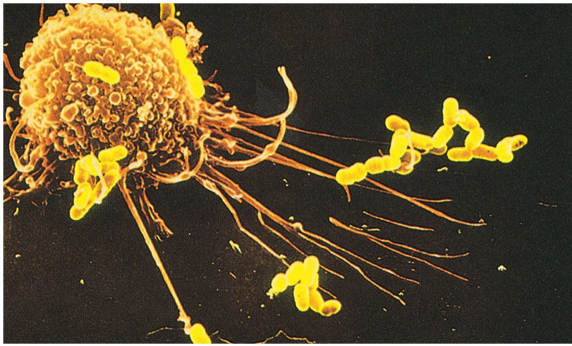


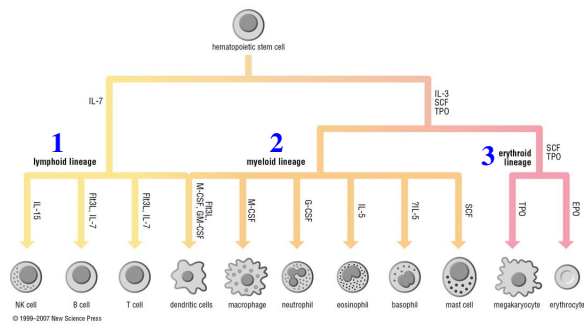
## Chapter 2. Cells and Organs of the Immune System



## Hematopoiesis

- **Hematopoiesis**- formation and development of WBC and RBC → bone marrow.
- **Hematopoietic stem cells (HSC)**- give rise to any blood cells (constant number, self renewing)
- Yolk sac (2 months) → liver & spleen (3-7 months) → Bone marrow (birth)

From **Immunity: The Immune Response in Infectious and Inflammatory Disease** by DeFranco, Locksley and Robertson



## Hematopoiesis

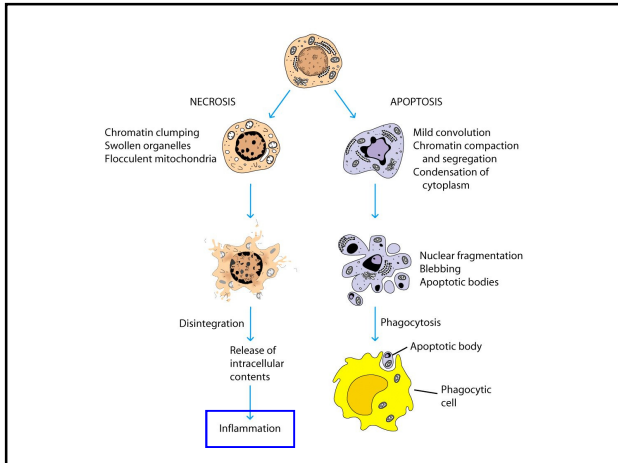
- Progenitor commitment depends on the influence of **growth factors and cytokines**
- In bone marrow **stromal cells** support the growth and differentiation of hematopoietic cells → **direct contact or growth factors**.
- **Stromal cells** – meshwork of fat cells, endothelial cells, fibroblasts & MΦs.
- Hematopoiesis – regulated at the **genetic level** through several transcription factors (GATA-2, Ikaros, Bmi-1, etc)

## Hematopoiesis

- **Hematopoiesis maintains steady levels of blood cells**
- **3.7 x 10<sup>11</sup> cells/day!!!**
- **Regulation:**
  - Cytokines produced by bone marrow stromal cells
  - Cytokines produced by non-hematopoietic cells (T cells, MΦs)
  - Regulation of receptors for hematopoietically active cytokines
  - Removal of cells by **programmed cell death**

