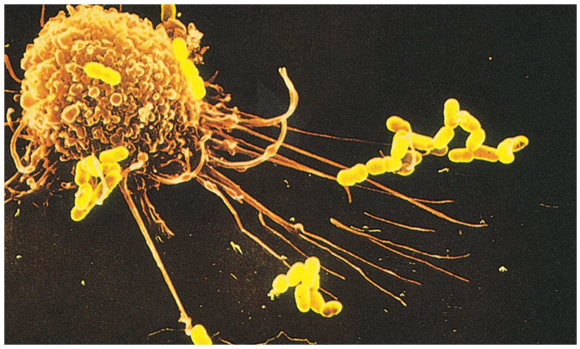
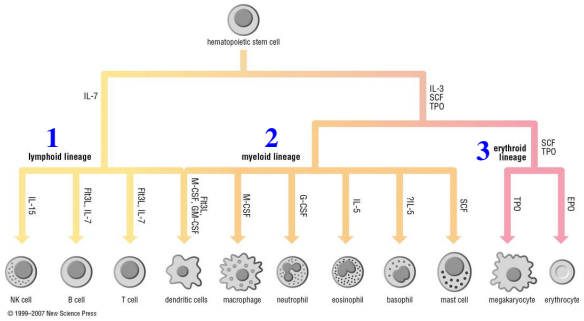
Chapter 2. Cells and Organs of the Immune System



Hematopoiesis

- Hematopoiesis- formation and development of WBC and RBC → bone marrow.
- Hematopoietic stem cell- 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
- **Regulation:**
  - Cytokines produced be 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?

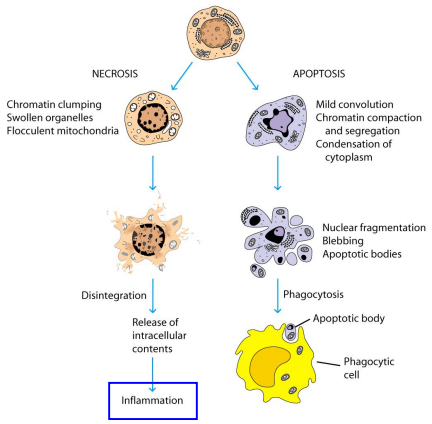
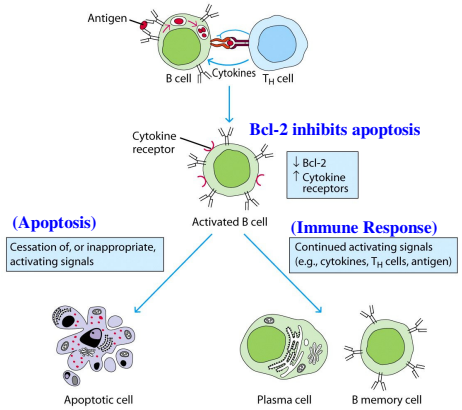


TABLE 2-2 Genes that regulate apoptosis

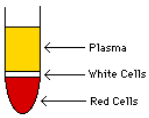
Gene	Function	Role in apoptosis
bcl-2	Prevents apoptosis	Inhibits
bax	Opposes *bcl-2*	Promotes
bcl-X_L (bcl-Long)	Prevents apoptosis	Inhibits
bcl-X_S (bcl-Short)	Opposes *bcl-X_L*	Promotes
caspase (several different ones)	Protease	Promotes
fas	Induces apoptosis	Initiates

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^3	Total leukocytes (%)
Red blood cells	5.0×10^6	
Platelets	2.5×10^5	
Leukocytes	7.3×10^3	(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

Lymphocytes

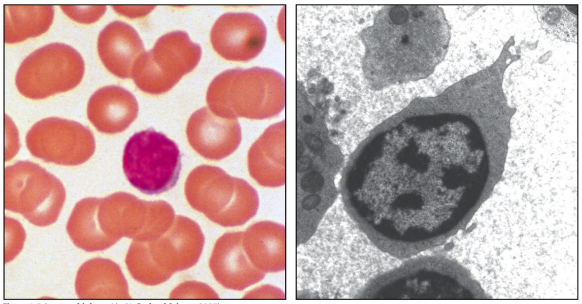
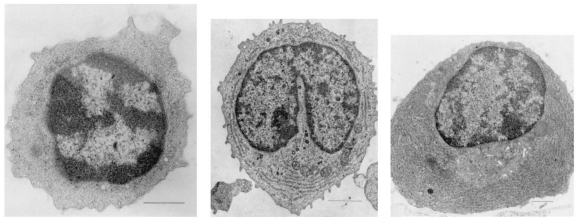


