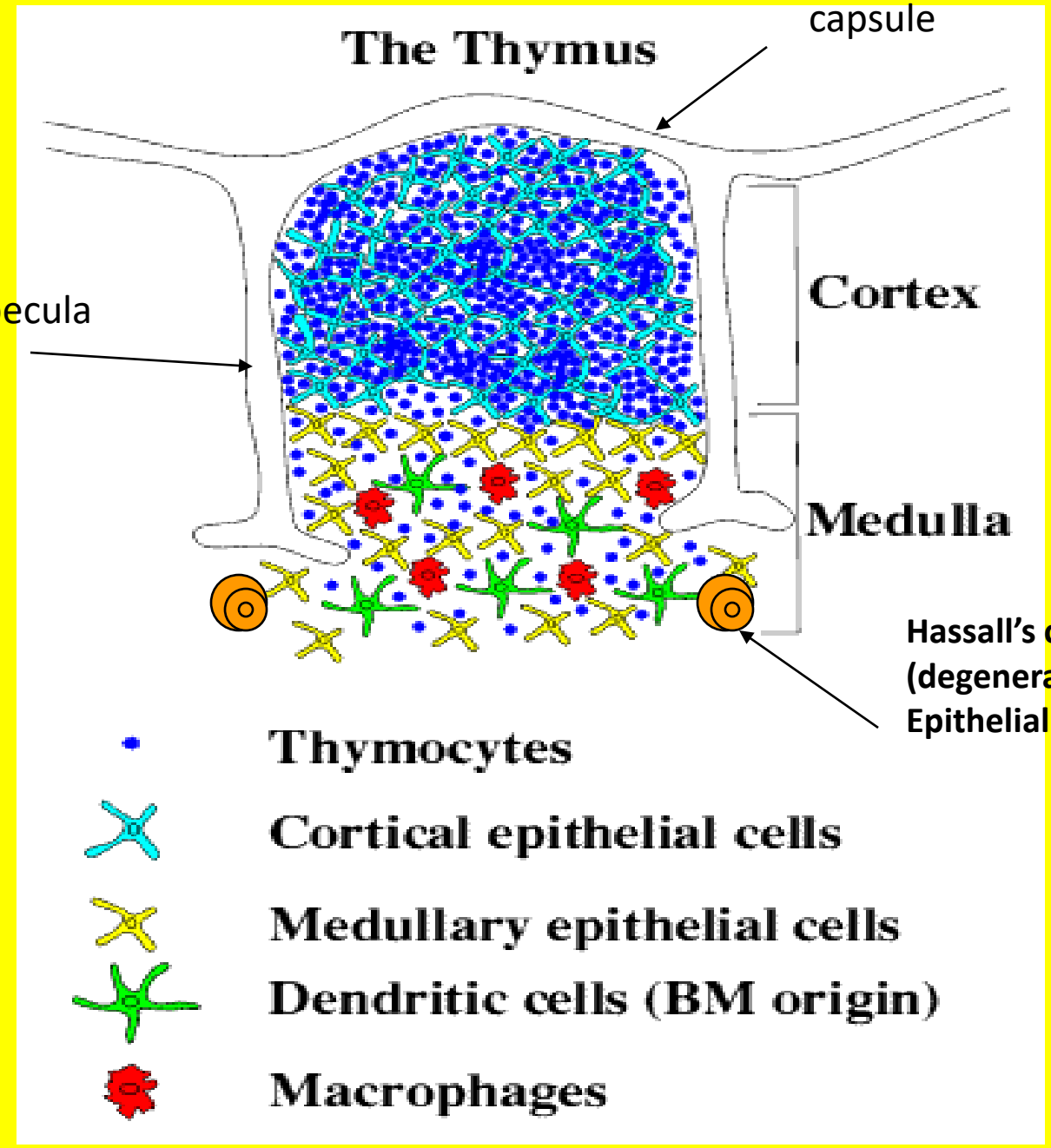


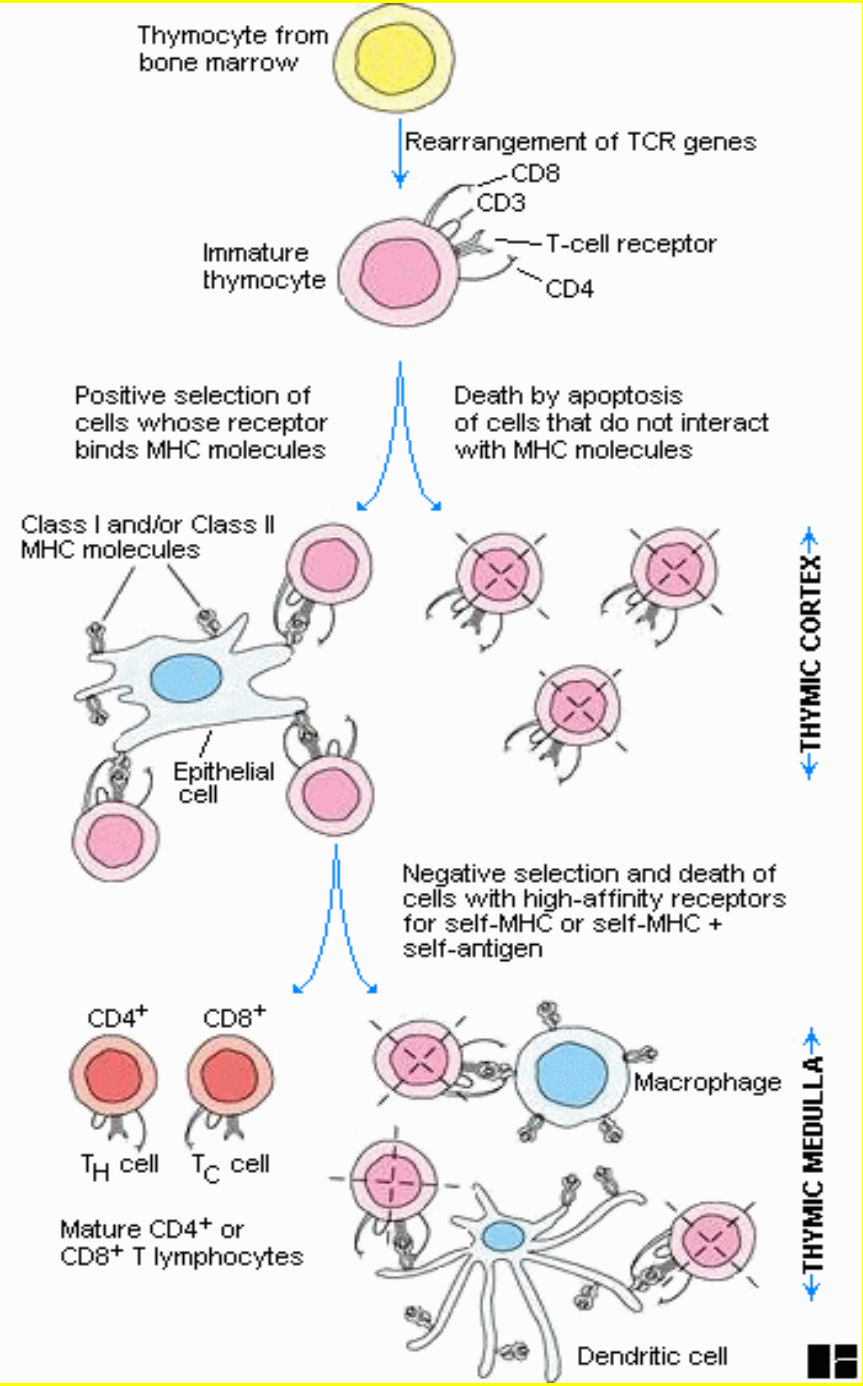
Figure 22-8

Thymus-structure/function

- **Thymic stroma--> network of epithelia-contains T cell precursors.**
- **Dendritic cells, macrophage and medullary epithelial cells in thymic medulla**
- **Sub-capsular epithelium underlying capsule-acts as barrier**



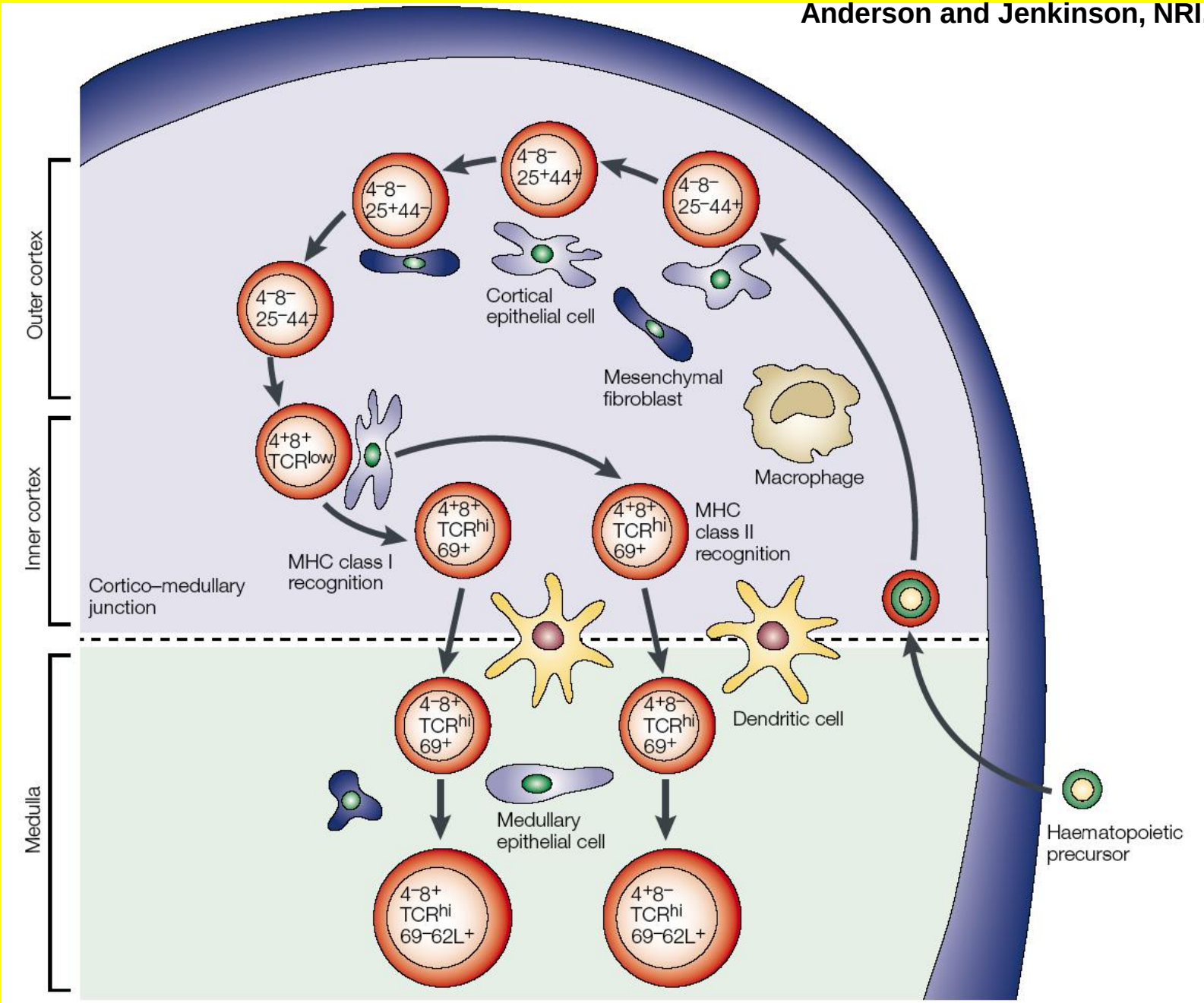

The Thymus
capsule
trabecula
Cortex
Medulla
Hassall's corpuscles
(degenerating layers of
Epithelial cells)
Thymocytes
Cortical epithelial cells
Medullary epithelial cells
Dendritic cells (BM origin)
Macrophages



Schematic diagram of T cell maturation within the thymus

Summary of Thymic Development

Anderson and Jenkinson, NRI, 2001



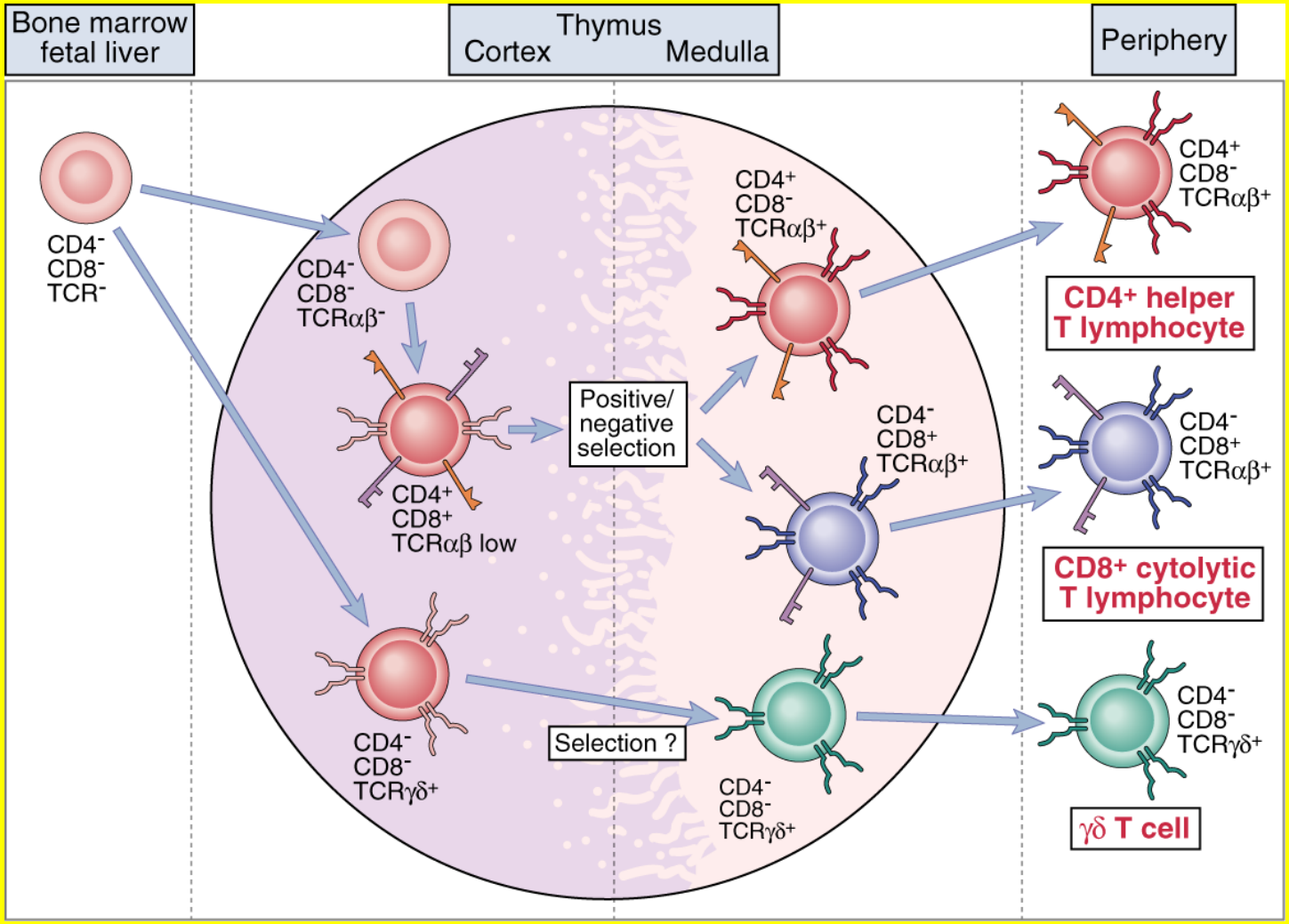
Major Thymocyte Subsets

$CD4^-CD8^-$ (Double Negative, DN) cells: 3-5% of total thymocytes
- Contain least mature cells, considerable cell division
- 2/3rds are triple negative (TN) based on TCR expression
- Can be further divided based on CD44 and CD25 (discussed later)
- *TCR* β, γ and δ rearrangements occur at this stage
- 1/3rd are TCR $\gamma\delta^+$

$CD4^+CD8^+$ (Double Positive, DP) cells: 80-85% of total thymocytes
- TCR α rearrangement occurs at this stage
- Most have rearranged TCR $\alpha\beta$ genes & express low levels (10% mature level) of TCR
- Small subset has high levels of TCR (most mature, positively selected cells)
- Small subset is actively dividing (earliest DPs)
- Most apoptosis occurs here, very sensitive to apoptosis inducing agents, especially sensitive to glucocorticoids