## Apoptosis

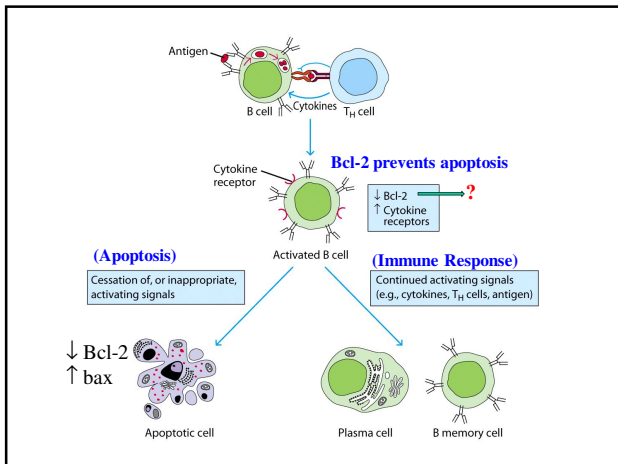
- Programmed cell death
- **Changes:** shrinking, rearrangement of cytoskeleton, alteration of cell membrane permeability, chromatin condensation, cytoplasm fragmentation
- **Difference between apoptosis and necrosis?**



**TABLE 2-2** Genes that regulate apoptosis

Gene	Function	Role in apoptosis
<i>bcl-2</i>	Prevents apoptosis	Inhibits
<i>bax</i>	Opposes <i>bcl-2</i>	Promotes
<i>bcl-X<sub>L</sub></i> ( <i>bcl-Long</i> )	Prevents apoptosis	Inhibits
<i>bcl-X<sub>S</sub></i> ( <i>bcl-Short</i> )	Opposes <i>bcl-X<sub>L</sub></i>	Promotes
caspase (several different ones)	Protease	Promotes
<i>fas</i>	Induces apoptosis	Initiates

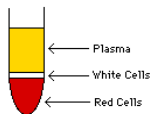
**bcl** - B cell lymphoma



## Cells of the Immune System

### Separation of blood constituents

- If **heparinized blood** is centrifuged, three layers are obtained:



- Top layer - yellow liquid - **plasma**
- Middle layer - white cells (**leukocytes**)
- Lowest layer - red cells (**erythrocytes**)

- If the blood is allowed to **clot first**, the yellow supernatant is depleted of clotting factors and is referred to as **serum**.

**TABLE 2-4** Normal adult blood cell counts

Cell type	Cells/mm <sup>3</sup>	Total leukocytes (%)
Red blood cells	$5.0 \times 10^6$	
Platelets	$2.5 \times 10^5$	
Leukocytes	$7.3 \times 10^3$	(NK cells 5-10%)
Neutrophil	$3.7-5.1 \times 10^3$	50-70
Lymphocyte	$1.5-3.0 \times 10^3$	20-40
Monocyte	$1-4.4 \times 10^2$	1-6
Eosinophil	$1-2.2 \times 10^2$	1-3
Basophil	$<1.3 \times 10^2$	<1

Table 2-4  
Kuby IMMUNOLOGY, Sixth Edition  
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## Lymphoid cells

- **Three populations:**
  - B cells
  - T cells
  - NK cells
- **Naïve lymphocyte** → Ag exposure → Lymphoblast → Effector cells & Memory cells
  - **Effector cells:** T helper (Th) or T cytotoxic (Tc) ---- **Tregs, Th17**

## Lymphocytes

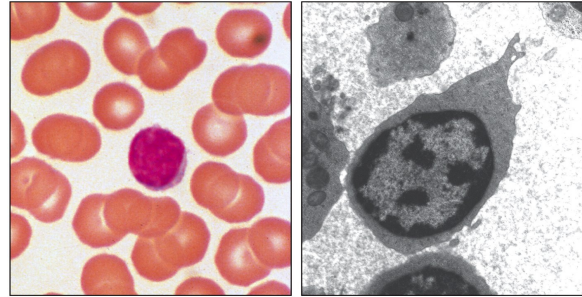
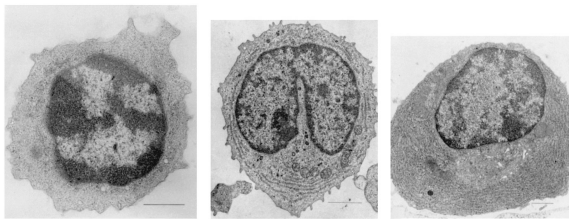


Figure 1-5 Immunobiology, 6/e. (© Garland Science 2005)



Small lymphocyte (T or B)  
6 μm diameter

Blast cell (T or B)  
15 μm diameter

Plasma cell (B)  
15 μm diameter

## B Lymphocytes

- **CD** - cluster of differentiation (unique lymphocyte surface molecules)
- **Surface markers:**
  - Surface Ig (free Ag)
  - MHC-II molecules
  - CD19 – Co-receptor
  - CD35 (CR1) and CD21 (CR2)
  - CD32 (FcγRII),
  - CD40 (signal transduction)
  - CD80 (B7-1) and CD86 (B7-2) –Signal transd

