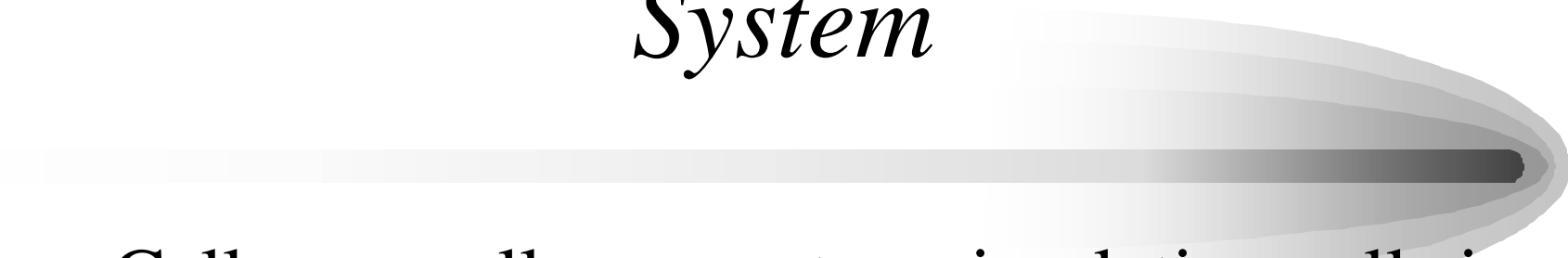


# *Cells and Tissues of the Immune System*



- Cells normally present as circulating cells in the blood and lymph, as collections in lymphoid organs, and as scattered cells in all tissues except the CNS
- The immune system has to be able to respond to a very large number of foreign antigens at any site in the body, and only a small number of lymphocytes specifically respond to any one antigen

# *Lymphocytes*

- These are the cells that specifically recognize and respond to foreign antigens
- The overall immune response depends on non-specific cells called accessory cells (mononuclear phagocytes, dendritic cells and Langerhans cells)
- There are generally two types of lymphocytes: T (thymus derived) and B (bone marrow derived) that exert different functions

# *Lymphocytes*

- Specificity of response due to lymphocytes: these are the only cells of the body capable of recognizing different antigenic determinants (epitopes)
  - small lymphocyte (8-10  $\mu\text{m}$  in diameter) has large nucleus and thin rim of cytoplasm. All lymphocytes originate in BM (shown by irradiation and BM transplants of different mouse strains)
  - in early stages of development cells do not have antigen receptors & do not respond to Ag

# *Lymphocytes*

- B lymphocytes
  - in birds first shown to mature in an organ called bursa of Fabricius (part of bird gut). There is no anatomic equivalent in mammals and early stages of development occur in BM.
  - These are the only cells capable of producing antibodies (Ab)
  - Antigen receptors are membrane bound Ab's (mIg), and binding to mIg stimulates activation of B cells

