Cells of the Immune System

Components of the Immune System

- Cells originate in the bone marrow
- Arise from pluripotent hematopoietic stem cells (HSCs)
- HSCs give rise to precursor cells which are myeloid progenitors and common lymphoid progenitors
- Myeloid progenitors give rise to granulocytes, macrophages, dendritic cells and mast cells
- Common lymphoid progenitors give rise to lymphocytes, dendritic cells and NK cells
- There are more myeloid progenitors in the bone marrow than lymphoid progenitors

Multiple cellular interactions take place in the BM

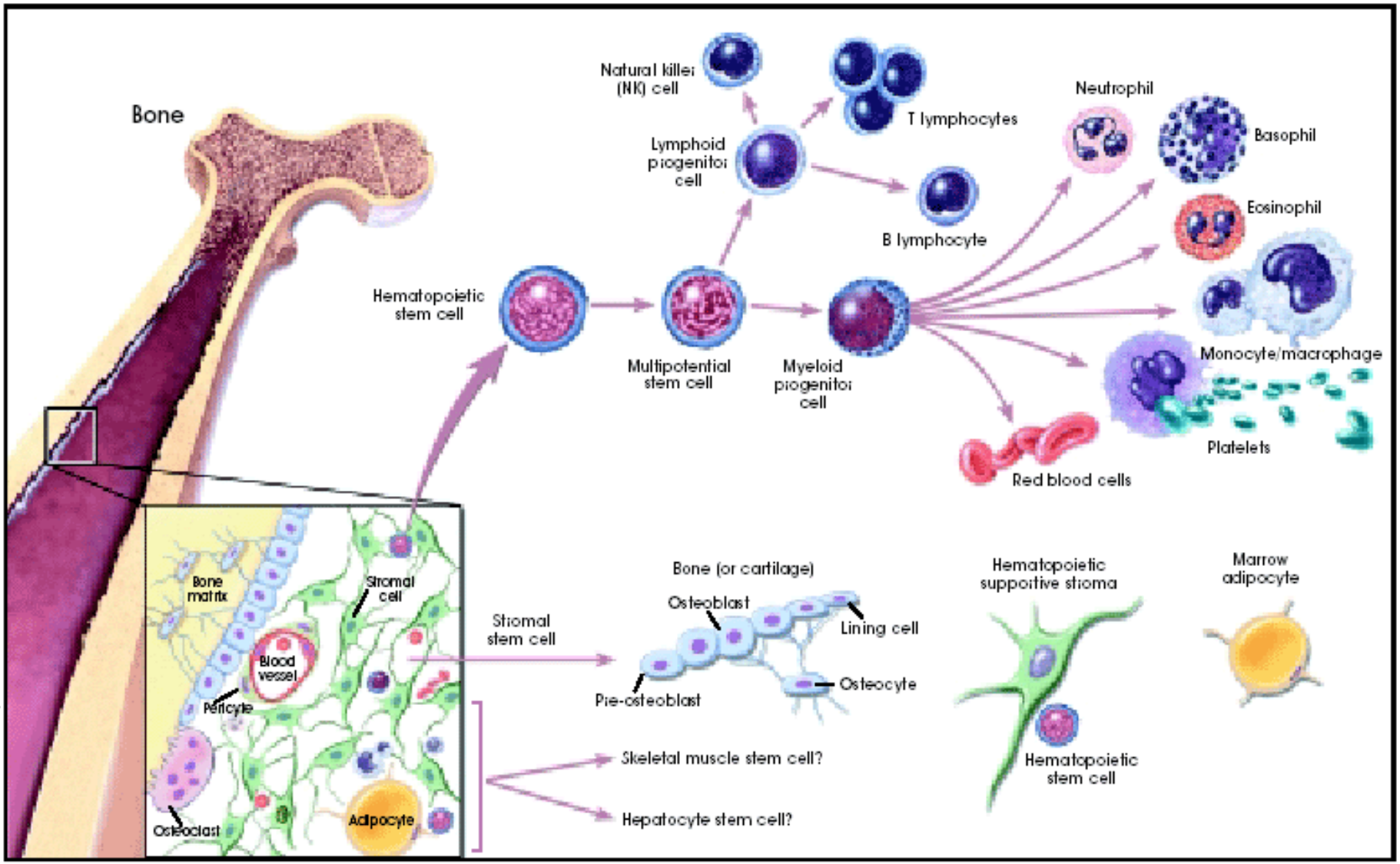
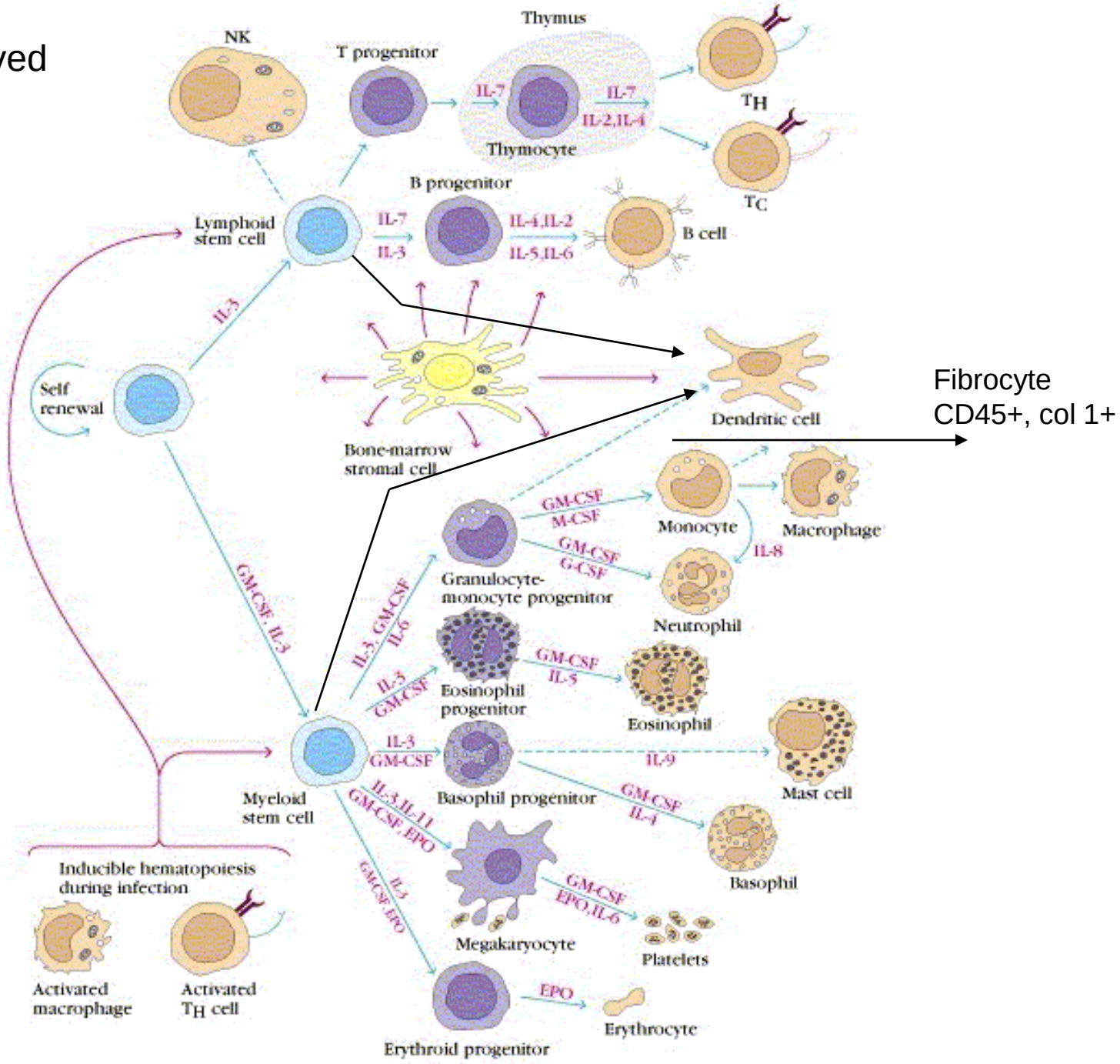


Figure 4.3. Hematopoietic and Stromal Stem Cell Differentiation.