Figure 1-5 Immunobiology, 6/e. (© Garland Science 2005)

Lymphocytes

- **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)



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
  - CD35 (CR1) and CD21 (CR2)
  - CD32 (FcγRII),
  - CD40
  - CD80 (B7-1) and CD86 (B7-2)

T lymphocytes

- **T cell receptor (TCR)** – recognizes Ag after processing and 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 B7 molecules)

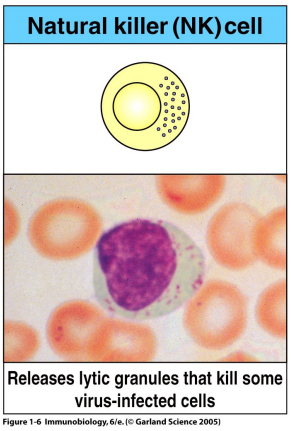
T cells

- There are two types of MHC molecule - 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+CD25+

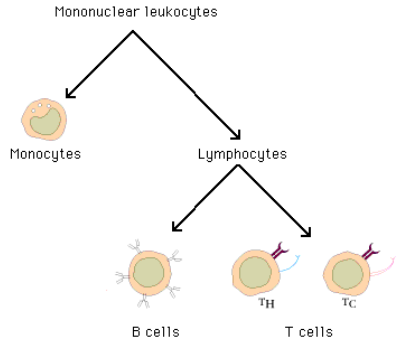
NK cells

- 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)
- **NK1-T cell:** T cell and NK cell. Expresses TCR, TCR interacts with CD1 (similar to MHC-1), express CD16, and cell killing.

• Role: destroys tumor cells and virus-infected cells

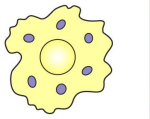
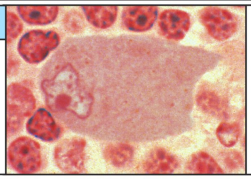


The mononuclear leukocytes consist of:



Macrophage

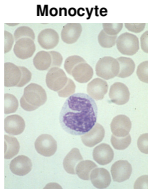
- Two main functions

Cell	Activated function
Macrophage  	Phagocytosis and activation of bactericidal mechanisms Antigen presentation

Macrophage (MΦ)

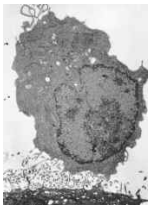
- **Monocytes develop in the bone marrow and circulate in blood, becoming macrophages upon entering the tissues – forming the mononuclear phagocyte system.**
- **Macrophages are long-lived cells.**
- **Free vs Fixed macrophages**

Monocyte



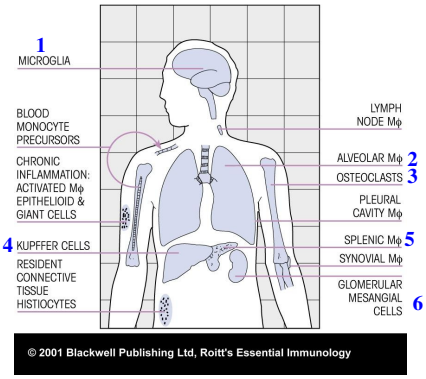
http://biomed.brown.edu/Courses/BIO189/Lab5/monocyte.htm

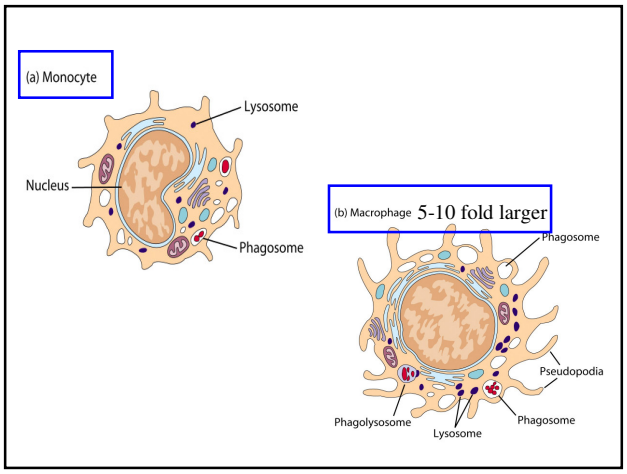
Macrophage



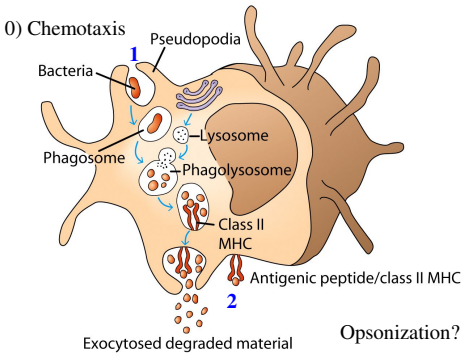
http://www.popcouncil.org/images/macrophage.jpg