# *Lymphocytes*

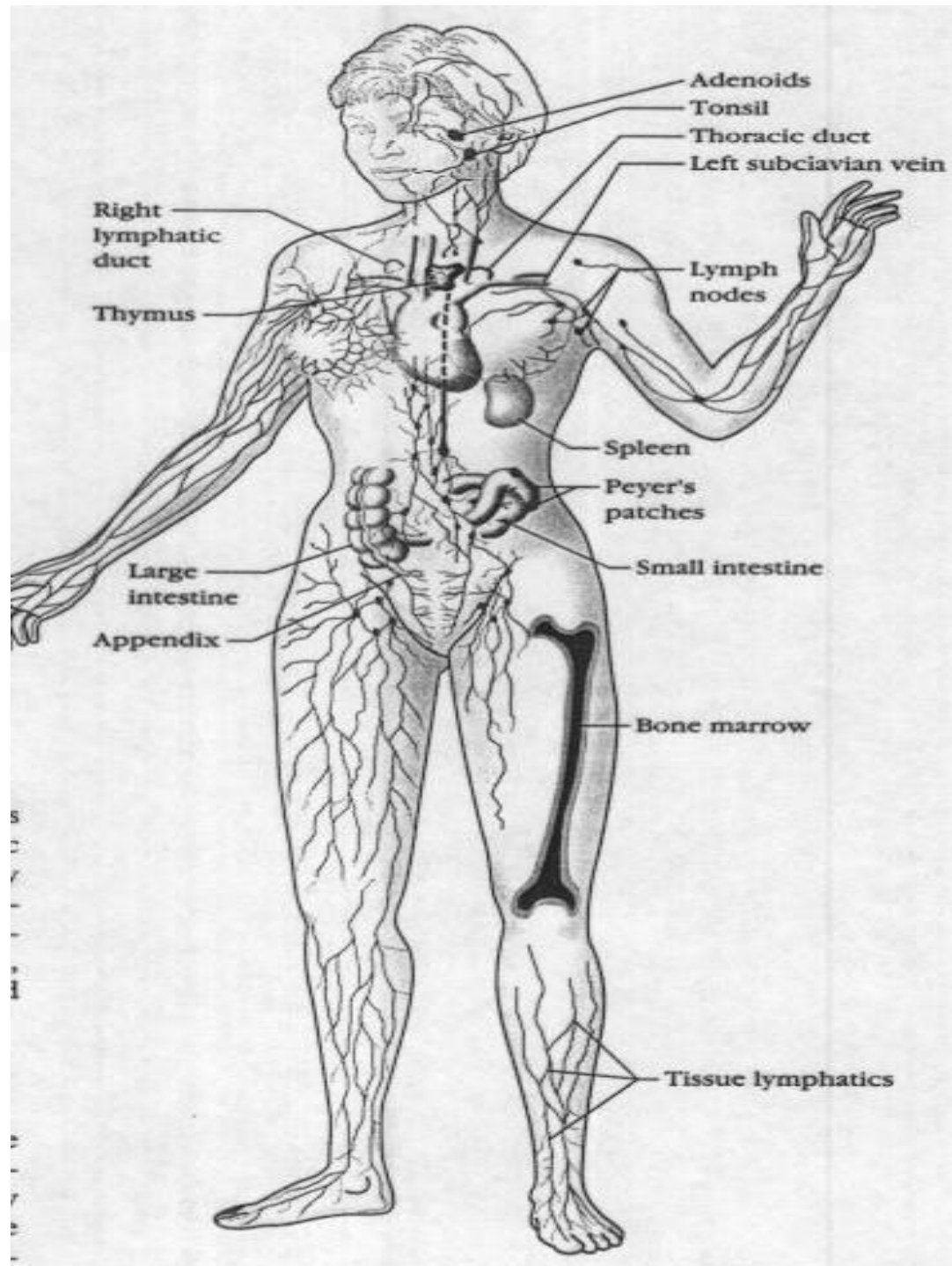
- T lymphocytes arise in BM and then migrate to and mature in the thymus
  - T helper ( $T_H$ ) cells are  $CD4^+$
  - T cytotoxic ( $T_C$ ) cells are  $CD8^+$
  - Ag receptors are distinct, but structurally related to antibodies, but recognize only peptide antigens that are attached to MHC proteins that are expressed on APC's (respond only to cell surface-associated antigens, not soluble Ag's, as do B cells)

# *T Lymphocytes*

- In response to Ag stimulation they secrete hormones called cytokines: these promote cell proliferation and differentiation of both T cells and B cells and macrophages.
  - Also recruit and activate inflammatory leukocytes
- T<sub>C</sub> cells lyse cells that produce foreign Ag's as well as producing other cytokines that regulate immune response
- Controversy about T suppressor (T<sub>S</sub>) cells

# *Cell Markers: CD antigens*

- Cluster of Differentiation Antigens
  - monoclonal antibodies can be made against each
  - distinct cell populations express distinct surface membrane proteins (Ag's)
  - can use these to determine cell type, maturity, ability to respond, etc... ( $T_H$  is  $CD3^+CD4^+CD8^-$ )
  - at least 80 different classes of CD Ag's
- 3<sup>rd</sup> type of lymphocyte is the Natural Killer (NK) cell





# Lymphocyte Classes

- **B lymphocyte**- *Ab production: Ag receptor is surface Ig: has Fc receptors and class II MHC: present in blood (10-15%), LN (20-25%), Spl (40-45%)*
- **T<sub>Helper</sub>**<sup>-</sup> *TCR (alpha & beta chains): CD3<sup>+</sup>CD4<sup>+</sup> CD8<sup>-</sup>: blood (50-60%), LN (50-60%), Spl (50-60%)*
- **T<sub>Cytotoxic</sub>**<sup>-</sup> *TCR: CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>+</sup>: blood (20-25%), LN (15-20%), Spl (10-15%)*
- **NK cells**- *Lysis of virus infected cells, tumor cells and ADCC (antibody-dependent cellular cytotoxicity): receptor ??: blood (<10%), LN (rare), Spl (<10%)*