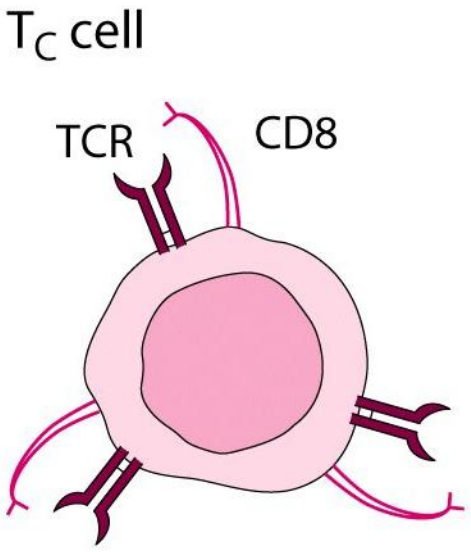
$CD4^+CD8^-$ and $CD4^-CD8^+$ (Single positive, SP) cells: 10-15% of total thymocytes
- Most are mature cells with high levels of CD3 and TCR $\alpha\beta$
- CD4:CD8 approx 2:1 ratio
- Most SP cells are functionally mature and are destined to leave the thymus
- Small subset of SP are immature (ISP) (CD8 in mouse, CD4 in human) and have low CD3 and no TCR $\alpha\beta$ - transitional cells that are on the way from DN -> DP

Major Phenotypes and Subsets of T Cell Development



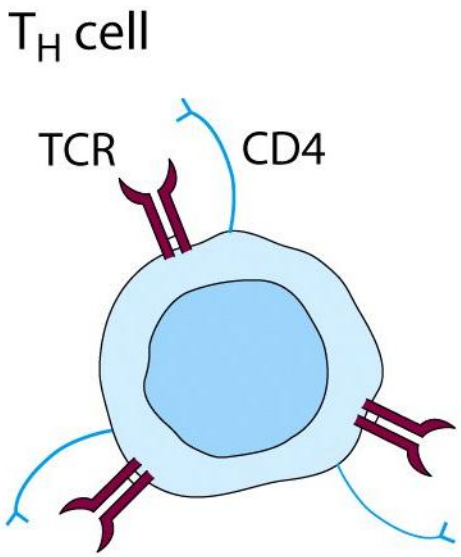
Abbas & Lichtman. Cellular and Molecular Immunology, 5th ed. W. B. Saunders 2003

T cells



Recognizes MHC I
on all cells

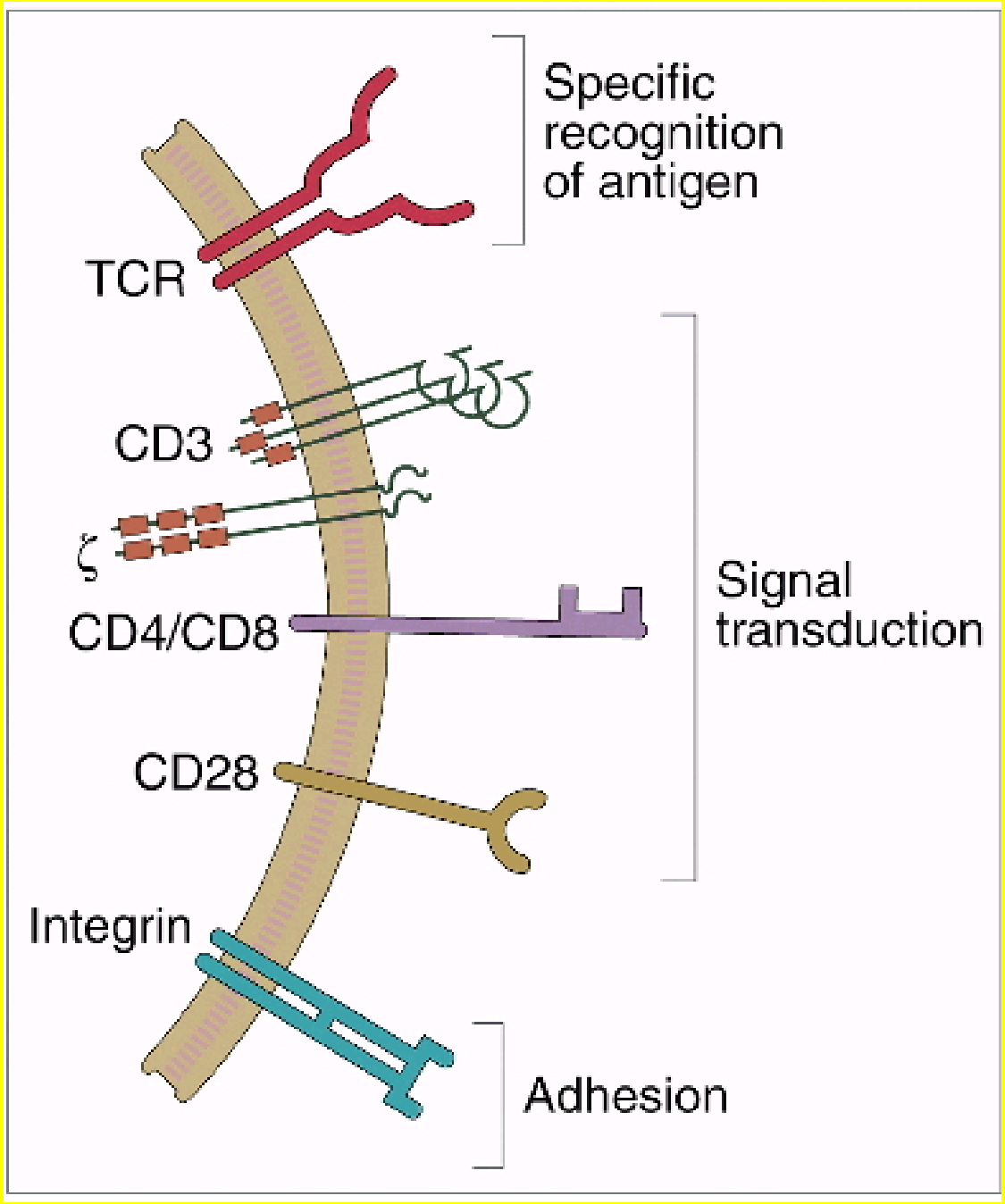
Kills:
Infected cells
Tumour cells



Recognizes MHC II
on APC

Helps:
B-cells
T cells
Macrophages

Accessory Molecules



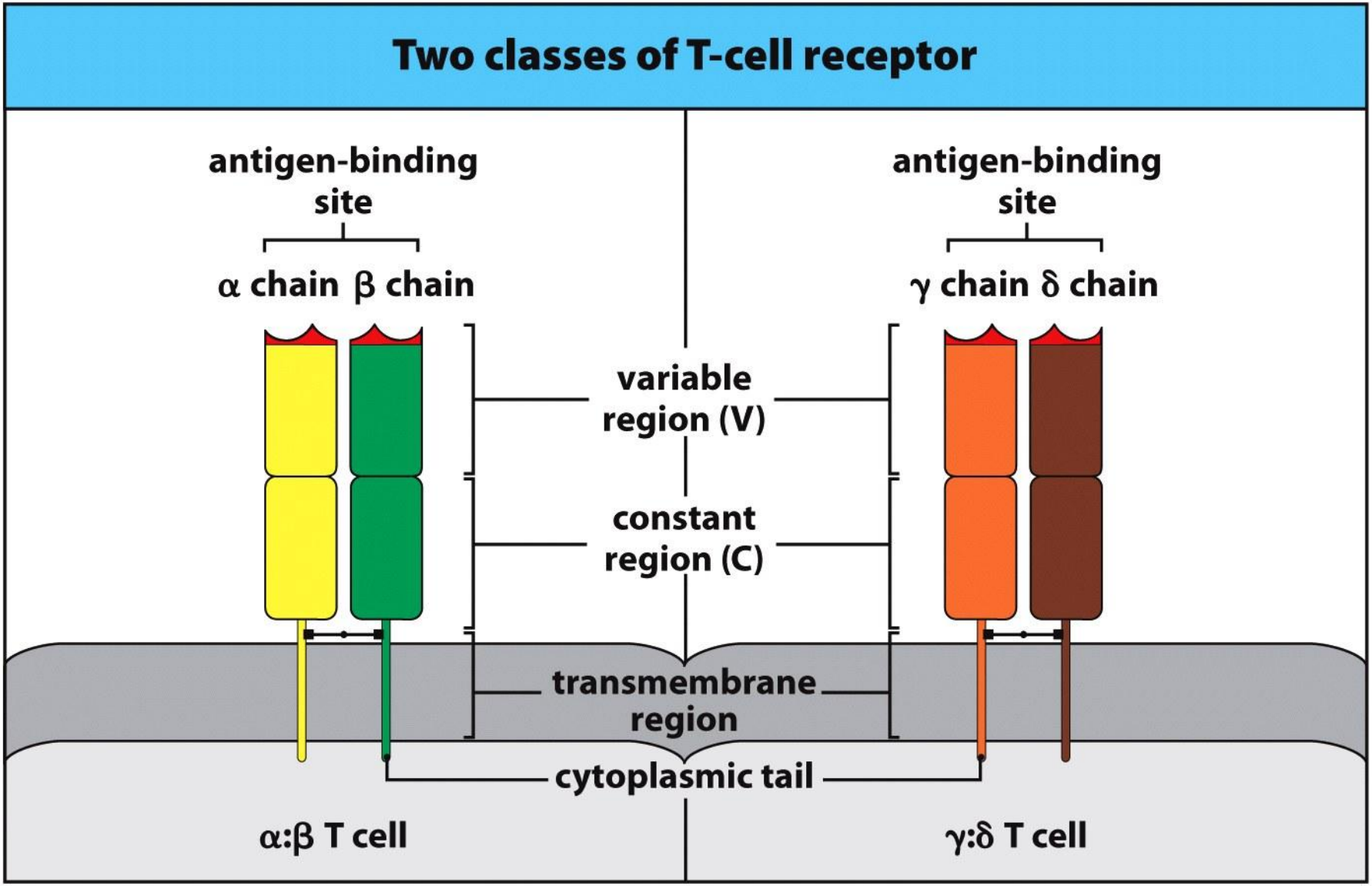
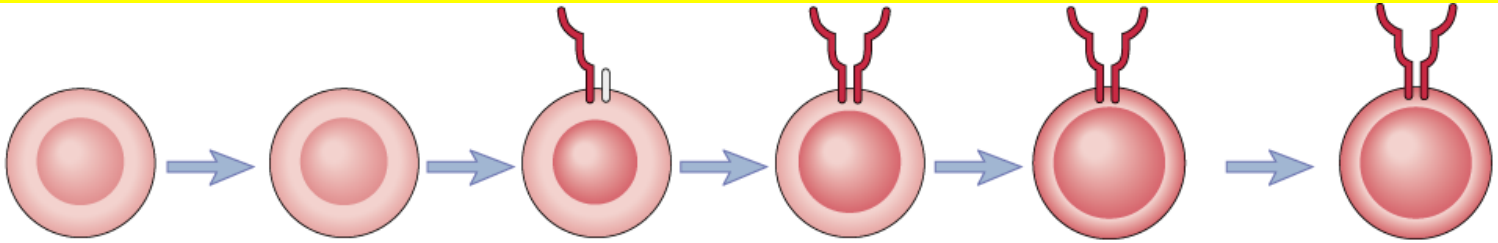


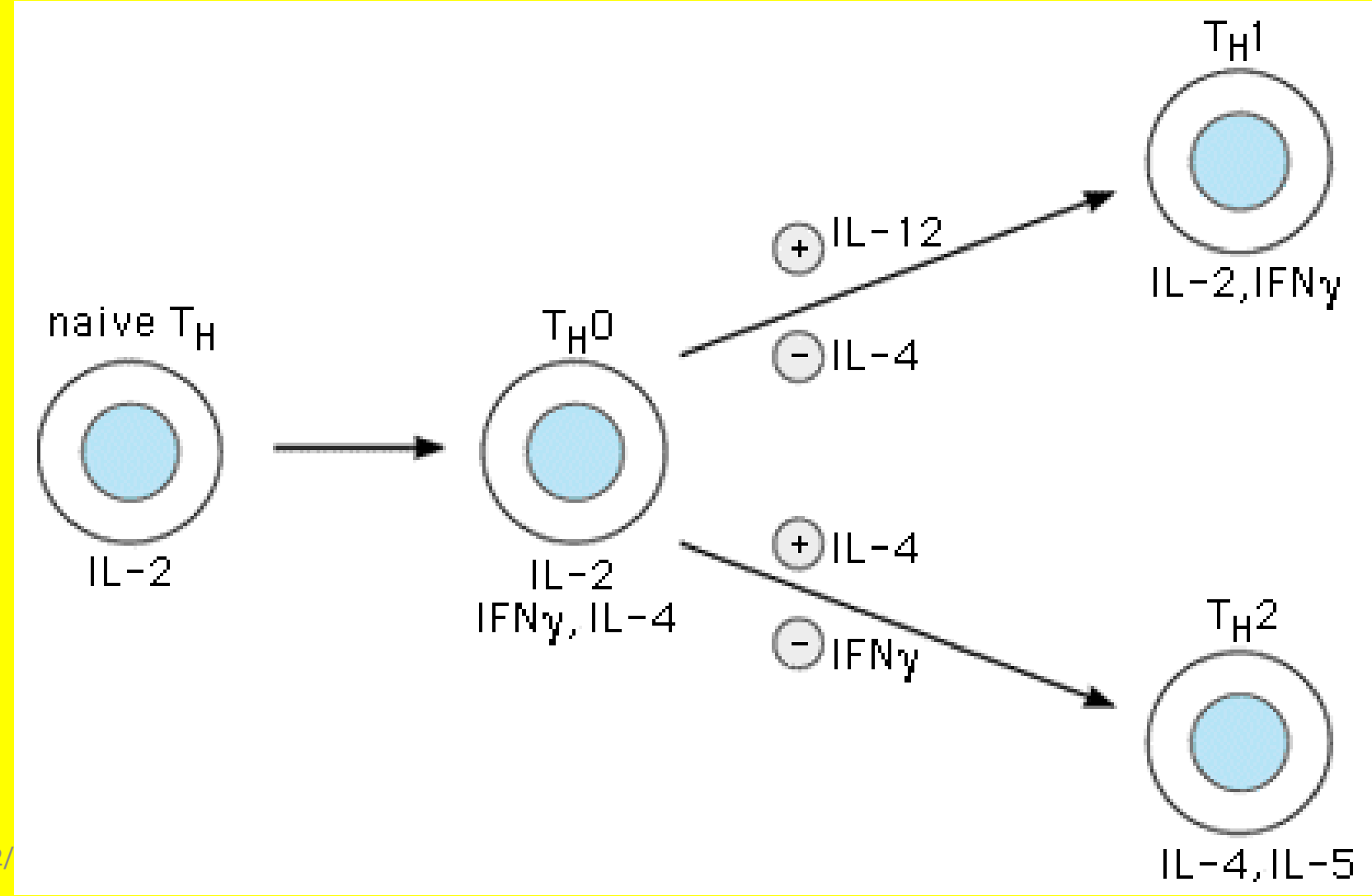
Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
RAG expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit* $^{+}$ $CD44^{+}$ $CD25^{-}$	c-*kit* $^{+}$ $CD44^{+}$ $CD25^{+}$	c-*kit* $^{+}$ $CD44^{+}$ $CD25^{+}$	$CD4^{+}CD8^{+}$ $TCR/CD3^{lo}$	$CD4^{+}CD8^{-}$ or $CD4^{-}CD8^{+}$ $TCR/CD3^{hi}$	$CD4^{+}CD8^{-}$ or $CD4^{-}CD8^{+}$ $TCR/CD3^{hi}$
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection	Negative selection	Activation (proliferation and differentiation)

Abbas & Lichtman. Cellular and Molecular Immunology, 5th ed. W. B. Saunders 2003

T cells


naive T_H
IL-2
T_H0
IL-2
IFNγ, IL-4
+ IL-12
− IL-4
T_H1
IL-2,IFNγ
+ IL-4
− IFNγ
T_H2
IL-4,IL-5

CD2

- CD2 is a glycoprotien present on more than 90% of mature T-cells and 50-70% of thymocytes.
- This molecule contains two extracellular Ig domains.
- The principle ligand for CD2 is LFA-3 (CD58).

CD2

- CD2 functions both as an adhesion molecule and signal transducer.
- The association of CD2 with the TCR complex helps to aggregate the TCR in the regions of cell–cell contact, allowing the stabilization of low-affinity TCR/MHC interactions.
- Finally, CD2 is involved in the regulation of cytokine production by T cells.
- Stimulation via the CD2 pathway can skew the cytokine profile toward a TH2-like phenotype.