## T lymphocytes

- **T cell receptor (TCR)** – recognizes Ag after processing and IF presented by major histocompatibility complex (MHC) molecules
- **Surface markers:**
  - TCR (processed Ag + MHC)
  - CD3 (signal transduction)
  - CD4 or CD8 (interacts with MHC molecules)
  - CD28 (interacts with CD80 and CD86 → B7 molecules)

## T cells

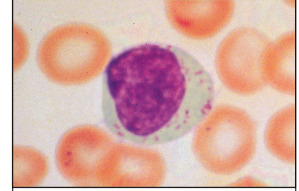
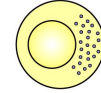
- There are two types of MHC molecules - class I MHC and class II MHC.
- Two types of T cells: Helper (CD4+) T cells and Cytotoxic (CD8+) T cells.
- CD4+ T cells recognize antigen presented on class II MHC. **Role:** Cytokine secretion
- CD8+ T cells recognize antigen presented on class I MHC. **Role:** Cell killing
- Normal ratio: 2:1 (CD4 to CD8)
- **Treg** – CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>

## NK cells

- Lack TCR of T cells or sIg of B cells
- Unique surface markers: **CD16** (FcγRIII) and **CD56**
- Action similar to Tc (CD8+) cells
- **Role:** destroys tumor cells and virus-infected cells
- Recognition due to altered expression of MHC-I and **ADCC** (Ab-Dependent Cell Cytotoxicity)
- **NKI-T cell:** T cell and NK cell. Expresses TCR, TCR interacts with **CD1** (similar to MHC-II), express CD16, and cell killing.

## Natural killer (NK) cell

- **Role:** destroys tumor cells and virus-infected cells



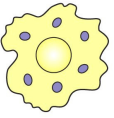
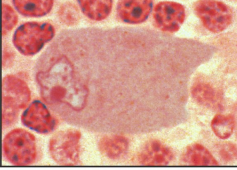
Releases lytic granules that kill some virus-infected cells

Figure 1-6 Immunobiology, 6/e, © Garland Science 2005

## Mononuclear Phagocytes:

### a) Macrophage

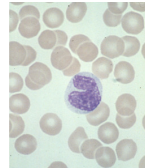
- Two main functions

Cell	Activated function
<b>Macrophage</b>  	Phagocytosis and activation of bactericidal mechanisms  Antigen presentation

## Macrophage (MΦ)

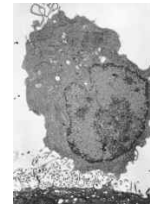
- Monocytes develop in the bone marrow and circulate in blood, becoming macrophages upon **entering the tissues** – forming the mononuclear phagocyte system.
- Macrophages are long-lived cells.
- **Free vs Fixed macrophages**

Monocyte



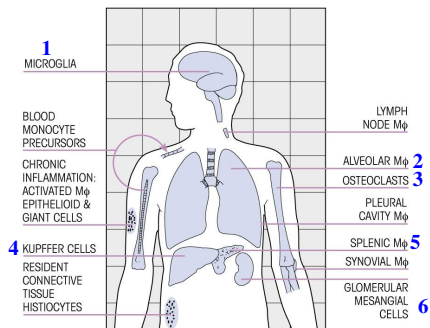
<http://biomed.brown.edu/Course/BIO189/Lab5/monocyte.htm>

Macrophage



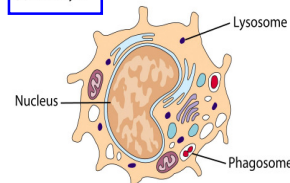
<http://www.popcouncil.org/imaging/macrophage.jpg>