# *Lymphocyte Activation*

- Very small fraction of total population of lymphocytes responds to any one Ag
  - To study mechanisms of activation use of polyclonal activators (Ab's against Ag receptors, mitogens) employed
    - Prior to Ag stimulation lymphocytes in G<sub>0</sub> stage of cell cycle. If do not encounter Ag then die w/i a few days
    - After Ag stimulation, enter G<sub>1</sub> (lymphoblast) and get larger (10-15 $\mu$ m) and have wider rim of cytoplasm (more organelles, more RNA)

# *Lymphocyte Activation*

- Progression to S stage and division (mitotic) for clonal expansion of responsive lymphocytes
- Antibody producing B cells develop into **plasma cells**
  - Plasma cells only found in lymphoid organs, **not** in general circulation or lymph
  - eccentric nuclei and perinuclear halo (clear region under nucleus)
- Clonal expansion leads to development of **effector** cells or **memory** cells for both T and B events. Memory cells can survive 20 years or more in absence of Ag'ic stimulation

# *Mononuclear Phagocytes*

- Mononuclear phagocyte system is the 2<sup>nd</sup> major cell population of the immune system and consists of cells that have a common lineage, and whose 1<sup>o</sup> function is phagocytosis
  - Cells that function in host defense by phagocytosis of foreign invaders are grouped collectively into the **RETICULOENDOTHELIAL SYSTEM (RES)**, and are found in Liver, Spleen, CNS, etc...)
  - Originate in BM, and first to leave is the monocyte (12-20  $\mu\text{m}$ ). When monocyte becomes settled in tissue they are called macrophages

# *Activation and Function of MΦ*

- **Functions in Natural Immunity**
  - 1. **Phagocytosis** of foreign particles (microbes and antigens, and even self-cells when injured or dying)
  - 2. **Secretion** of enzymes and oxidative metabolites (respiratory burst- oxygen radicals, NO, prostaglandins)
  - 3. **Cytokine** production which recruit other inflammatory cells, as well as growth factors for fibroblasts and vascular endothelial cells
  - 4. **Antigen-Presentation** Processing and re-expression - of MHC II + Foreign Ag eptide
  - 5. **Opsonization**- Fc receptor for IgG

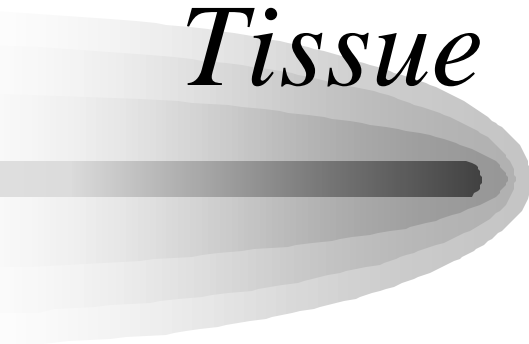
# *Granulocytes*

- **Granulocytes** contain cytoplasmic granules and participate in the effector phase of the immune response (also called inflammatory cells)
  - **Neutrophils** (polymorphonuclear leukocytes)- multilobed nuclei, respond w/I 24 hours of stimulus (MΦ responds at 48 hours). Activated by cytokines and have Fc receptors to help opsonize.
  - **Eosinophils**- have Fc receptors for IgE and therefore important in parasitic infections that are resistant to other granulocyte lysosomal enzymes
  - **Basophils**- circulating counterparts of tissue mast cells. Receptors for IgE

# *Functional Anatomy of Lymphoid Tissue*

- Need to optimize cellular interactions that are necessary for the cognitive, activation, and effector phases of specific immune responses. To do this:
  - the majority of lymphocytes, mononuclear cells and other accessory cells are localized and concentrated in discrete organs as well as specific areas within these organs
  - There are the Primary (generative) organs and the Secondary (peripheral) organs


# *Functional Anatomy of Lymphoid Tissue*



- Primary Organs
  - Bone marrow (where all lymphocytes arise) and Thymus (where T cells mature and reach a stage of functional competence)
- Secondary Organs
  - lymph nodes, spleen, and mucosa-associated lymphoid tissue, and cutaneous immune system