Marrow-Derived Cells



Myeloid cells in circulation

- Within the myeloid lineage, monocytes are the circulating cells which will become macrophages in the tissue
- Dendritic cells can circulate as immature cells
- Mast cells are bone marrow derived, but their circulating precursors are not defined
- Mast cells reside in tissues

Granulocytes in circulation

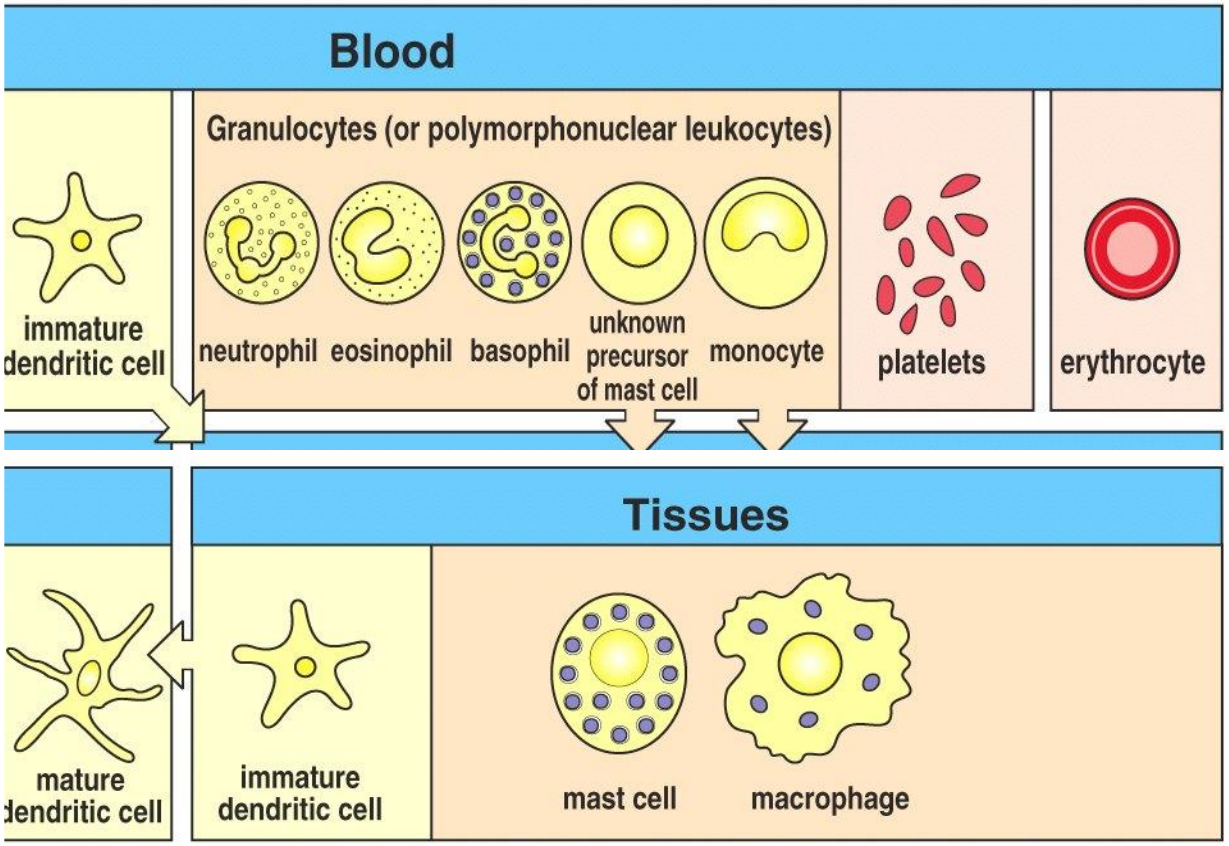
- Granulocytes (neutrophils, eosinophils and basophils) are given their name because of the dense staining granules in the cytoplasm
- They are also called polymorphonuclear (PMN) leukocytes due to their odd-shaped nuclei
- In general however, the term PMN refers to neutrophils specifically
- Neutrophils are the most numerous of the innate immune cells and they function to phagocytose and kill pathogens
- Eosinophils and basophils –these cells enter tissue during allergic inflammation or infection