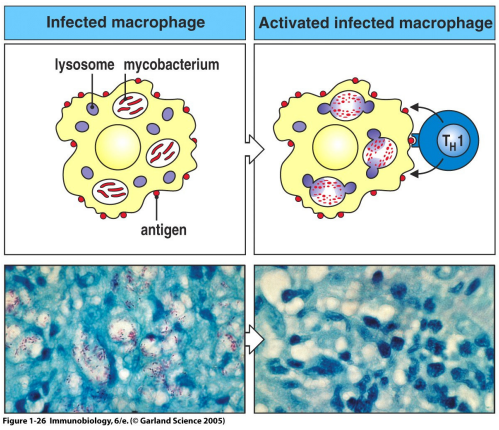
The mononuclear phagocyte system



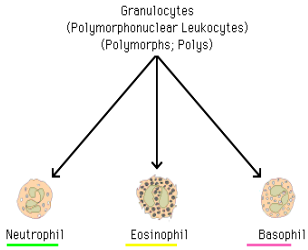


Phagocytosis





Granulocytes



Granulocytes consist of:

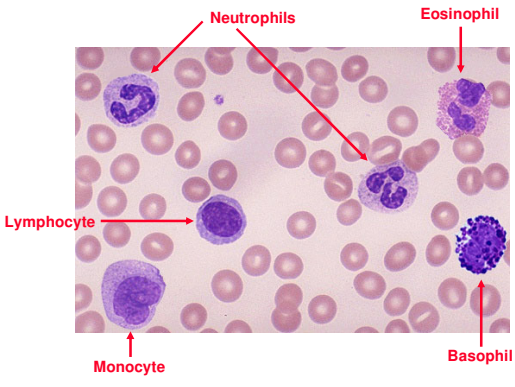
Basophils - stained by basic dyes

Eosinophils - stained by acidic dyes

Neutrophils - stained by both

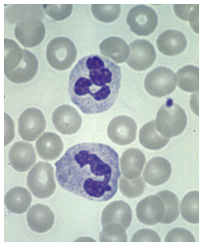
The ability to bind basic vs. acidic dyes reflects the charge of the cell, which reflects the molecules present in the cell, which determines the function of the cell. In addition to binding different dyes, these three cell types are functionally different.

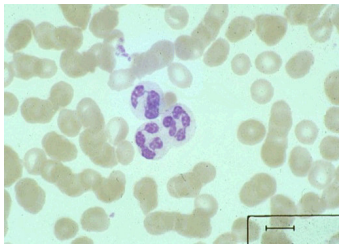
Blood Cells



- from http://medstat.med.utah.edu/WebPath/HEMEHTML/HEME100.html

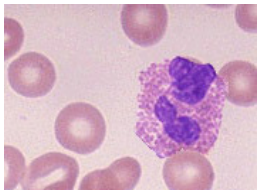
Neutrophils:
- about 50-70% of blood leukocytes are neutrophils
- have a multilobed nucleus and cytoplasmic granules
- granules are bactericidal
- main phagocytic (acute) cell. Better than MΦs
- ↑ in neutrophils – leukocytosis and infection
- recruited to site of infection/inflammation





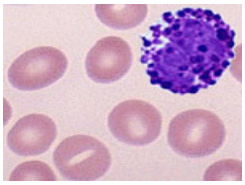
Eosinophils:

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



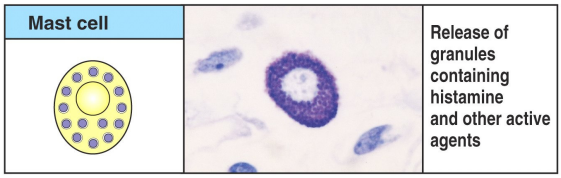
Basophils:

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



MAST CELLS (~ BASOPHILS):