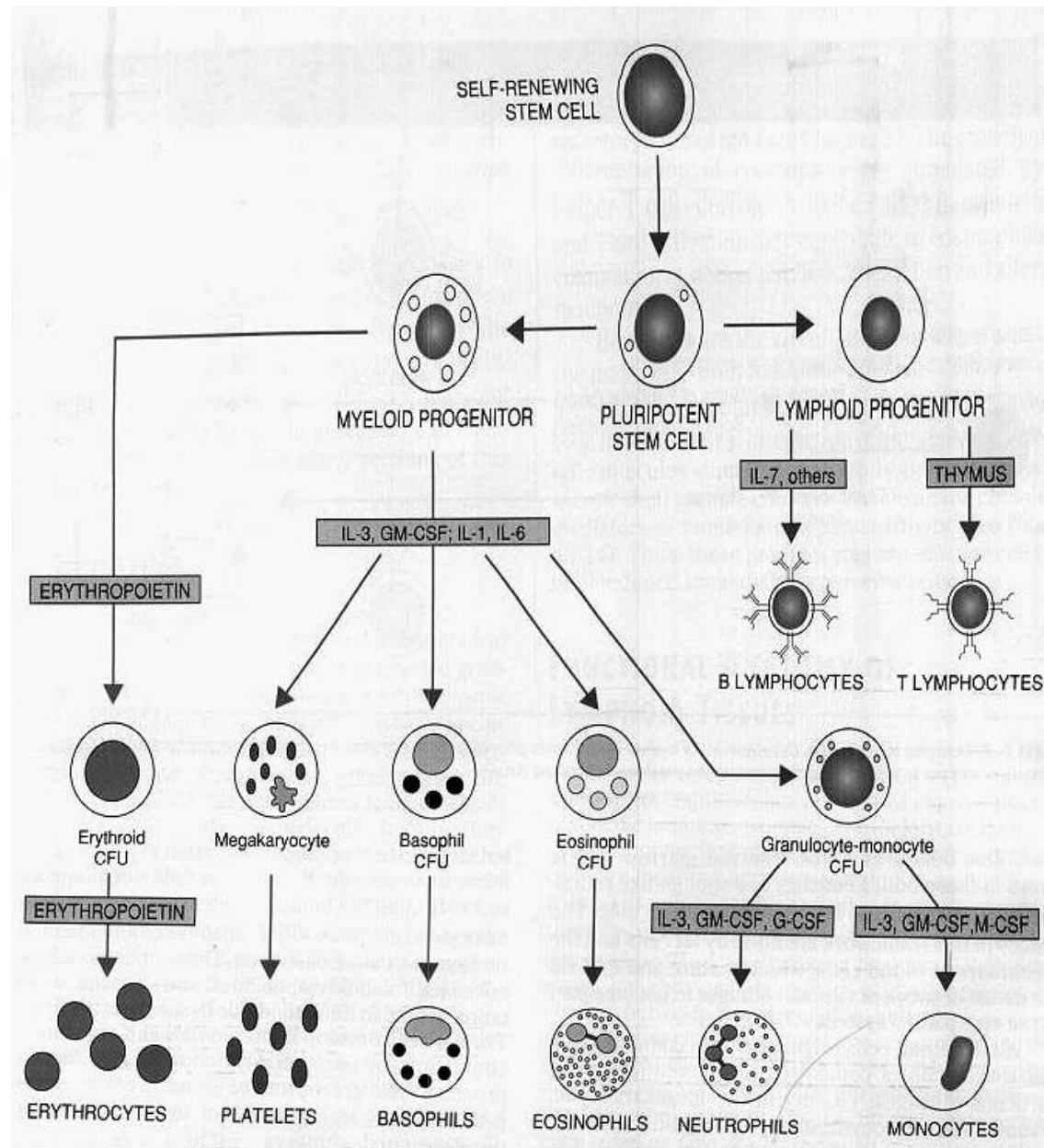


# *Functional Anatomy of Lymphoid Tissue*



- Bone Marrow:
  - Hematopoiesis- generation of all blood cells
    - all cells originate from a common stem cell
    - cytokines regulate differentiation and growth (T cells produce IL-3, GM-CSF; M $\Phi$  produce GM-CSF, G-CSF and M-CSF, IL-1 and IL-6)
  - Flat bones- red and yellow marrow
  - begins in yolk sac and spleen