CD3

- TCRs occur as either of two distinct heterodimers, αβ or γδ, both of which are expressed with the non-polymorphic polypeptides γ, δ, ε, and ζ.
- The CD3 polypeptides, especially and its variants, are critical for intracellular signaling.

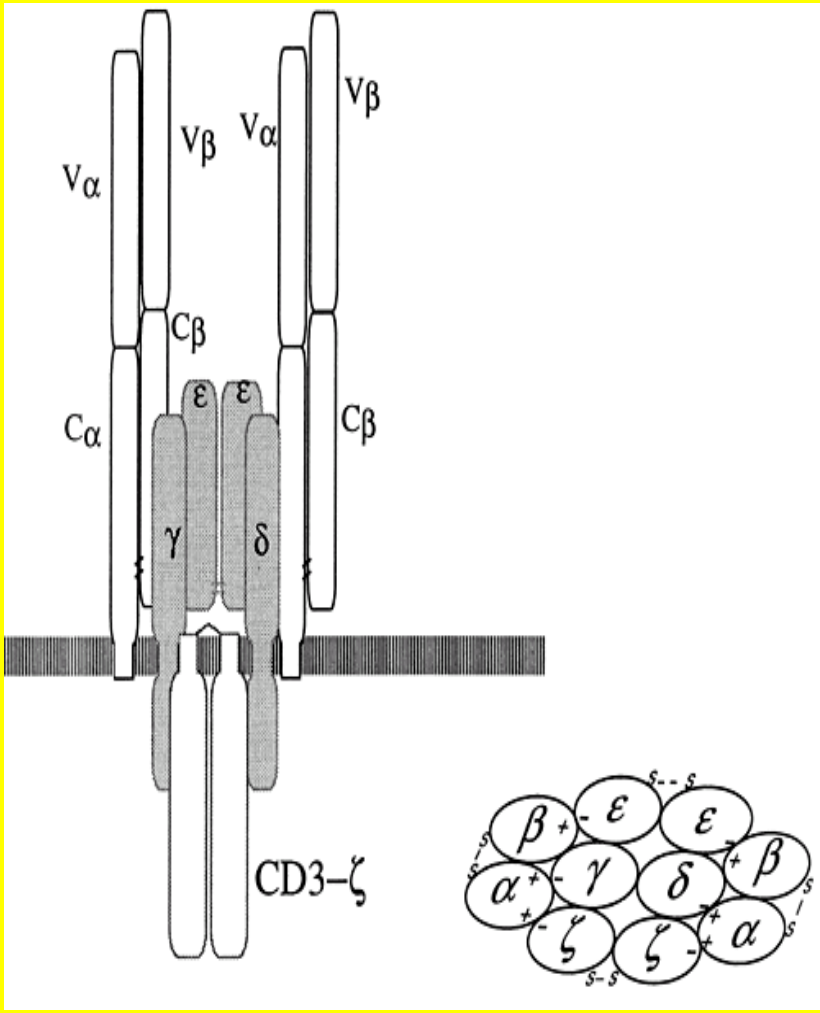


TABLE 9-1 Comparison of αβ and γδ T cells

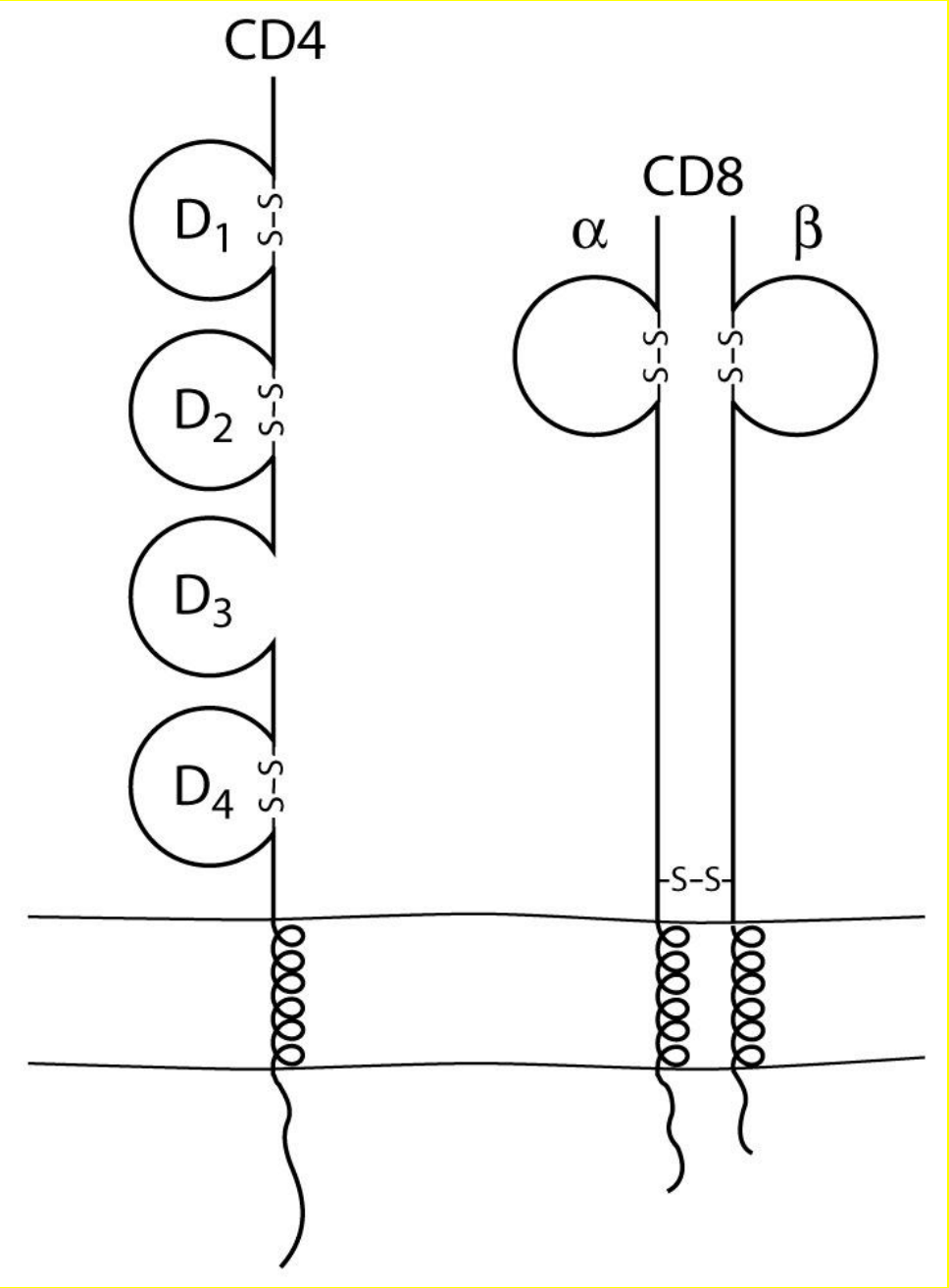
Feature	αβ T cells	γδ T cells
Proportion of $CD3^+$ cells	90–99%	1–10%
TCR V gene germ-line repertoire	Large	Small
CD4/CD8 phenotype		
$CD4^+$	~60%	<1%
$CD8^+$	~30%	~30%
$CD4^+CD8^+$	<1%	<1%
$CD4^-CD8^-$	<1%	~60%
MHC restriction	$CD4^+$: MHC class II	No MHC restriction
	$CD8^+$: MHC class I	
Ligands	Peptide + MHC	Phospholipid antigen

SOURCE: D. Kabelitz et al., 1999, *Springer Seminars in Immunopathology* **21**:55, p. 36.

TCR Accessory Molecules

TABLE 9-4 Selected T-cell accessory molecules

Name	Ligand	FUNCTION: Adhesion	FUNCTION: Signal transduction	Member of Ig superfamily
CD4	Class II MHC	+	+	+
CD8	Class I MHC	+	+	+
CD2 (LFA-2)	CD58 (LFA-3)	+	+	+
LFA-1 (CD11a/CD18)	ICAM-1 (CD54)	+	?	+/(−)
CD28	B7	?	+	+
CTLA-4	B7	?	+	−
CD45R	CD22	+	+	+
CD5	CD72	?	+	−


CD4
D1
D2
D3
D4
S–S
CD8
α
β
S–S
S–S
S–S
S–S

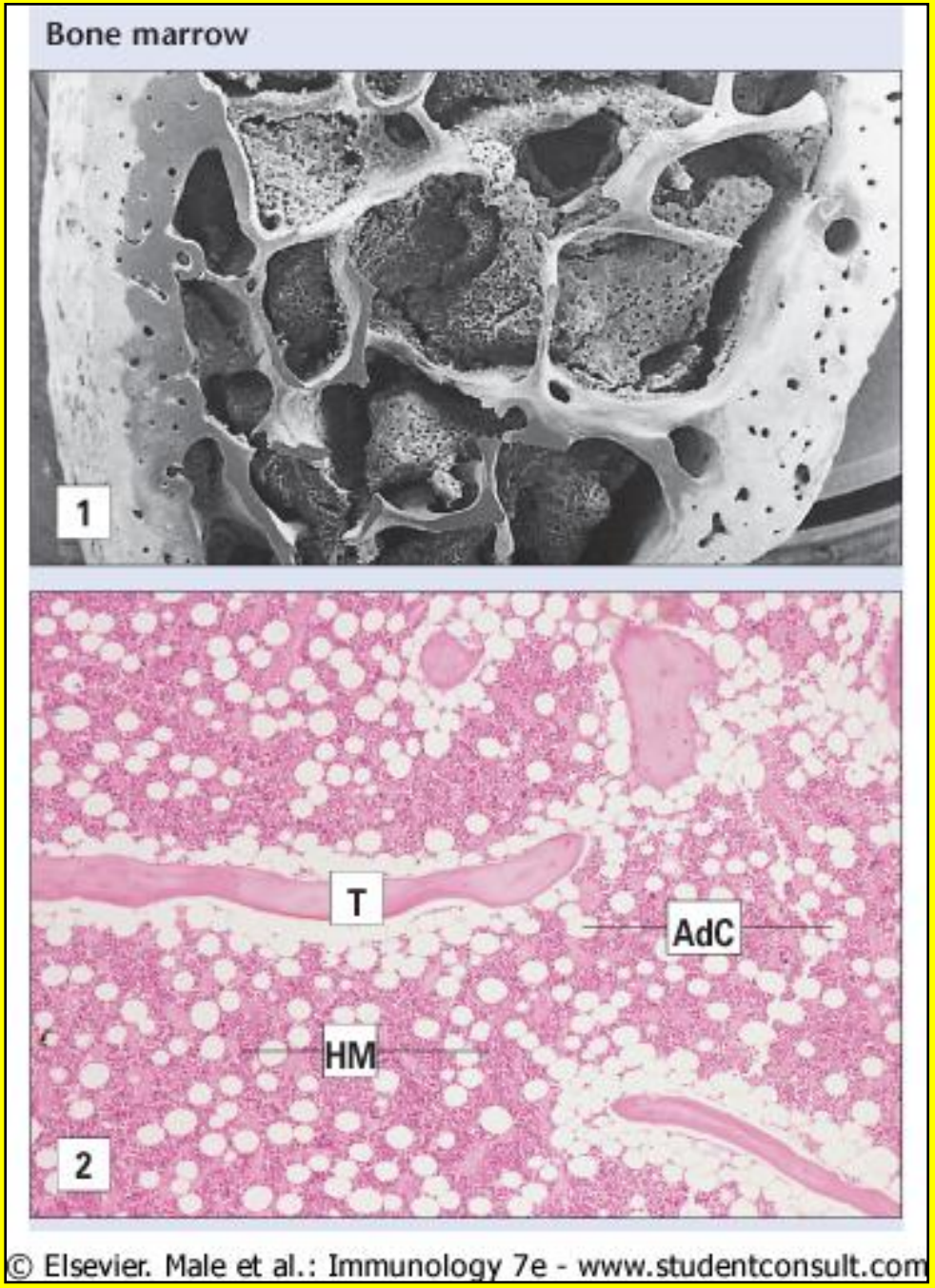
Diseases related to Thymic Defects

- DiGeorge's syndrome-congenital birth defect in humans; no functional thymus
- Nude mice-fail to develop a thymus
- Experimentally, you can thymectomize mice at a young age as well.

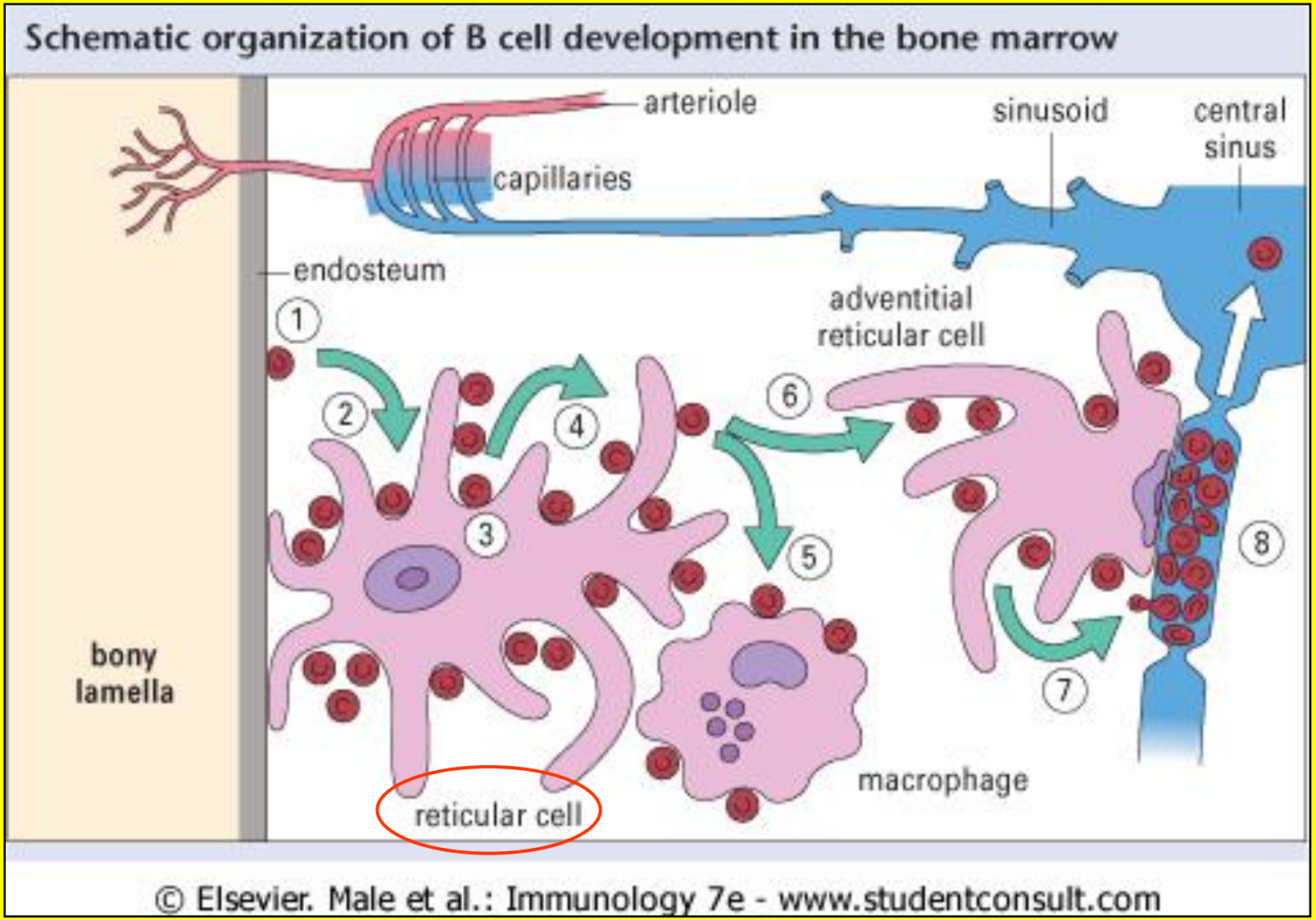
Bone Marrow

1. The site of generation of all immune and blood cells
   <= Hematopoietic Stem Cell

2. Provides Cell-cell interactions and Cytokines for the development of all immune cells.
   <= Stromal reticular cells & other cells



B cell development in the Bone Marrow



Bone marrow stromal cells drive Pro-B cell proliferation and maturation.