## The mononuclear phagocyte system

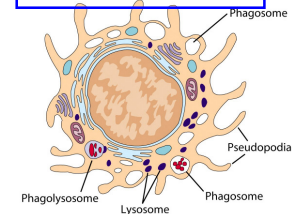


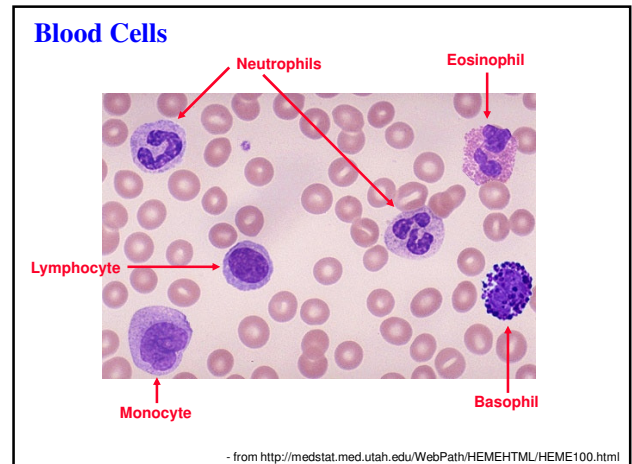
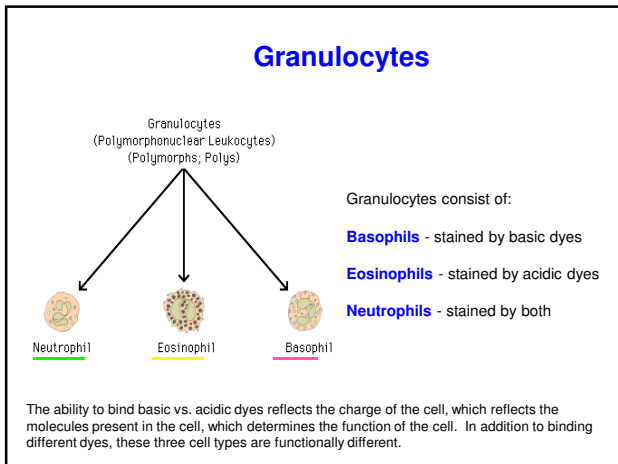
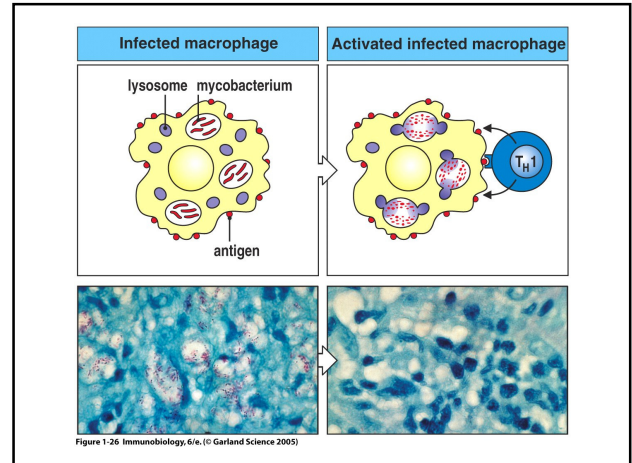
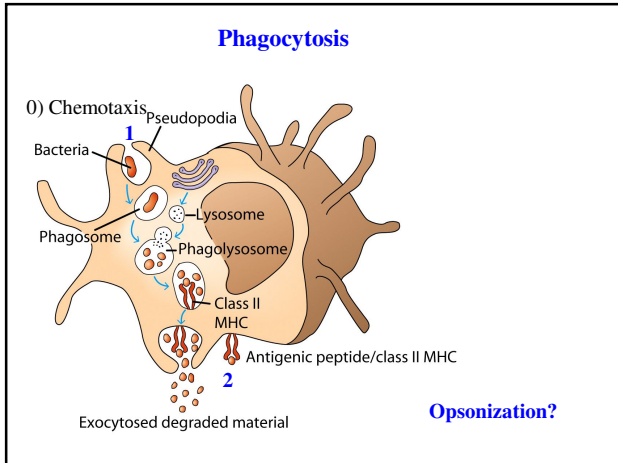
© 2001 Blackwell Publishing Ltd, Roitt's Essential Immunology

(a) Monocyte



(b) Macrophage **5-10 fold larger**





### Neutrophils:

- about 50-70% of blood leukocytes are neutrophils
- have a multilobed nucleus and cytoplasmic granules
- granules are bactericidal
- main **phagocytic (acute)** cell. Better than MΦs
- ↑ in neutrophils – leukocytosis and infection
- recruited to site of infection/inflammation