- Present mostly in tissues



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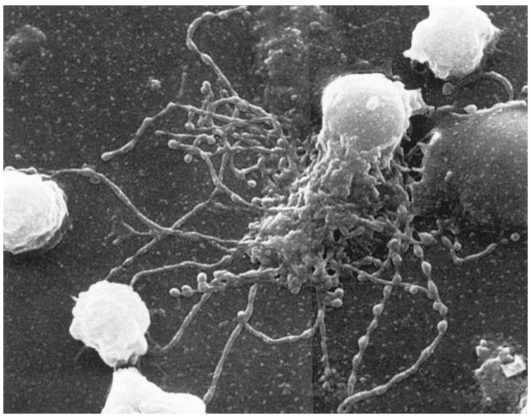

Dendritic Cells

- 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 B7 (CD80, CD86)
- **Follicular dendritic cells:** Unique type of cells, lacks MHC-II but interact with B cells (Ag-Ab complexes)
  * Localized to B cell follicles

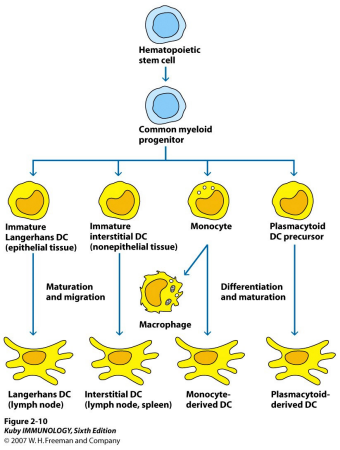

Figure 2-10
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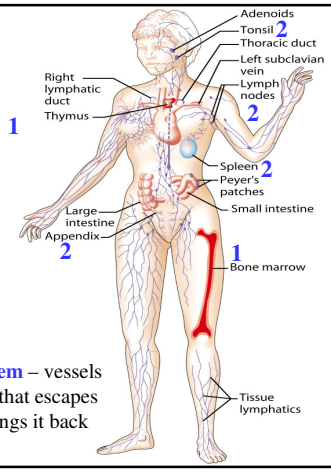
Organs of the Immune System

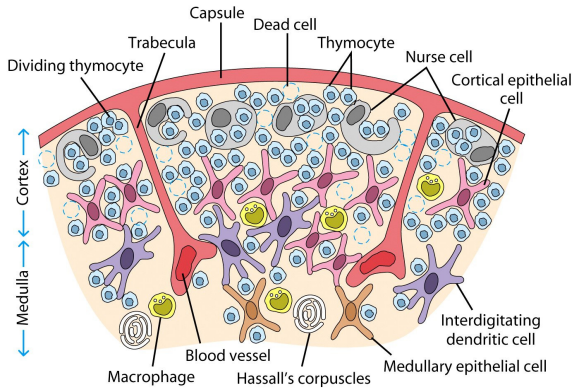
- **Primary Lymphoid Organs**
  - Bone marrow and Thymus
  - Origen and maturation of lymphocytes
- **Secondary Lymphoid Organs**
  - Lymph nodes, Spleen, Mucosal-associated lymphopid tissues (MALT)
  - Trap antigen for interaction with lymphocytes
  - Where IRs take place!



Lymphatic System – vessels that collect fluid that escapes the blood and brings it back to the blood

THYMUS

- Site of T cell development and maturation
- Two compartments: CORTEX and MEDULLA
  - 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



Secondary Lymphoid Organs

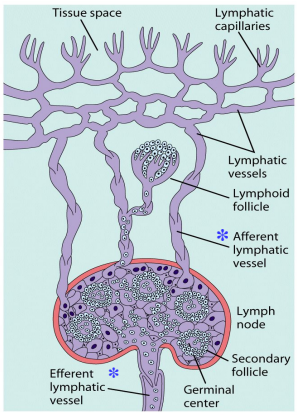
- Lymph nodes, Spleen, Mucosal-associated lymphopid tissues (MALT)
- Trap antigen for interaction with lymphocytes
- Where IRs take place!