Important molecules and interactions:
SCF-cKit
IL-7-IL-7R

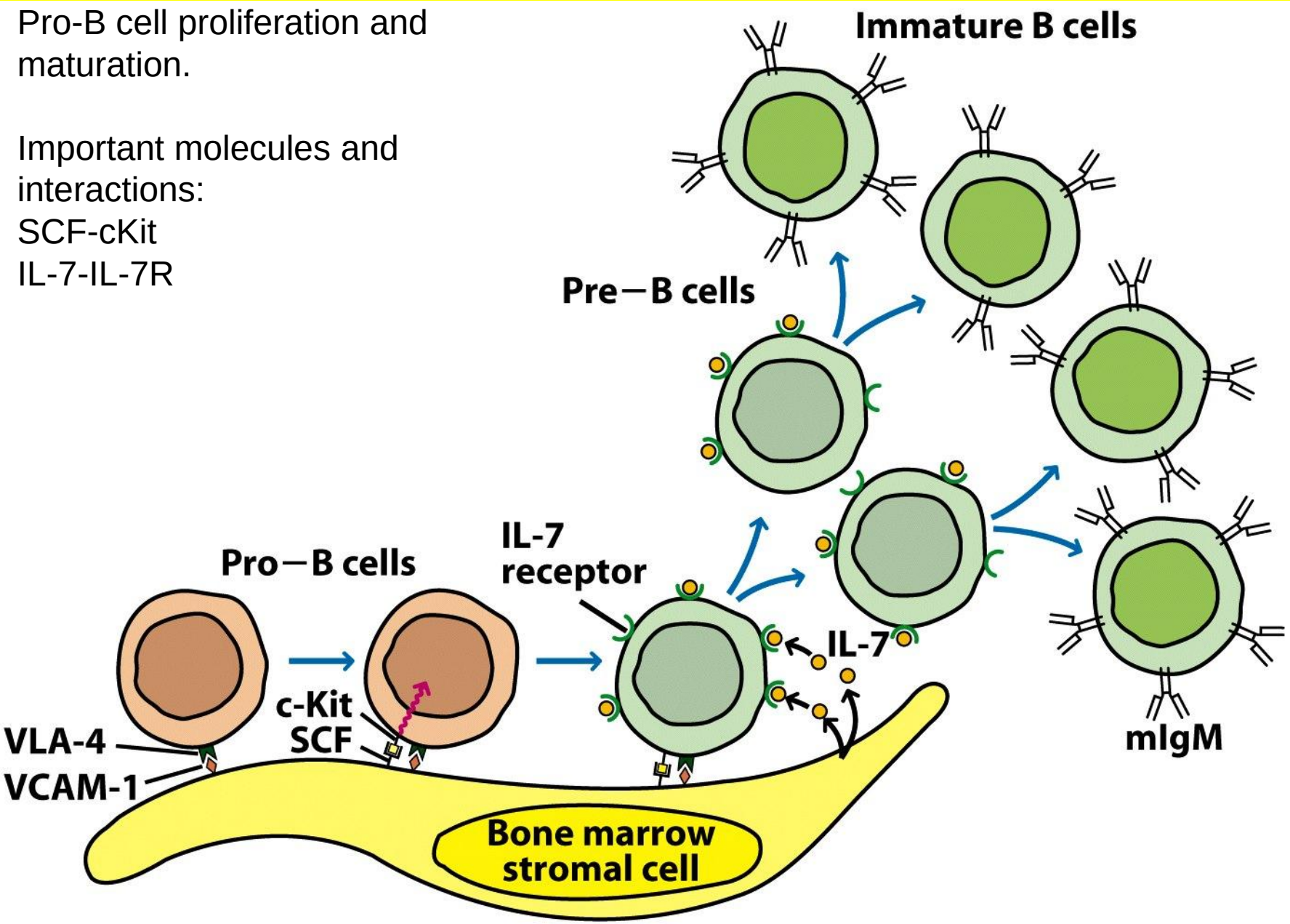


Figure 11-2

Pro–B cell

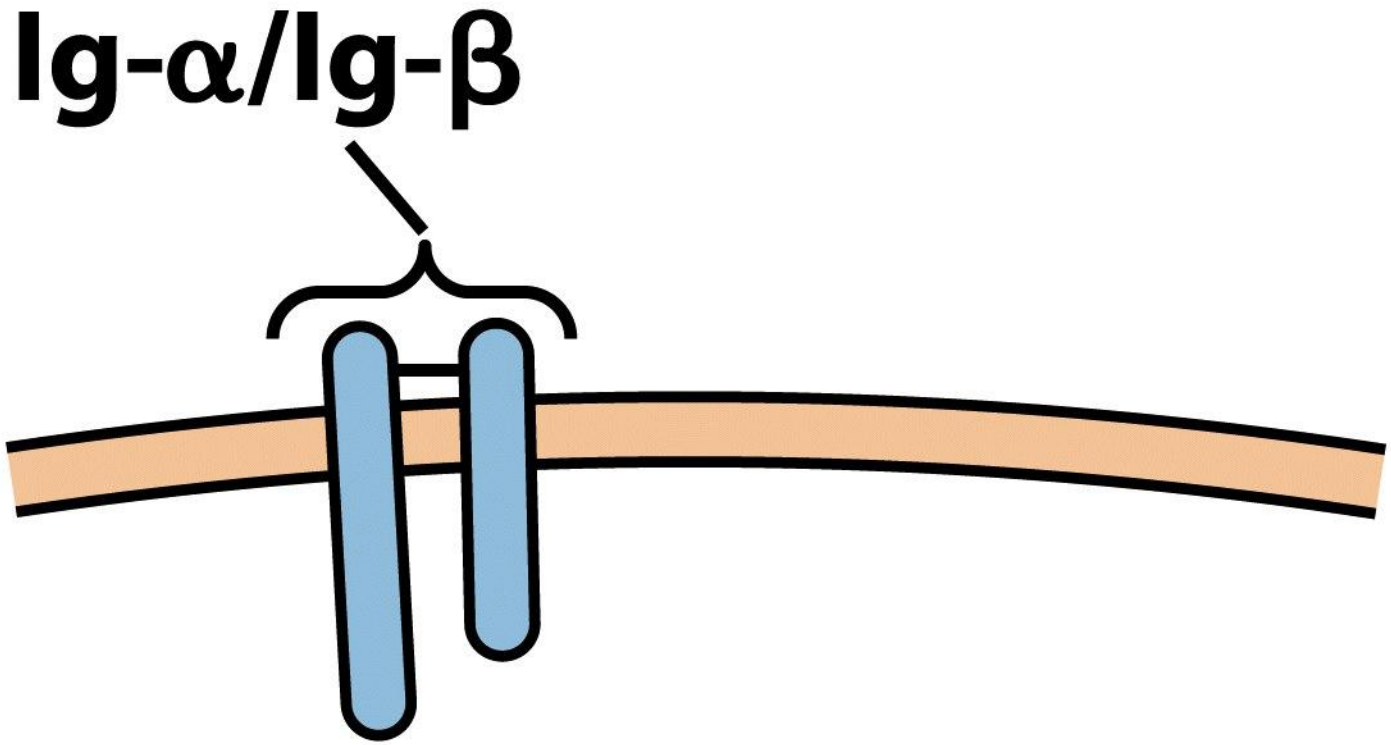


Figure 11-4 part 1
Kuby IMMUNOLOGY, Sixth Edition

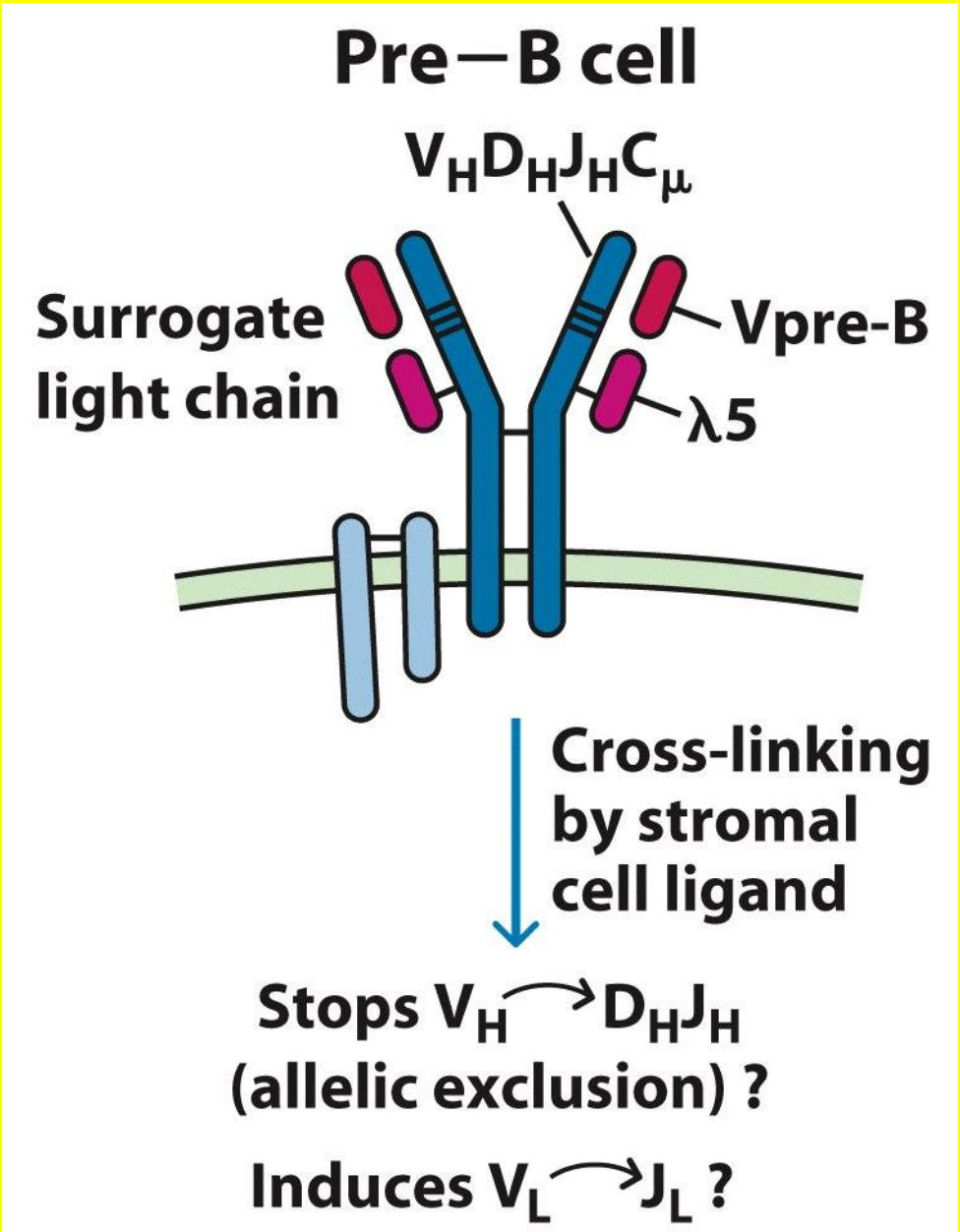


Figure 11-4 part 2
Kuby IMMUNOLOGY, Sixth Edition

Stages in B-cell maturation in the bone marrow

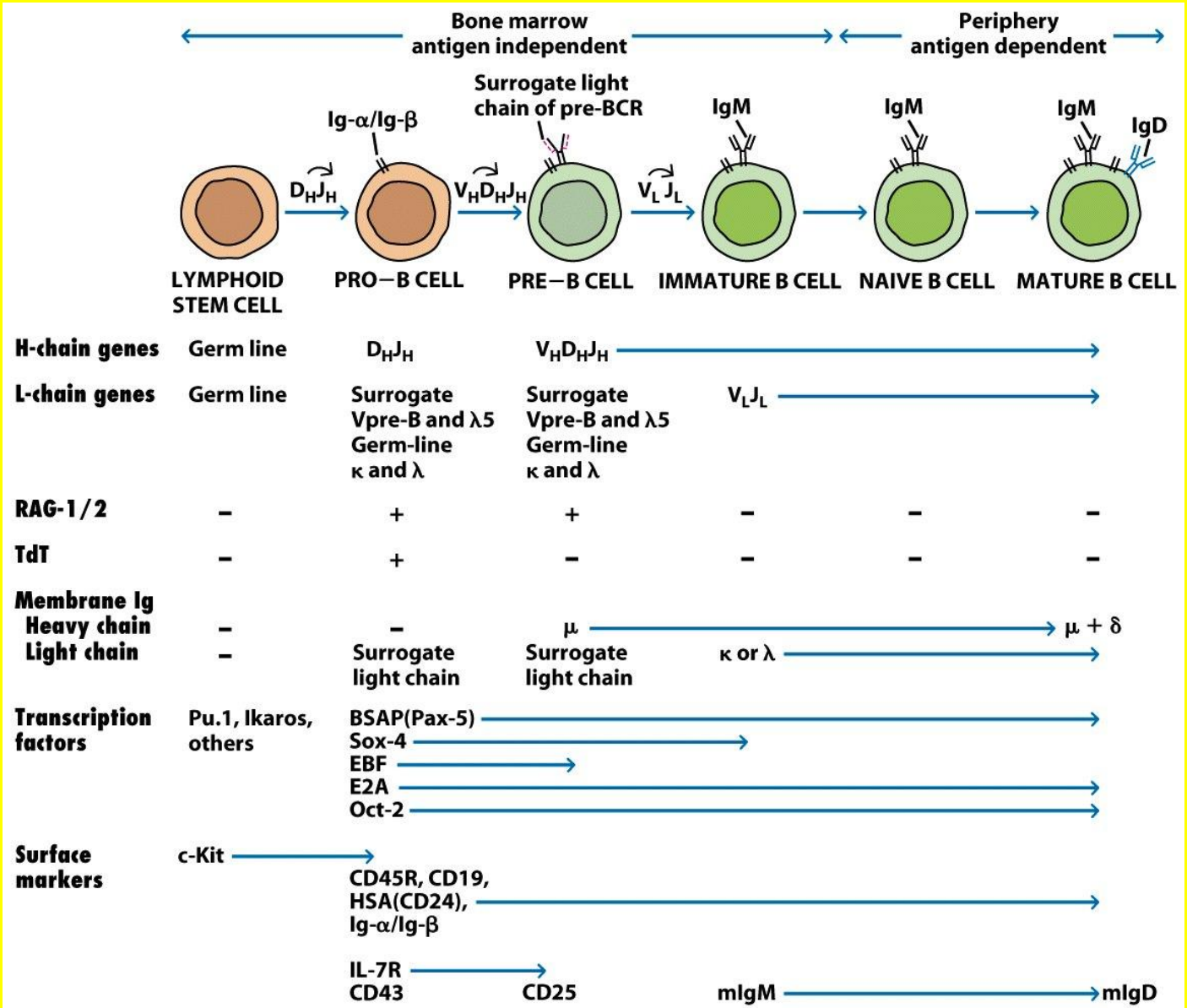


Figure 11-3
Kuby IMMUNOLOGY, Sixth Edition

Igα and Igβ are Signaling Subunits of the B Cell Receptor (BCR; surface Ig molecule)

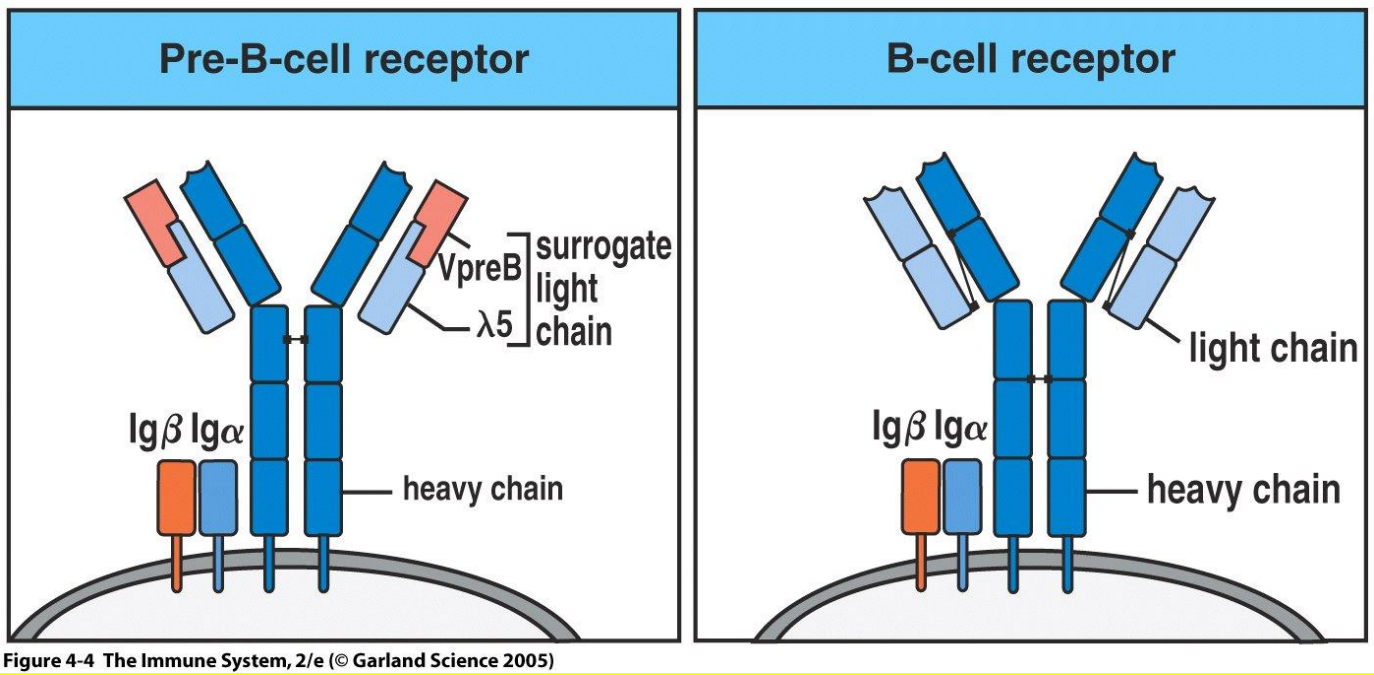


Figure 4-4 The Immune System, 2/e (© Garland Science 2005)