# Blood Cells-- Hematopoiesis



# *Thymic Structure*

- **Bilobed**, each lobe divided into lobules, and each lobule consisting of an outer cortex and an inner medulla
  - cortex contains a dense collection of T lymphocytes, and the medulla has less lymphocytes
  - Thymocytes are in various stages of development
  - Precursors that bind to endothelial blood vessel receptors enter into thymic cortex
  - These cells migrate towards medulla and come in contact with m $\Phi$ , dendritic cells and epithelial (Nurse) cells; as they migrate into medulla they begin to express receptors for Ag's and surface markers

# *Thymic Structure*

- At first the cells have no CD antigens
  - form both CD4 and CD8 antigens (and CD3)
  - as further maturation occurs they randomly lose either CD4 or CD8 to become T<sub>H</sub> or T<sub>C</sub> cells
  - Also obtain the TCR (T cell receptor)
- Only those cells that recognize self MHC and foreign Ag are allowed out the peripheral blood (Thymic education of self vs non-self)
- About  $50 \times 10^6$  immature cells enter thymus/day and  $< 1 \times 10^6$  leave
- Thymus undergoes involution with age

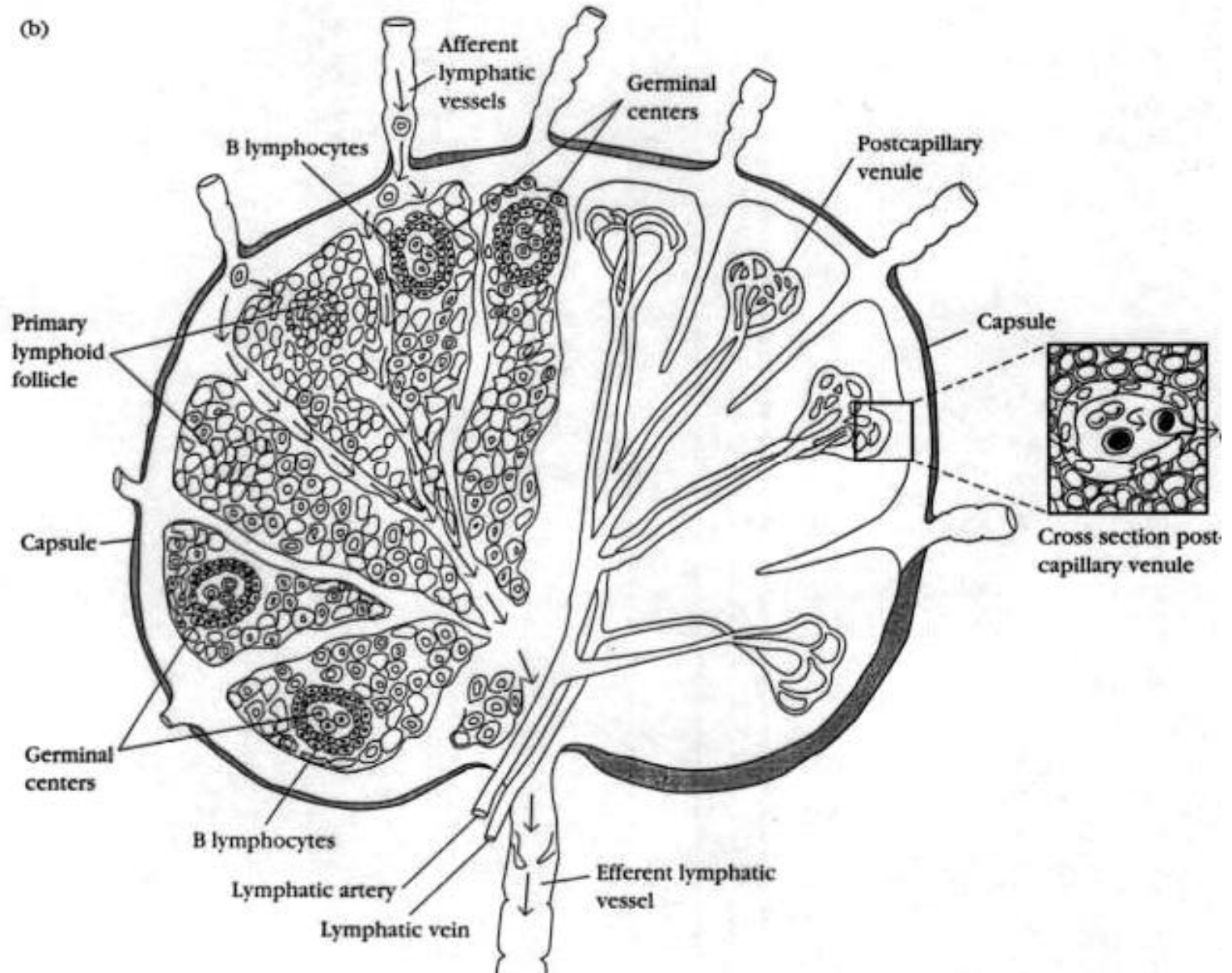
# *Lymph Node Structure*

- Most organs have lymphatics associated with their structure. Ag's that enter through almost any portal will go through lymph system and lymph nodes
  - Each node surrounded by fibrous capsule. Node consists of outer cortex, where there are aggregates of cells in follicles, some of which have germinal centers
  - Medulla contains fewer lymphocytes but has accessory cells in close proximity to Lymphocytes

# *Lymph Node Structure*

- Follicles without germinal centers are called *primary follicles*: contain mature, resting B cells that have NOT been stimulated recently by Ag.
  - Germinal centers occur after Ag stimulation and contain activated B lymphocytes. This is where B cells differentiate and mature into Ab secreting cells. Also follicular dendritic cells found which capture and present Ag to cells