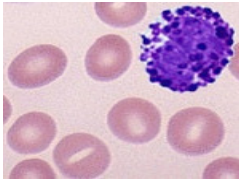
### Eosinophils:

- Somewhat phagocytic; Comprise 1-3% of leukocytes
- Important in defense against invading parasites and **worms** (helminths) → toxic granules
- Worm infections are often accompanied by eosinophilia.
- Release eosinophilic granules that damage parasites



### Basophils:

- Comprise <1% of leukocytes
- Non-phagocytic
- Release of pharmacologically active chemicals from granules → allergic reactions



### MAST CELLS (~ BASOPHILS):

- Present mostly in tissues

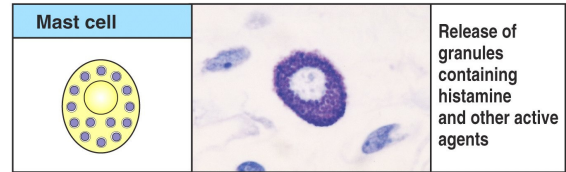
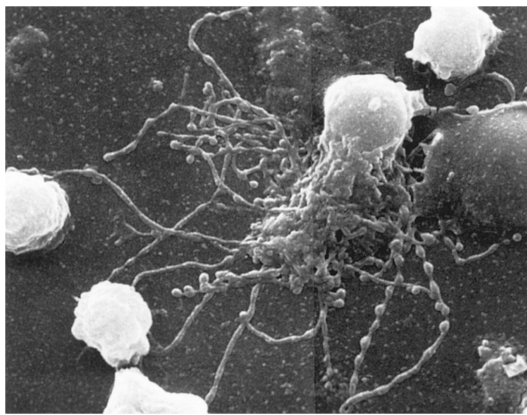


Figure 1-4 part 3 of 3 Immunobiology, 6/e, (© Garland Science 2005)



### Dendritic Cells

- 4 Types
- **Major role:** Ag uptake in peripheral sites, and presentation to Th cells in lymph nodes
- Best APC
- Constitutive expression of MHC-II and CD80, CD86 (B7)
- **Follicular dendritic cells:** Unique type of cells, lacks MHC-II but interact with B cells (Ag-Ab complexes)  
\* Localized to B cell follicles

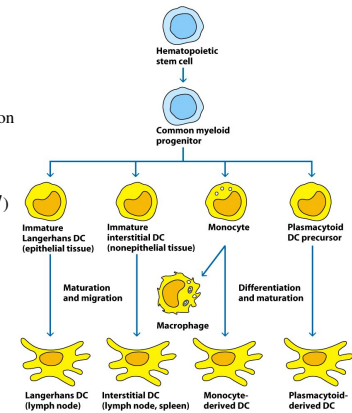


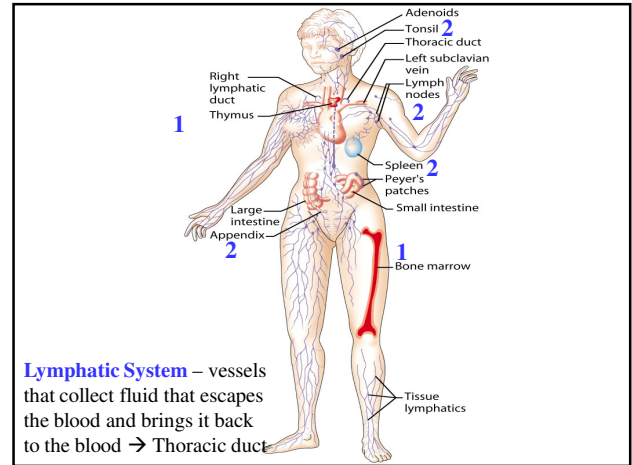
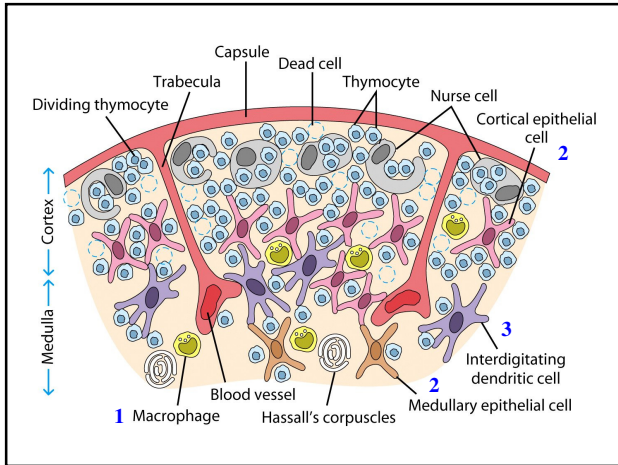
Figure 2-10  
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### Organs of the Immune System