Notes

1. The Ig molecule (either pre-BCR or BCR) can not travel to the surface of the B cell without Igα and Igβ
2. The pre-BCR and BCR consist of an Ig molecule plus Igα and Igβ
3. Igα and IgB genes turned on at the pro-B-cells stage and remain on until cell becomes and antibody secreting plasma cell
4. Igα and Igβ send signals when receptors are engaged (bound antigen)

Peripheral or Secondary lymphoid tissues

- **Trap antigen-bearing dendritic cells**
- **Initiation of adaptive immune response**
- **Provide signals that sustain recirculating lymphocytes**

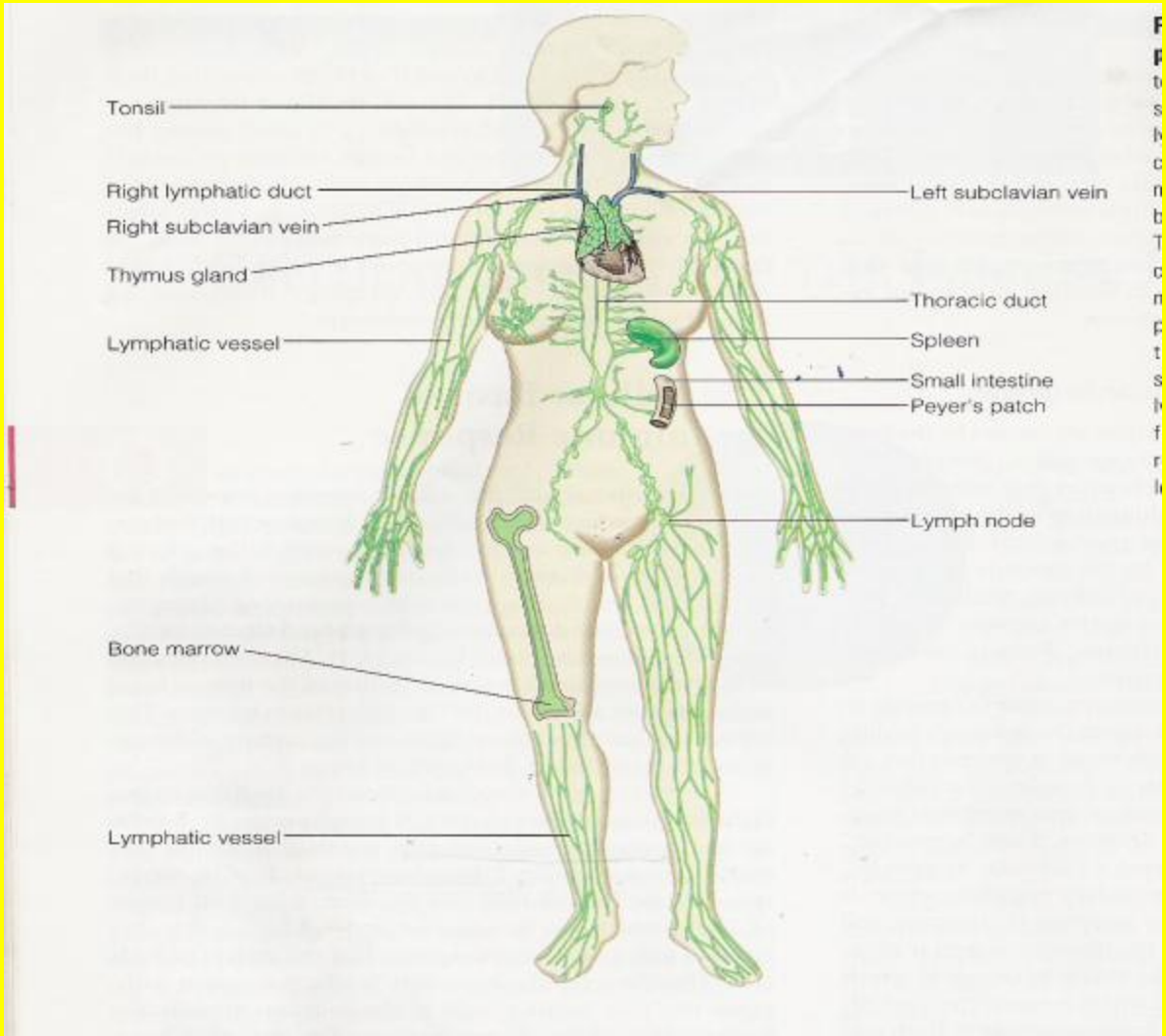
Lymph Nodes

- **Sites of Immune responses**
- **Encapsulated bean-shaped structures, reticular network, full of lymphocytes, macrophages, and dendritic cells.**
- **First organized lymphoid structure to encounter antigens-reticular structures trap antigen**

Lymph Nodes

- **Cortex**
  - **Contains mostly B cells, macrophages and follicular dendritic cells**
- **Paracortex**
  - **Primarily T lymphocytes, and dendritic cells**
- **Medulla**
  - **Sparsely populated with lymphoid lineage cells (mostly plasma cells)**

Where are these lymph nodes?



Lymph Nodes

- Range from 1–25 mm diameter

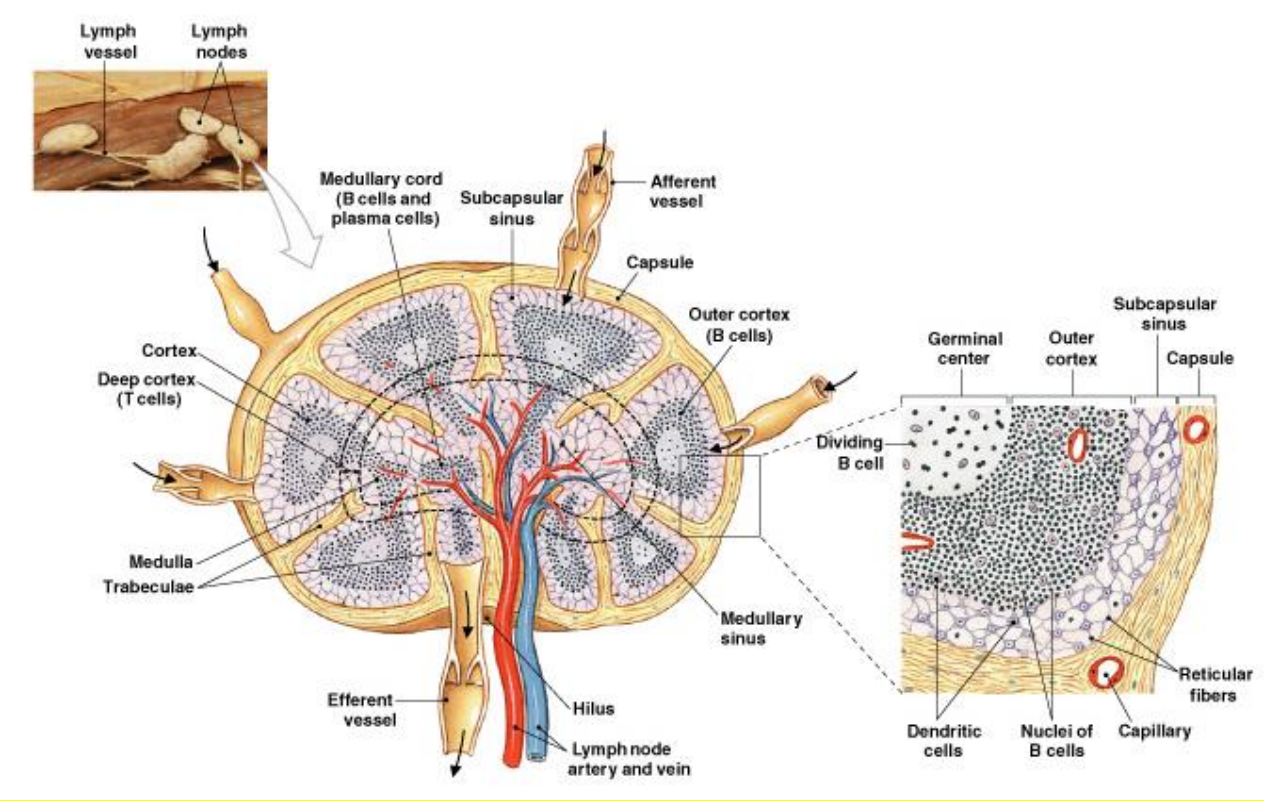


Figure 22-7

Lymphatic System: Anatomy

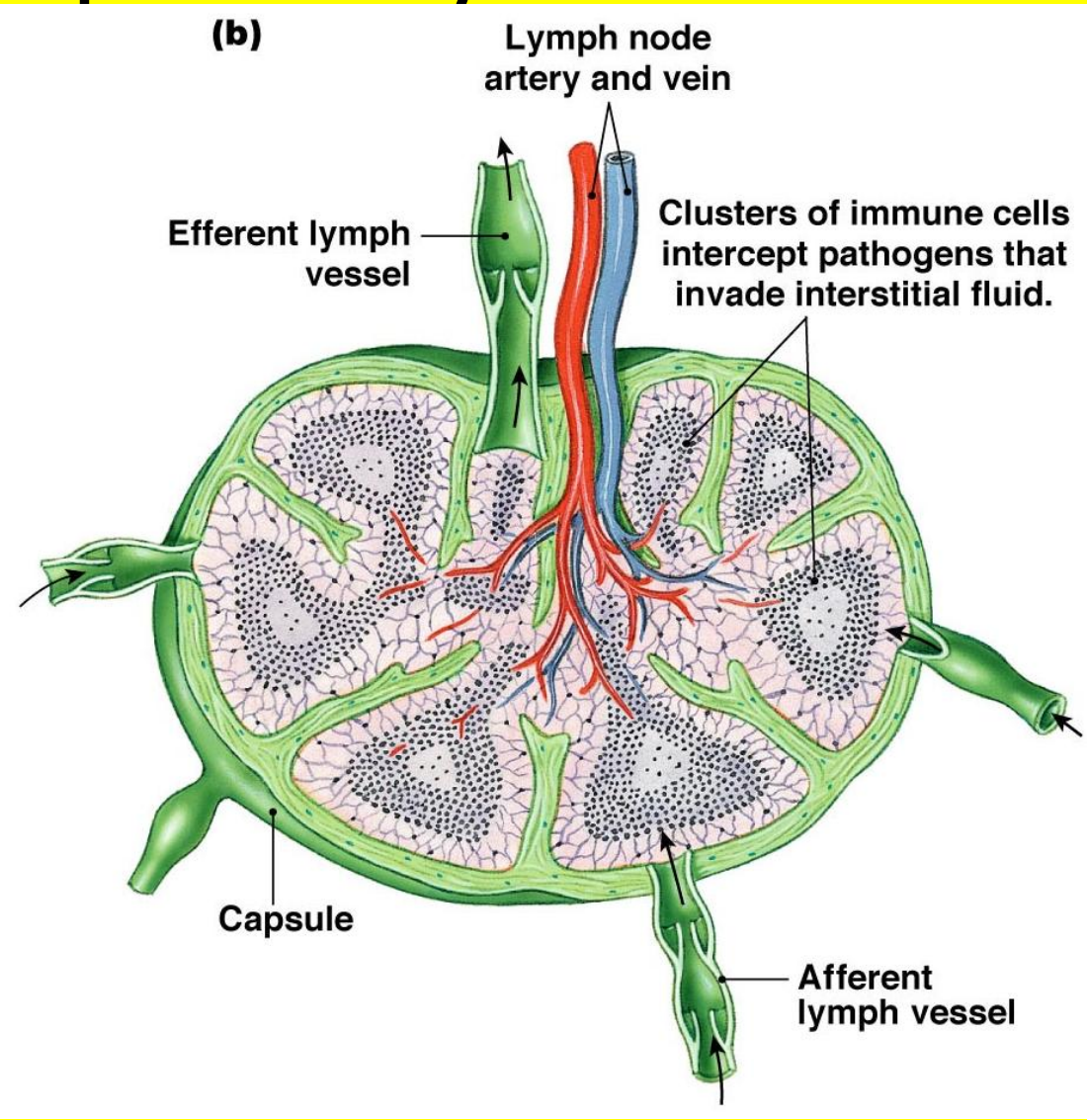


Figure 24-2b

Structure/function of the Lymph Node

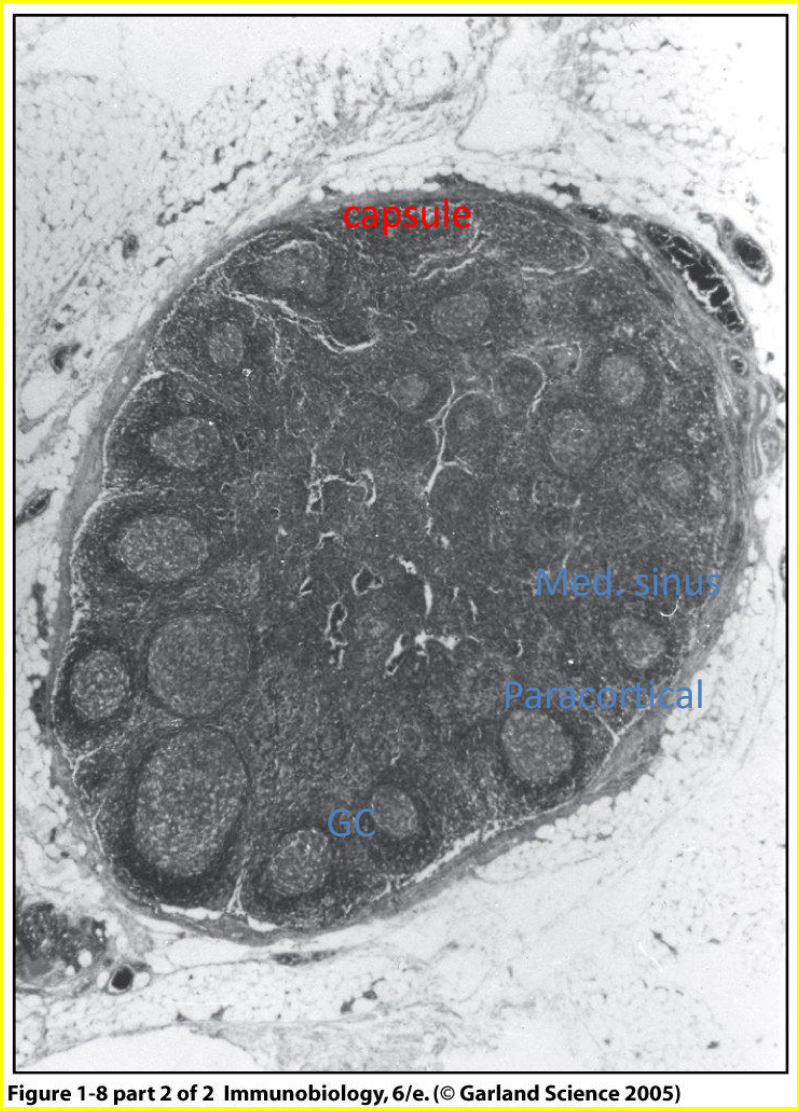


Figure 1-8 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Germinal center foci
Reach maximum
Size within 4 to 6
days of antigen
challenge.