- T lymphocytes found primarily in interfollicular areas of cortex and paracortical zones of medulla. Some T<sub>H</sub> cells also scattered in follicle/germinal center

# *Morphology of Lymph Nodes*



# *Activation of Lymphocytes*

- **Compartmentalized by specific adhesions of different lymphocytes with stromal cells or extracellular matrix proteins**
- **Using labeled Ag's: Activation**
  - **protein Ag enters LN and is trapped by MΦ and dendritic cells and degraded**
  - **Stimulate T<sub>H</sub> cells by presentation of MHC II and Ag fragment**
  - **Mitotic activity w/i 48 h: proliferation of B cells follows, after which germinal centers develop and Ab's secreted**
  - **Effector T cells leave and respond to Ag at site of immunization**



# *Activation of Lymphocytes*

- In previously immunized animals where circulating Ab's already present, challenge with Ag leads to the formation of Ag-Ab complexes, which bind to surfaces of follicular dendritic cells in germinal centers. The Ag is undegraded and is recognized by memory B cells generated during 1st response
- Germinal centers gradually regress after Ag stimulus is eliminated.

# *Spleen Morphology*

- Weighs about 150 g in adults
- located in upper left quadrant in abdomen
- single splenic artery enters through hilum and divides into small arterioles
  - small arterioles surrounded by lymphocytes, called periarteriolar lymphoid sheaths, attached to follicles, some of which have germinal centers. These dense lymphoid tissues are the White Pulp of the spleen

# *Spleen Morphology*

- The arterioles end in vascular sinusoids, scattered among large numbers of MΦ, and dendritic cells, with few lymphocytes and plasma cells = Red Pulp
- Periarteriolar sheaths contain mainly T cells (about 2/3 are CD4<sup>+</sup> and 1/3 CD8<sup>+</sup>)
- Follicles and germinal centers contain predominantly B cells
- Spleen is major site of immune response to blood borne Ag's, LN respond to Ag in lymph