- **Primary Lymphoid Organs**
  - Bone marrow and Thymus
  - Origen and maturation of lymphocytes
- **Secondary Lymphoid Organs**
  - Lymph nodes, Spleen, Mucosal-associated lymphoid tissues (MALT)
  - Trap antigen for interaction with lymphocytes
  - Where IRs take place!

### THYMUS

- Site of T cell development and maturation
- **Two compartments:**
  - **CORTEX:** Packed with immature T cells (Thymocytes)
  - **MEDULLA:** Sparsely populated with mature T cells
- **Function:** Generate populations of T cells with “correct” TCRs
- Only 5% of incoming thymocytes exit the thymus
- **DiGeorge’s syndrome (H)** and **nude mice**



**Lymphatic System** – vessels that collect fluid that escapes the blood and brings it back to the blood → Thoracic duct

## Lymphatic System

- Plasma “leaks” → ~2.9 l/day (interstitial fluid)
- Returned through lymphatic vessels → lymph
- Muscles → one way flow

## Secondary Lymphoid Organs

- Lymph nodes, Spleen, Mucosal-associated lymphoid tissues (MALT)
- Trap antigen for interaction with lymphocytes
- Primary vs secondary follicles
- **Where IRs take place!**
- 98% naïve lymphocytes (2% blood)
- HEV

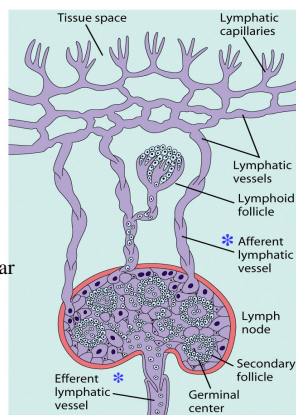
## LYMPH NODES

- Site for immune responses for antigens in lymph
- Interstitial fluid
- Perfect design to encounter antigens from tissues

### Three regions:

- CORTEX – Primary follicles containing B cells, MΦ, follicular DC into Primary Follicles
- PARACORTEX- T cell area
- MEDULLA- MΦ and Plasma cells

### Role of immature DC?



## A lymph node

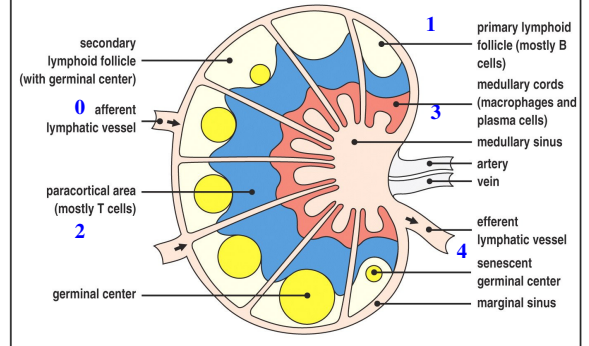


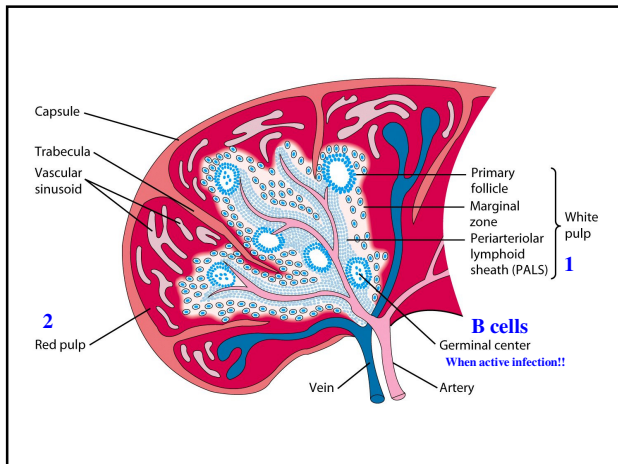
Figure 1-8 part 1 of 2 Immunobiology, 6/e. © Garland Science 2005