Spleen

- **Major role in mounting immune responses to antigens in the bloodstream**
  - **Filters blood and traps antigens**

- **Not supplied with lymphatic vesicles**
  - **Splenic artery carries antigens and lymphocytes**

Structure of the Spleen

- **Surrounded by a capsule from which a number of trabeculae extend into interior (compartmentalized structure)**

Structure of the Spleen

- **Spenic red pulp consists of a network of sinusoids**
  - **Populated by macrophages, RBCs, and a few lymphocytes**
  - **Site where old and defective RBCs are destroyed and removed**
  - **Macrophage engulf RBCs**

Structure of the Spleen…

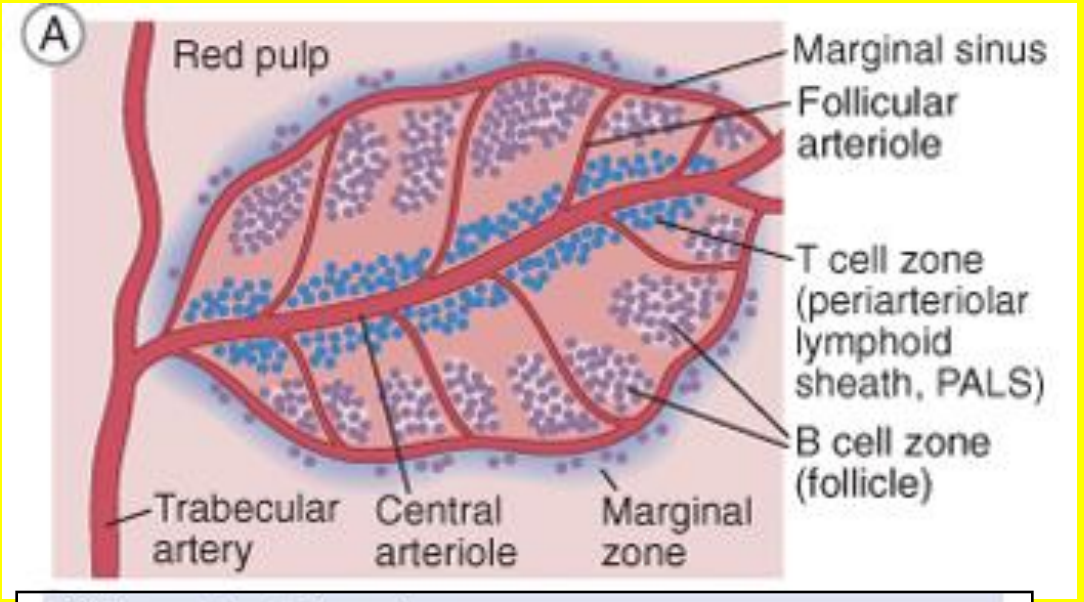
- **Spenic white pulp surrounds the branches of the splenic artery**
  - **Forms periarteriolar lymphoid sheath (PALS), populated primarily by T cells.**
  - **Primary lymphoid follicles are attached to the PALS, are rich in B cells and some contain germinal centers**
  - **Marginal zone, peripheral to the PALS, is populated by lymphocytes and macrophages**

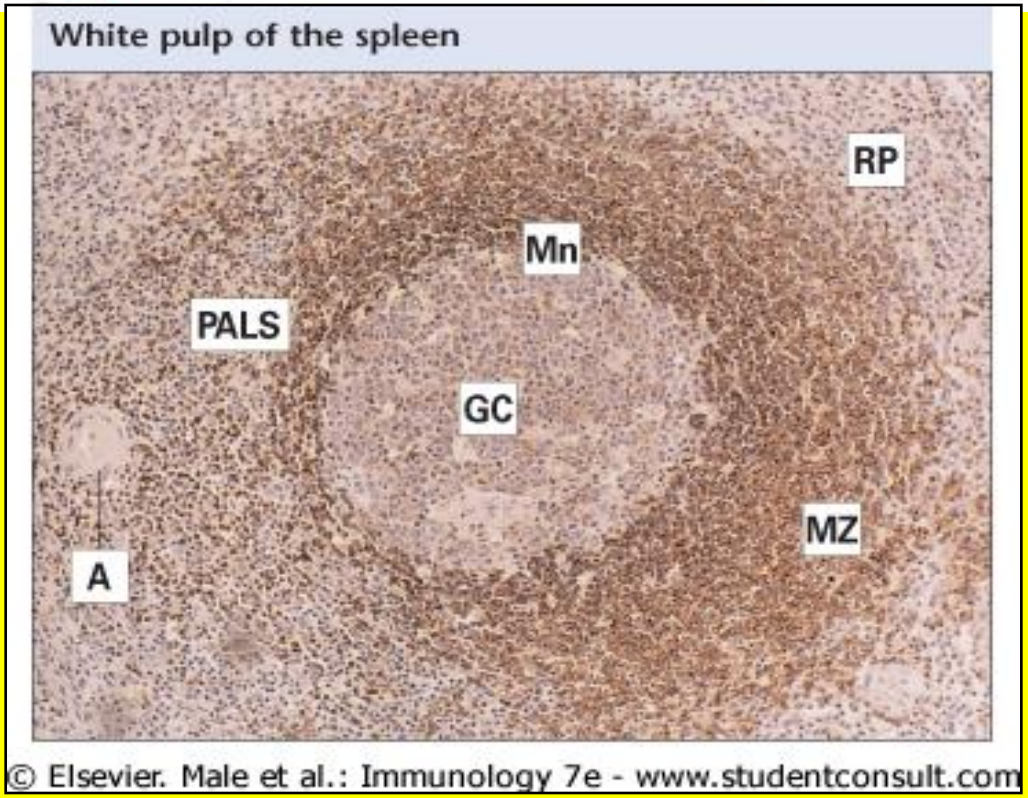
Spleen

1. The site of immune responses to blood Ags
   => A filter of blood

2. White pulp => T cell & B cell zones
   Marginal zone (MZ)
   Red pulp (RP)

3. T cells => periarteriolar lymphoid sheaths
   B cells => follicle
   => marginal zone





Organization of a germinal center in the spleen

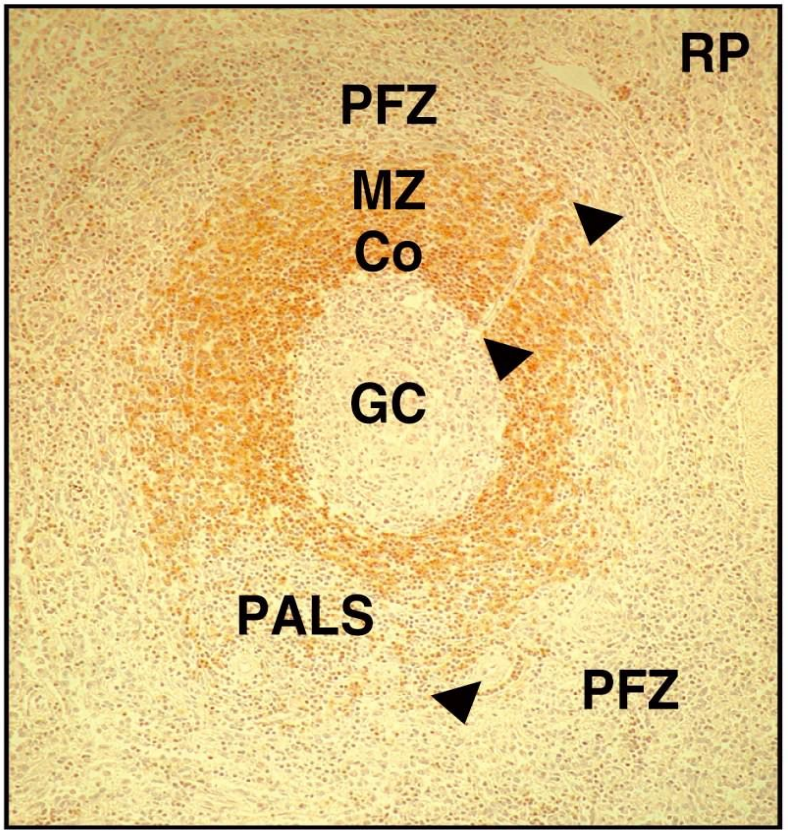


Figure 1-9 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

- **PFZ-perifollicular zone**
- **PALS-periarticular lymphoid sheath**
- **Co-follicular B-cell corona**
- **MZ-marginal zone**
- **RP-red pulp**

Loss of spleen (splenectomy)

- **Severity depends on age**
- **In children, splenectomy often leads to increased incidence of bacterial sepsis**
- **Few adverse effects in adults, can lead to some increase in blood-borne bacterial infections (bacteremia)**

MALT or Mucosa-assoc. Lymphoid Tissue

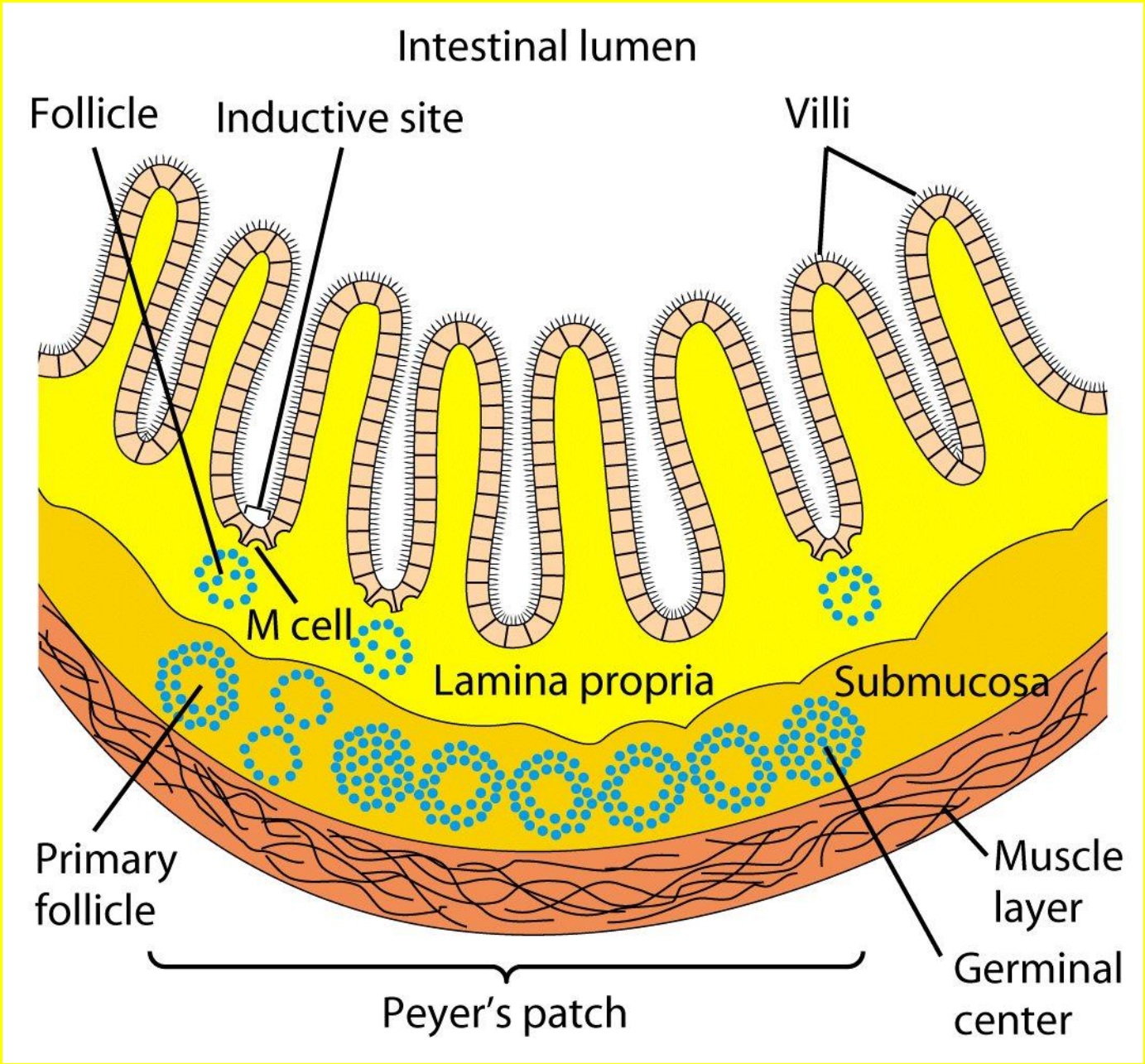
- **Mucous membranes lining digestive, respiratory and urogenital system are the major sites of entry for most pathogens.**

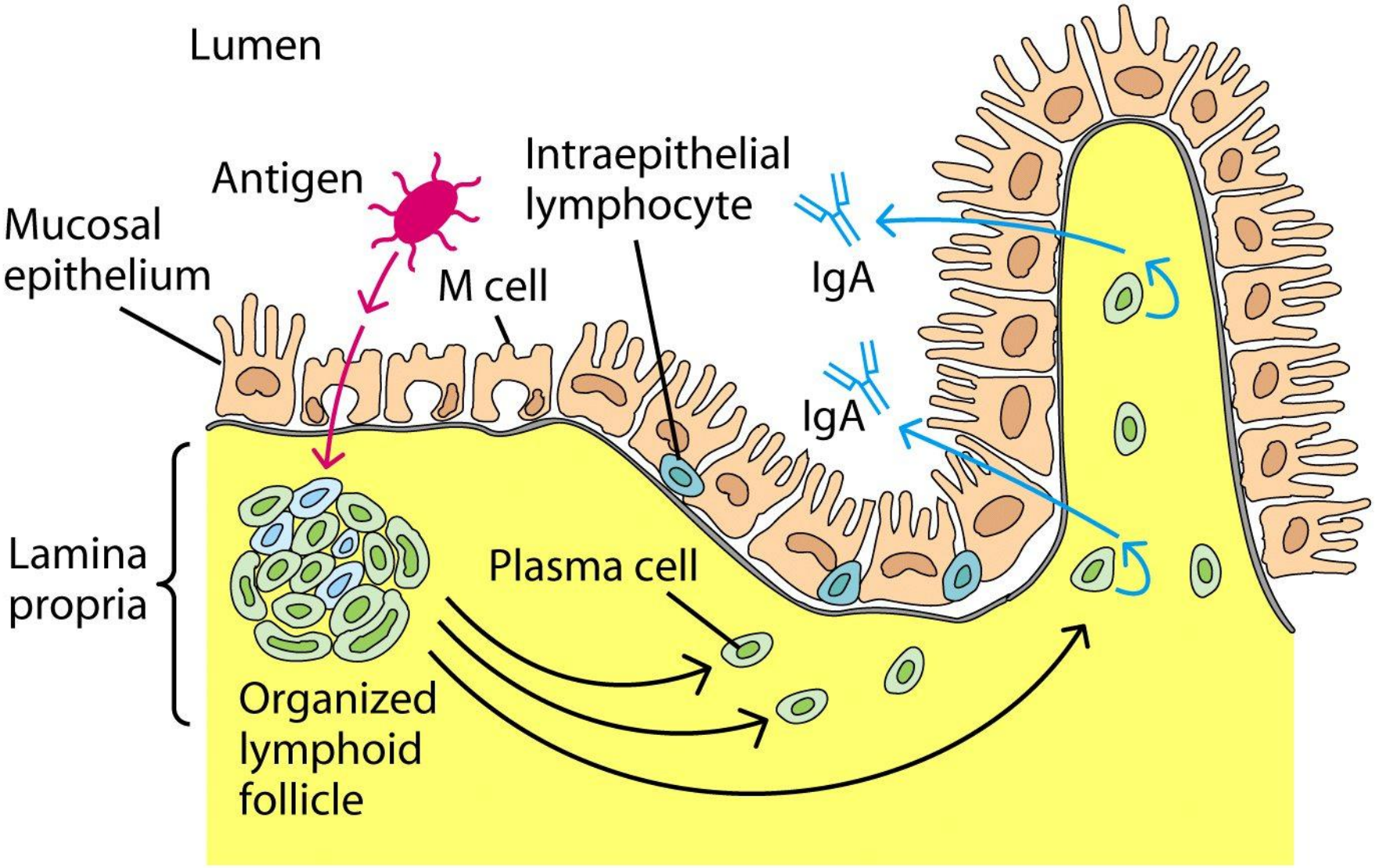
BALT -Bronchus-associated (respiratory)

GALT-gut-associated (digestive tract)

MALT…

- **Have different organizations.**
  - **Peyer's patches in intestinal lining well organized**
  - **Barely organized clusters of lymphoid cells in lamina propria of intestinal villi**
  - **Tonsils**
  - **appendix**
- **Large nos. of plasma cells (more than in the spleen and lymph Nodes)**


Intestinal lumen
Follicle
Inductive site
Villi
M cell
Lamina propria
Submucosa
Primary follicle
Muscle layer
Germinal center
Peyer's patch