# Spleen Morphology

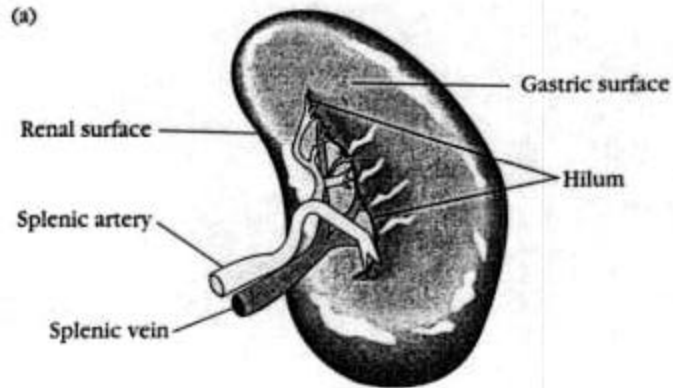
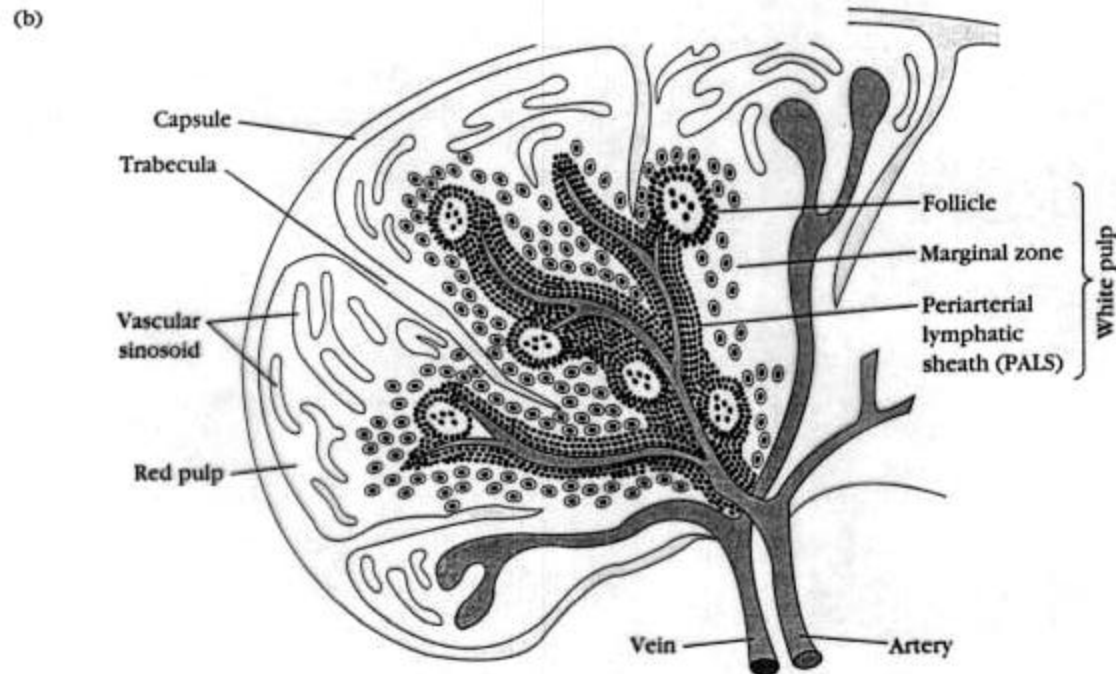
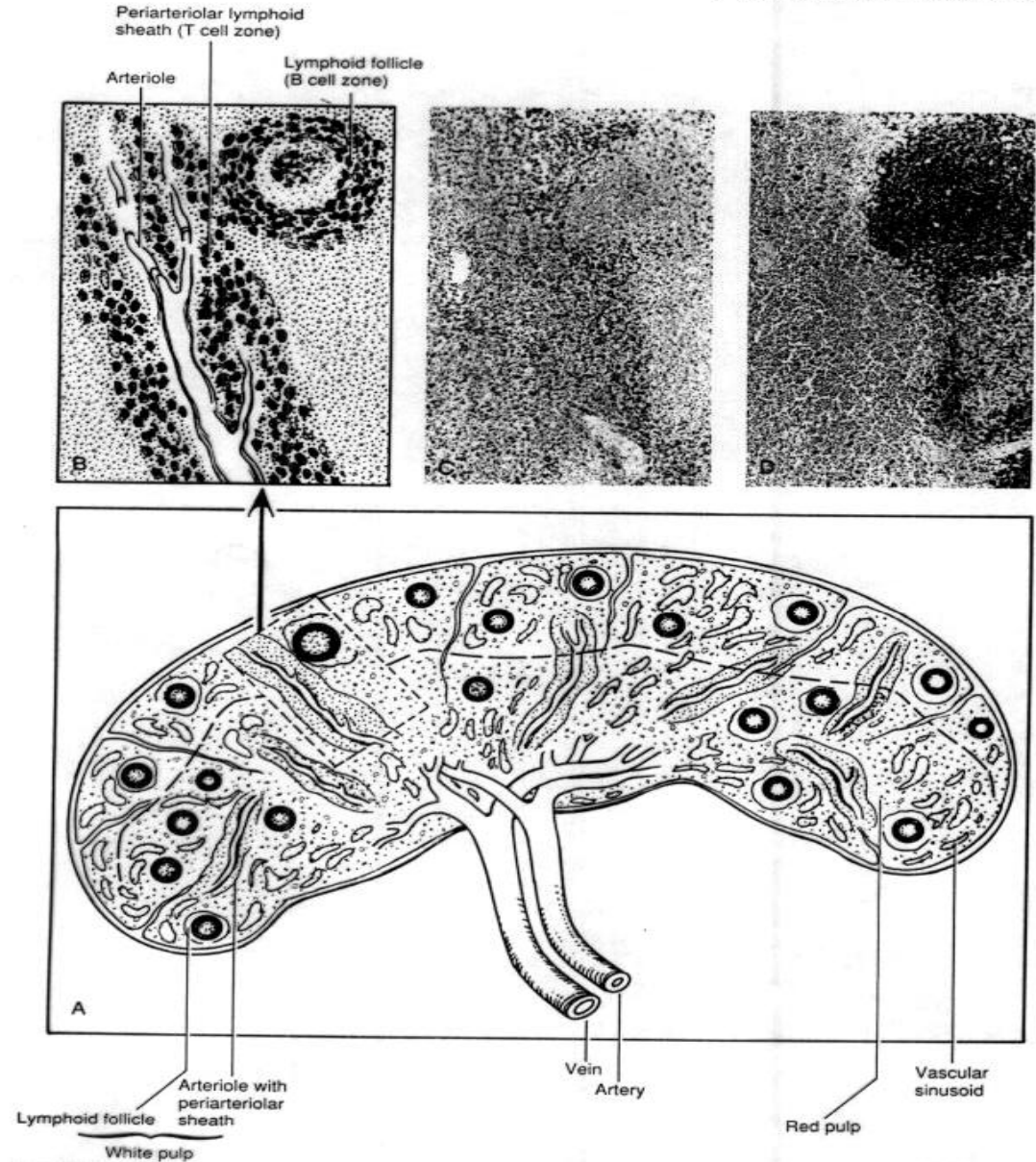