## High Endothelial Venules (HEV)

- Venules that allow recruitment of NAÏVE lymphocytes from the blood
- After Ag stimulation increase recruitment of lymphocytes from the blood → swelling
- Exception → Spleen
- L-selectin (L-sel)

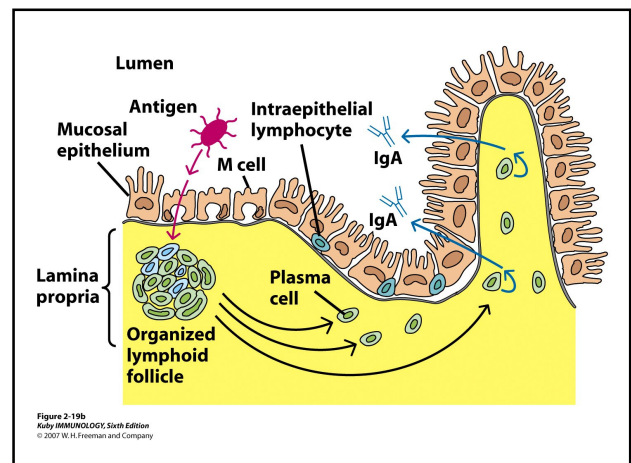
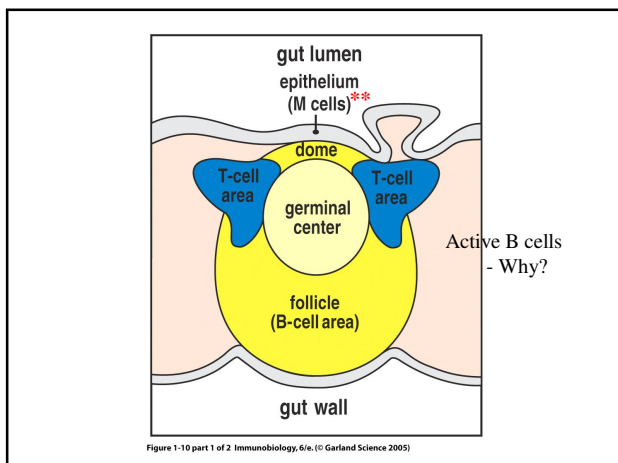
## SPLEEN

- Contains 25% of total lymphocytes!
- Collects antigens from the blood through the splenic artery. Removes old RBCs
- **Two regions:** RED and WHITE PULP
- **RED PULP:** MΦ and RBC
- **WHITE PULP:** Lymphoid tissue. Surrounds the splenic artery to form the periarteriolar lymphoid sheath (PALS). Populated by T cells and B cells
- **MARGINAL ZONE:** MΦ

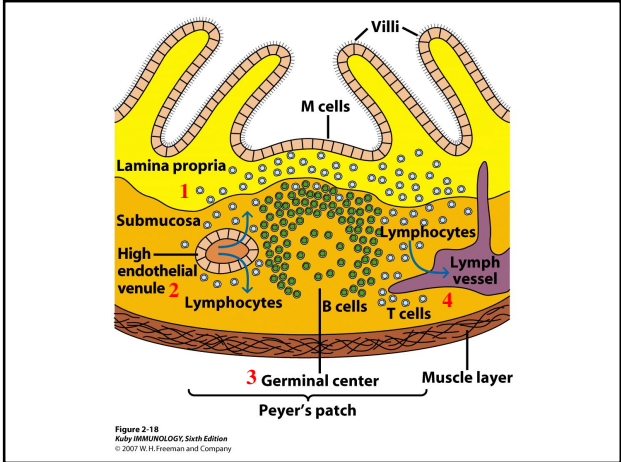


## Mucosal Associated Lymphoid Tissue (MALT)

- **Role:** Collects antigens from Respiratory, Gastrointestinal, and Urogenital tracts.
- In small intestine: **GALT**
  - Lymphoid tissue in Payer's Patches
  - Antigen delivered by M cells to DC
  - In Payer's Patches – B cell follicles are constitutively active → Germinal center







The End