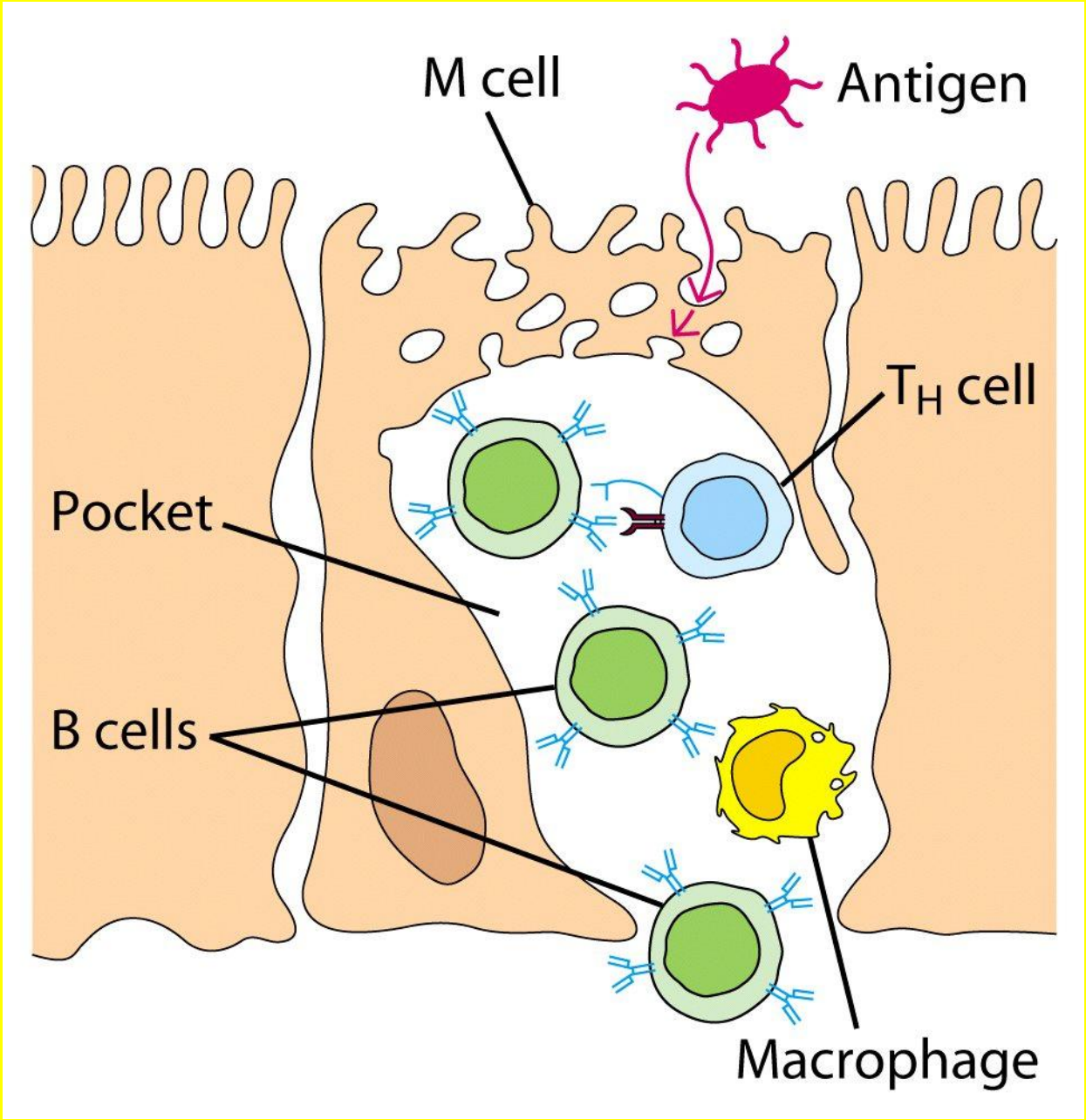

Lumen
Antigen
Intraepithelial lymphocyte
Mucosal epithelium
M cell
IgA
IgA
Lamina propria
Plasma cell
Organized lymphoid follicle

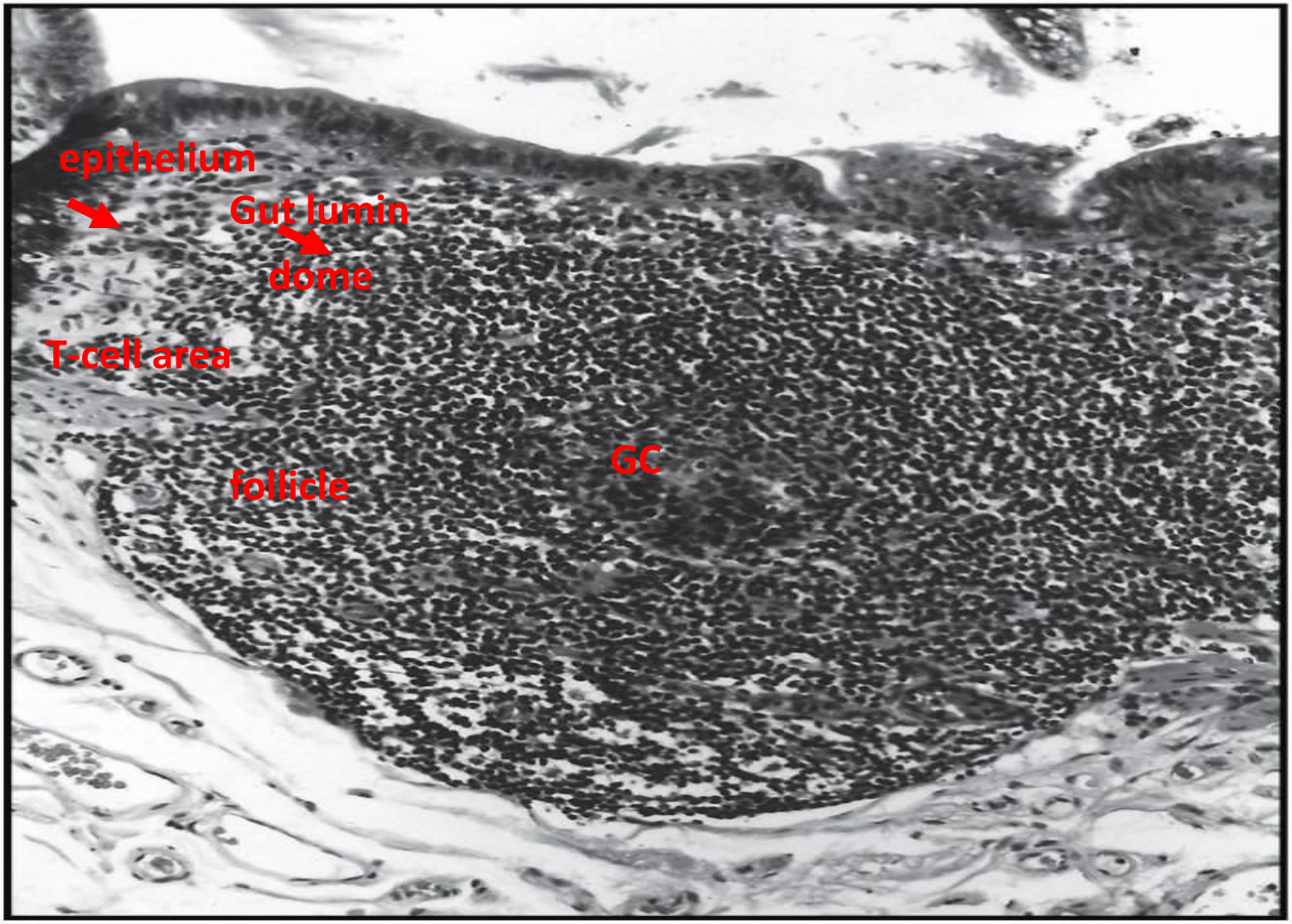
M Cells.

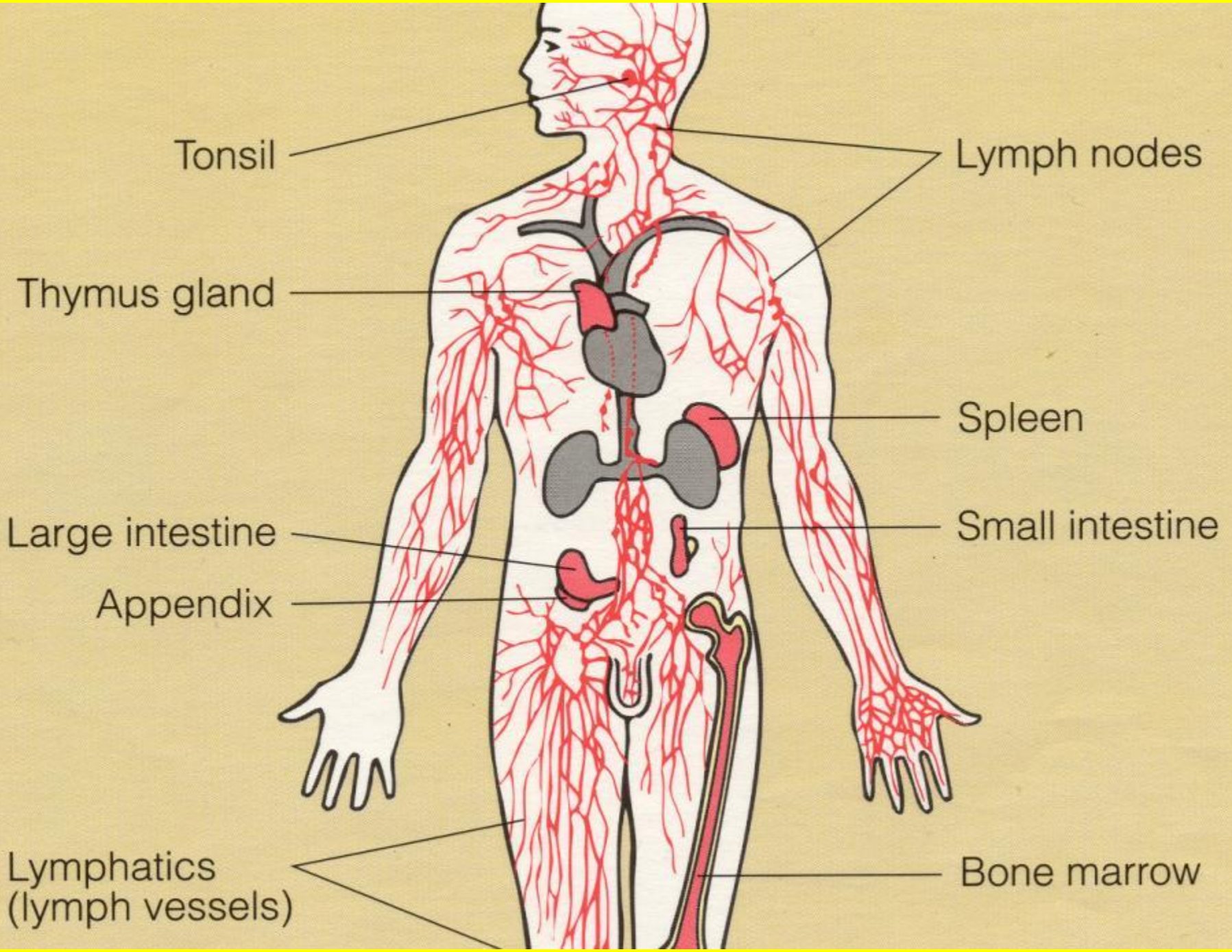
Have a deep invagination or pocket, in the basolateral plasma membrane, which is filled with a cluster of B cells, T cells and Macrophage.

Antigens in intestinal lumen are endocytosed into vesicles and Transported from the luminal membrane to underlying pocket Membrane

Vesicles fuse with the pocket membrane, delivering antigens To lymphocytes and macrophage


M cell
Antigen
T_H cell
Pocket
B cells
Macrophage


epithelium
Gut lumin
dome
T-cell area
GC
follicle


Tonsil
Lymph nodes
Thymus gland
Spleen
Large intestine
Small intestine
Appendix
Lymphatics
(lymph vessels)
Bone marrow

Lymphoid Nodules

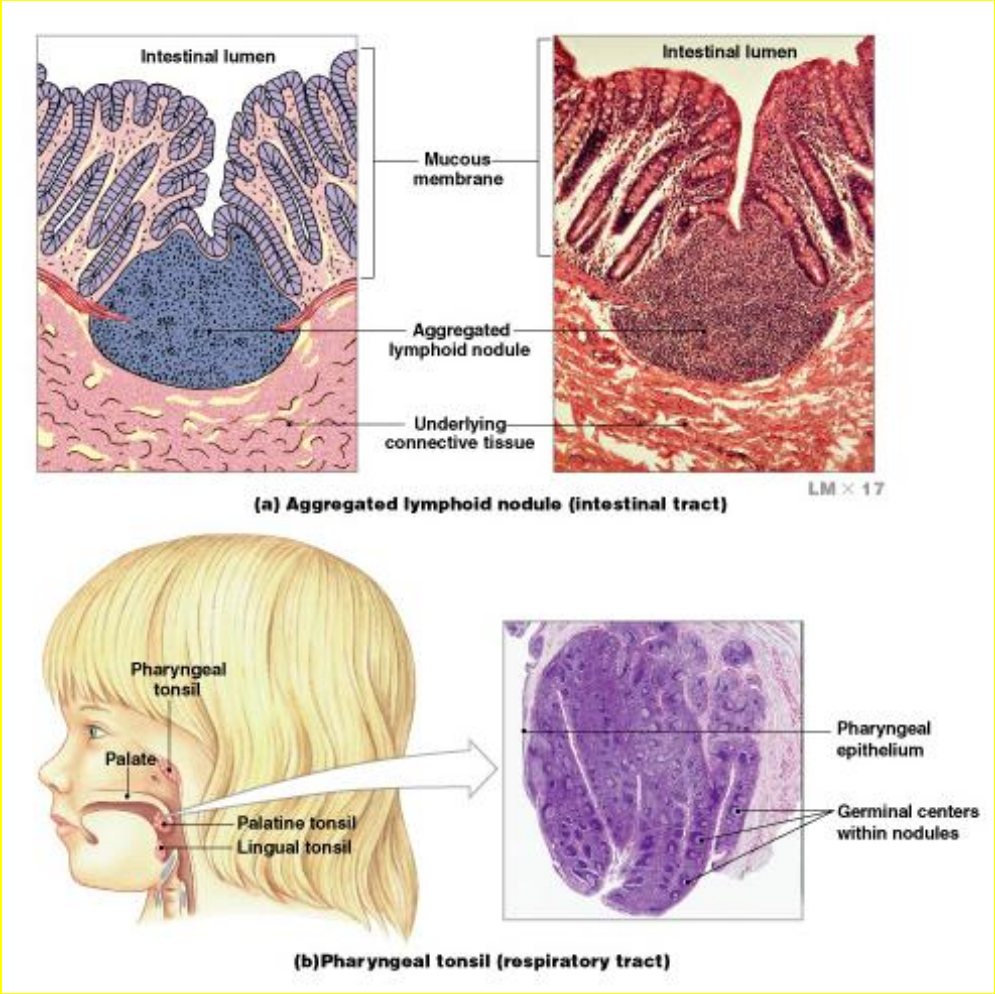


Figure 22-6

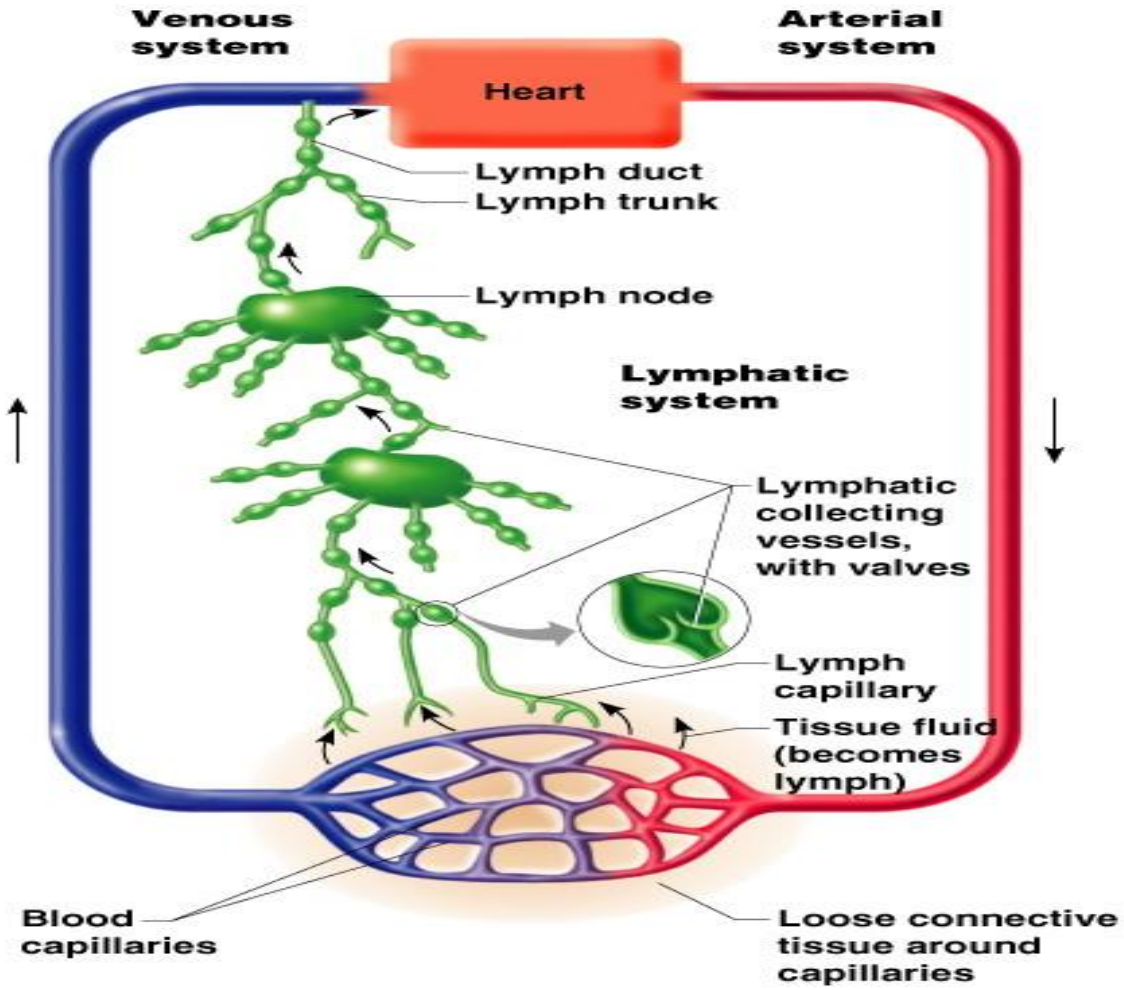
Jobs of Lymphatic System:

Lymphatic System which consists of vessels and organs plays **two vital roles** in our lives:

1) The vessels essentially maintain interstitial fluid levels by **carrying excess fluids as well as any plasma proteins, back into the CVS**.
2) The organs, house critical immune cells such as lymphocytes which carryout our **body defense against infection and disease as well as offer *ACQUIRED IMMUNITY .***

Lymphatic Characteristics

- **Lymph** – excess tissue fluid carried by lymphatic vessels (general definition)
- **Properties of lymphatic vessels**
  - One way system toward the heart
  - No pump
  - Lymph moves toward the heart
    - Milking action of skeletal muscle
    - Rhythmic contraction of smooth muscle in vessel walls



Composition of Lymph

- Lymph is usually a clear, colorless fluid, similar to blood plasma but low is protein
- Its composition varies from place to place; after a meal, for example, lymph draining from the small intestine, takes on a milky appearance, due to lipid content.
- Lymph may contain macrophages, viruses, bacteria, cellular debris and even traveling cancer cells.

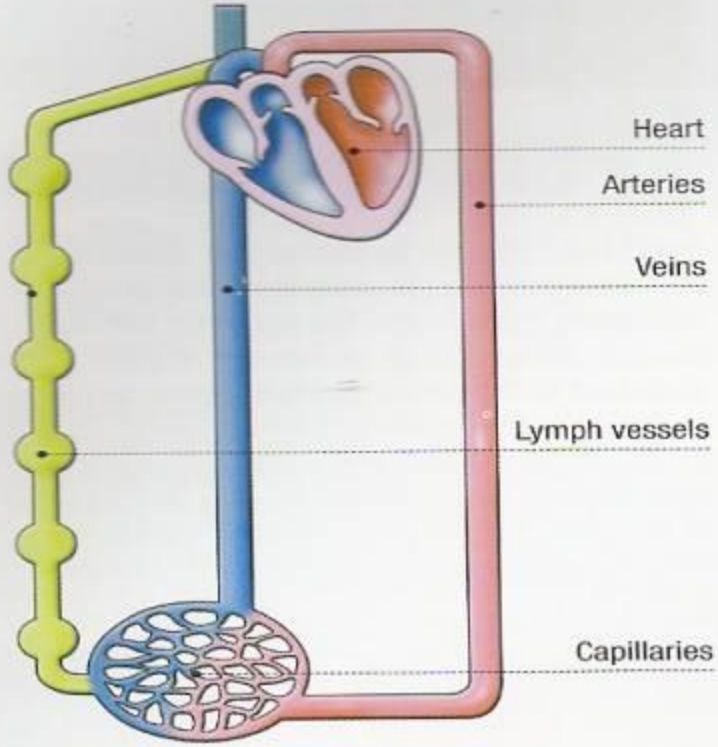
What Type of Vessels Make up the Lymphatic System?

- The vessels are called lymphatics.
- They are thin-walled and are analogous to veins.
- Small lymphatics are similar to capillaries only more porous; Larger vessels are called collecting vessels: both have valves.
- 2 large Ducts: Right **LYMPHATIC DUCT** and **THORACIC DUCT (BOTH EMPTY INTO THE RT AND LT *SUBCLAVIAN VEINS*)**
- Lymph flows only TO THE HEART (ONE WAY).
- This is a **low-pressure, pumpless system**. Lymph moves via skeletal muscles and pressure changes in thorax during breathing only.

CIRCULATION IN THE LYMPH VESSELS

Lymph vessels do not have a central pump equivalent to the heart. Their performance depends especially on their **compression** caused by adjacent muscles. A regular decrease in pressure that occurs inside the thoracic cage during inhalation makes it easy for the lymph to go up from the legs to the trunk of the body. Inside the lymph vessels, there is a **valve system** that ensures lymph circulation in just one direction and prevents its backflow.

RELATIONSHIP BETWEEN LYMPH CIRCULATION AND BLOOD CIRCULATION



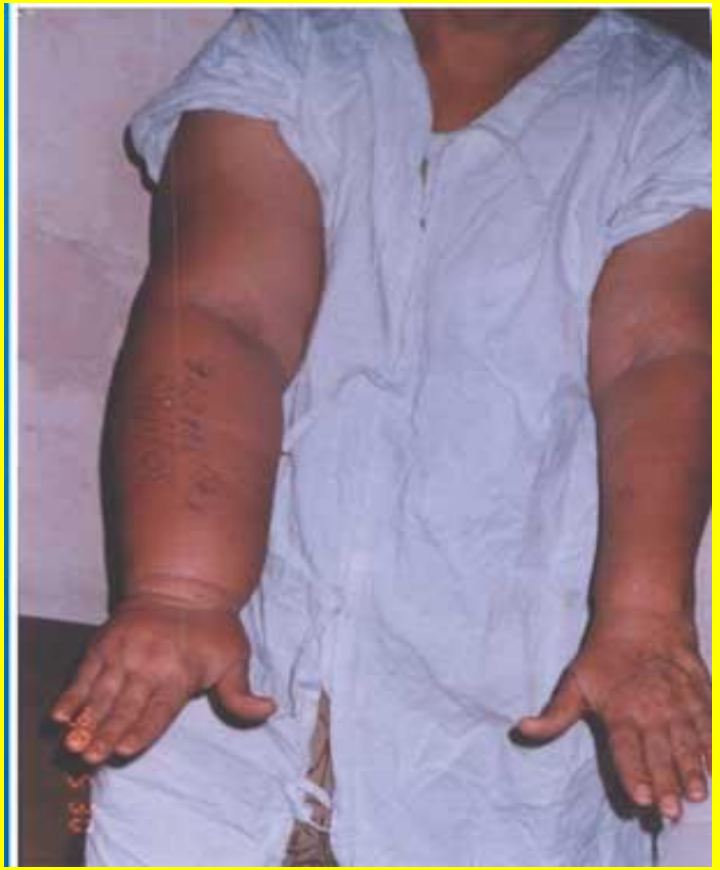
SECTION OF A LYMPH VESSEL

Lymph Carries …

- Harmful materials that enter lymph vessels
  - Bacteria
  - Viruses
  - Cancer cells
  - Cell debris

EDEMA

- **Edema is the excess accumulation of fluids in tissue spaces**. This can retard normal exchange of nutrients and metabolites. Filtration of the extracellular fluid exceeds drainage. Anything that causes increased capillary pressure, such as decreased plasma protein, increased capillary **permeability or lymphatic blockage**, can result in swelling and congestion of the extravascular compartment.



Lymphatic Vessels and Valves

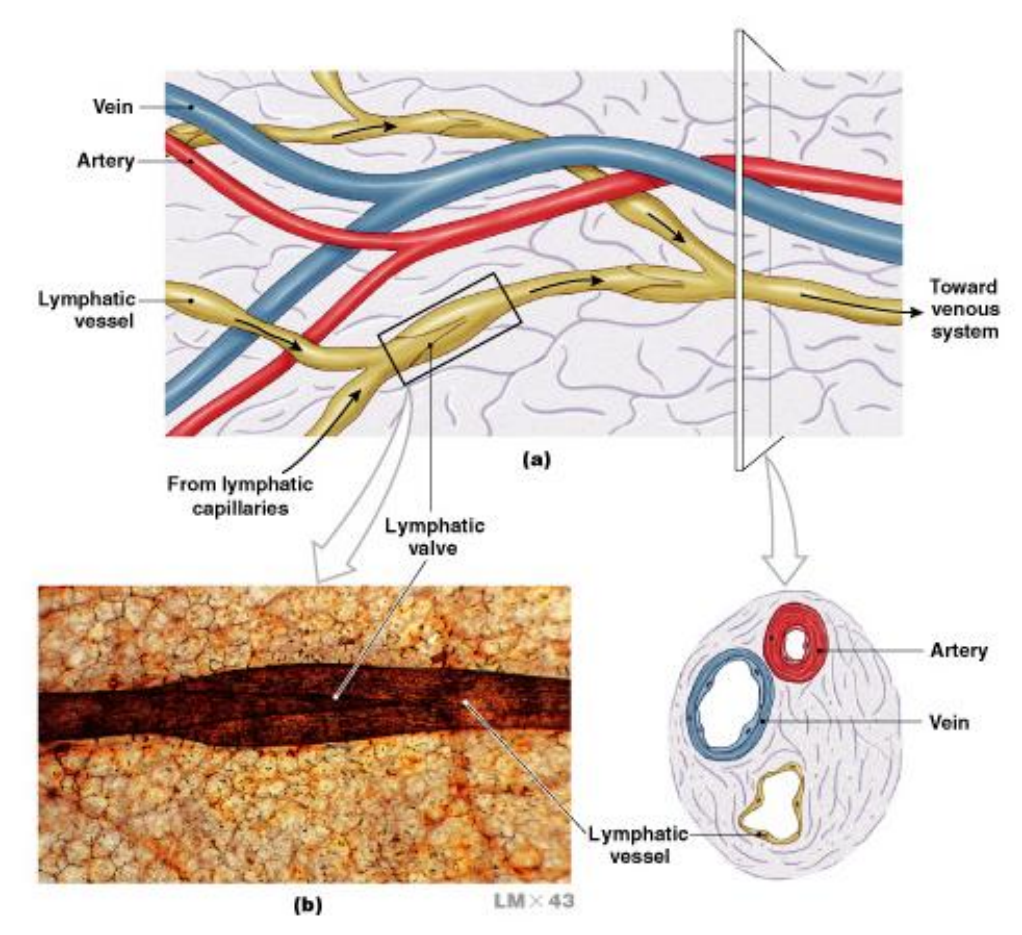


Figure 22-3

Lymphatic System

- **Blood circulates under pressure, fluid component (plasma) seeps through capillaries into surrounding tissues**
  - **Called interstitial fluid**
  - **An adult-3 liters or more per day**
  - **Returned to blood through walls of the venules (prevents edema)**
  - **Remainder of fluid enter lymphatic system**

Lymphatic System…

- **Porous architecture of lymphatic vessels (allows fluids and cells to enter)**
- **Thoracic duct = largest lymphatic vessel**
  - **Empties into L. subclavian vein (lymph from all the body except r. arm and r. side of head)**
- **Ensures steady-state levels of fluid within the circulatory system**

Lymphatic System…

- **Heart does not pump lymph**
- **Lymph flow is achieved by movements of the body's muscles**
- **Series of one-way valves produces one-way movement through vessels**
- **Foreign antigen is picked up by the lymphatic system and carried to lymph nodes**

Circulation of lymphocytes in response to infection

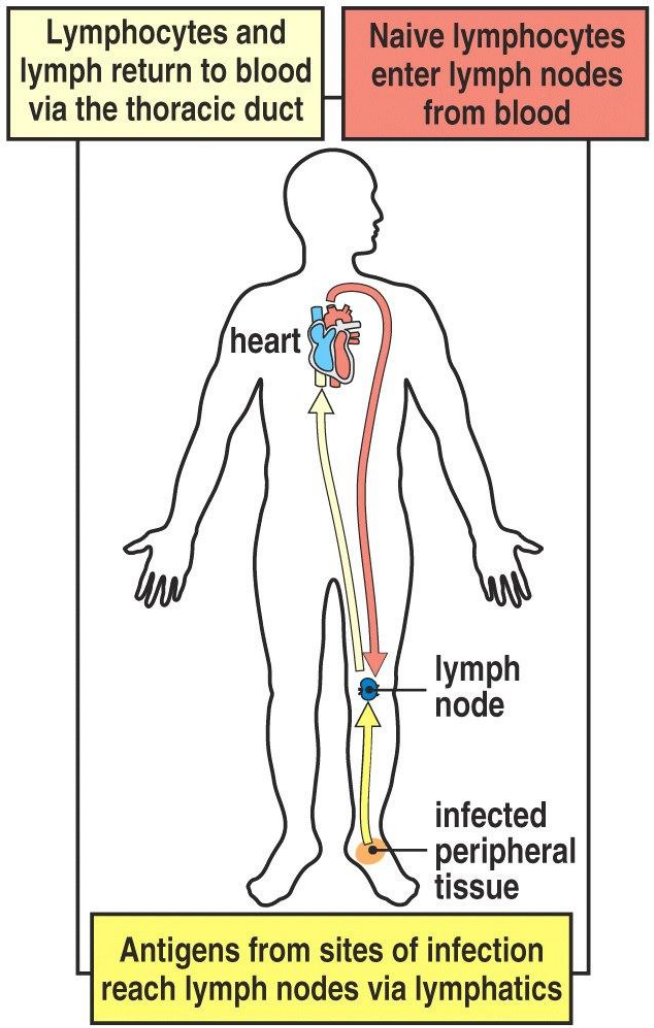


Figure 1-11 Immunobiology, 6/e. (© Garland Science 2005)

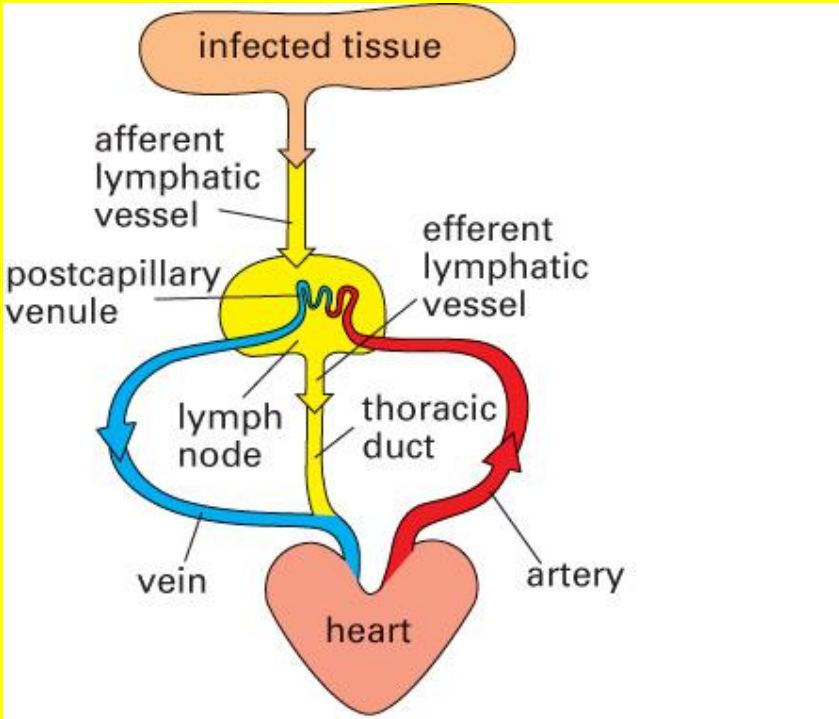


Figure 24–14. Molecular Biology of the Cell, 4th Edition.