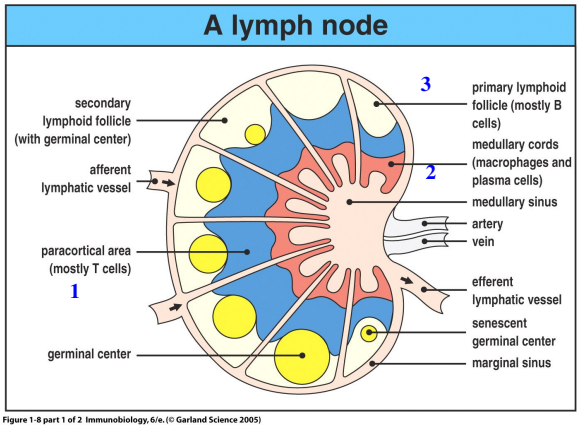
LYMPH NODES

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

-Three regions: CORTEX, PARACORTEX and MEDULLA

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

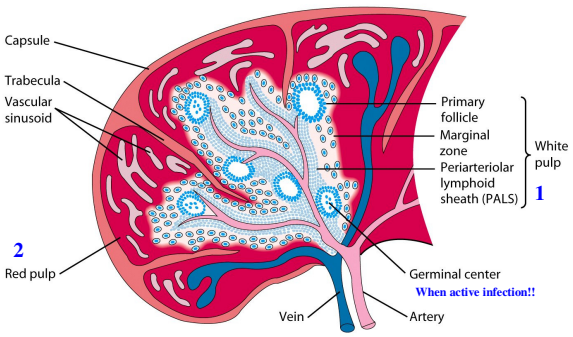




SPLEEN

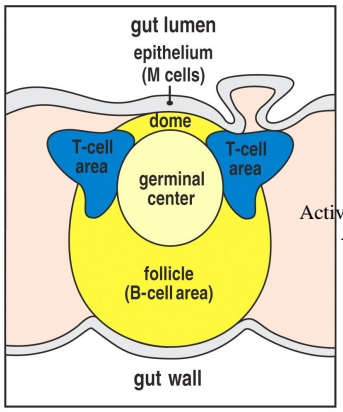
- Contains 25% of total lymphocytes!
- Collects antigens from the blood through the splenic artery. Removes old RBCs
- Two regions: RED and WHITE PULP

-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 DC
-MARGINAL ZONE: MΦ



Mucosal Associated Lymphoid Tisssue (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 <u>constitutively</u> active → Germinal center



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Active B cells - Why?

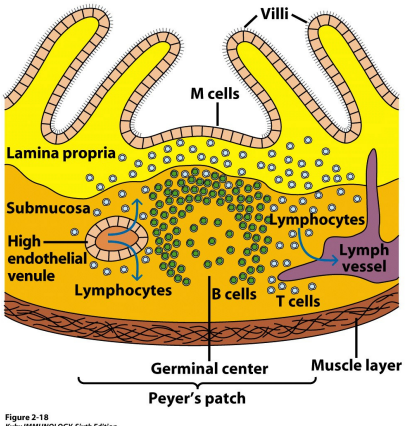

Figure 2-18
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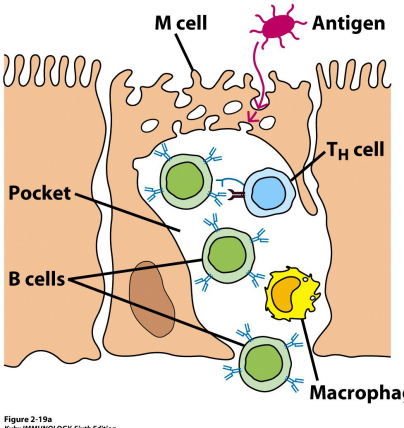

Figure 2-19a
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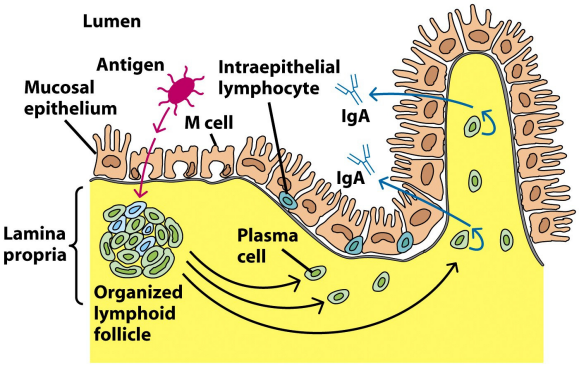

Figure 2-19b
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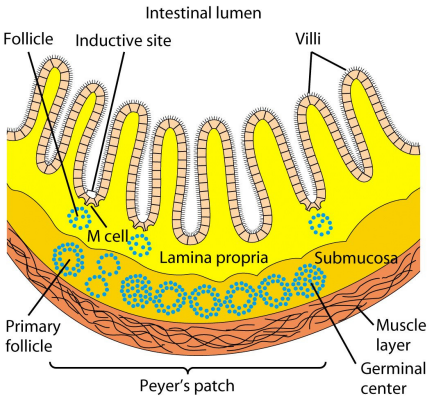
GUT ASSOCIATED LYMPHOID TISSUE- GALT



The End