FIGURE 3-22

Structure of the spleen. (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens. (b) Diagrammatic cross section of the spleen. The arteriole blood supply pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarterial lymphoid sheath (PALS) around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, a B-cell-rich area containing lymphoid follicles that can develop into germinal centers.





**FIGURE 2-11. Morphology of the spleen.**  
 A. Schematic diagram of the spleen. Note that the white pulp, made up of dense lymphoid tissues in periarteriolar sheaths and follicles, is intermingled with the red pulp, composed of vascular sinusoids and scattered cells.  
 B. Diagram of an arteriole and the adjacent lymphoid tissues composing the white pulp.  
 C. T lymphocytes in the periarteriolar lymphoid sheath, detected by an immunoperoxidase stain with an antibody specific for T cells. (Courtesy of Dr. G. S. Pinkus, Department of Pathology, Brigham and Women's Hospital, Boston.)  
 D. B lymphocytes in a lymphoid follicle, detected by an immunoperoxidase stain with an antibody specific for B cells. (Courtesy of Dr. G. S. Pinkus, Department of Pathology, Brigham and Women's Hospital, Boston.)

# *Other Peripheral Lymphoid Tissues*

- Mucosal Immune System- lymphocytes, MΦ, and other cells located below mucosal epithelium
- Peyer's Patches- in the small intestine, appendix, tonsils and upper airway
- Cutaneous Immune System- Skin (imp't APC is *Langerhans* cell)

# *Lymphocyte Recirculation*

- **Only a small number of lymphocytes can recognize one specific Ag. In order to increase the likelihood that specific immunocompetent cells will see an Ag, the lymphocytes ( $T_H$ ) continuously circulate through the body**
  - lymphocytes move from blood into tissues by diapedesis, then may stay there or move into lymph and back to blood
  - naïve T cells directly enter LN to “look” for Ag
  - memory T cells migrate to sites of inflammation where Ag levels high

# *Lymphocyte Recirculation*

- Some post-capillary venules in organs have specialized receptors that help the migration of circulating lymphocytes= high endothelial venules (HEV's)
- These develop due to response to cytokines produced by Ag-stimulated T cells
- Different T cells express receptors for molecules unique to HEV's of different tissues, therefore there is directed migration of specialized lymphocytes



# *Lymphocyte Recirculation*

- Thus, these receptors are called “homing receptors” or vascular addressins
  - MEL-14 Ag or “peripheral lymph node receptor” present on all murine lymphocytes that home to peripheral LN but absent on lymphocytes that home to peyer’s patches
  - VLA-4: integrin; increased in memory T cells
  - CD44- increased on memory T cells, present on T cells that bind to both LN and peyer’s patch HEVs