Monocytes circulate about 8 h and then migrate to tissue.

Once in the tissues, the monocytes, can differentiate into specialized tissue-specific phagocytes.

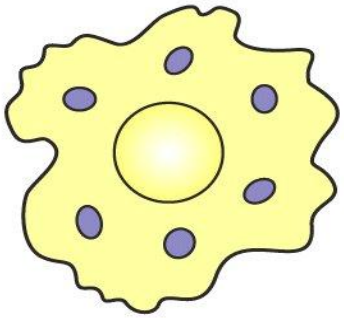
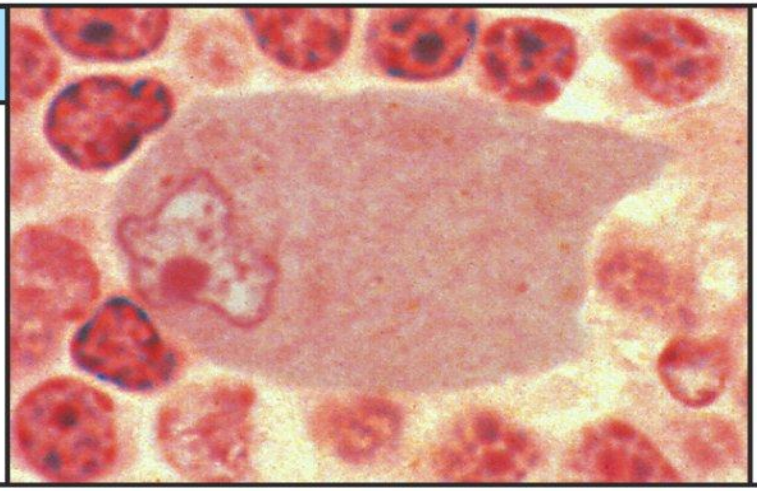
Examples are alveolar macrophages in the lung, Kupffer cells in the liver, mesangial cells in the kidney, microglial cells in the brain and osteoclasts in bone.

Macrophages can live several months in vivo



Macrophages are generally 5-10 times larger than monocytes and contain more organelles (esp. lysosomes) and pseudopodia

Myeloid Cell Functions

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

Macrophages are activated by a variety of stimuli, but most often via phagocytosis of a pathogen or recognition of a pathogen via TLRs. Cytokines can further activate macrophages during an immune response. Activated macrophages are more effective than resting ones. Activated macrophages are better at phagocytosis, increase bacterial killing mechanisms, increase secretion of inflammatory mediators and increase MHC class II to better activate Th cells. Additionally, macrophages can secrete toxic products (e.g. peroxides) to eliminate pathogens, virally-infected cells or tumors.

Macrophages and Disease

- Macrophages are deactivated in sepsis which makes them poor at host defense
- Macrophages are the predominant cell type in granulomas
- Macrophages are the predominant cell type in atherosclerotic plaques
- Macrophages are believed to support tumor growth in lung cancer

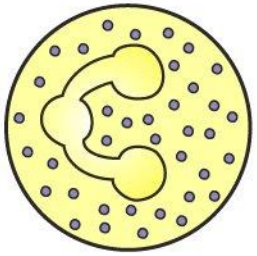
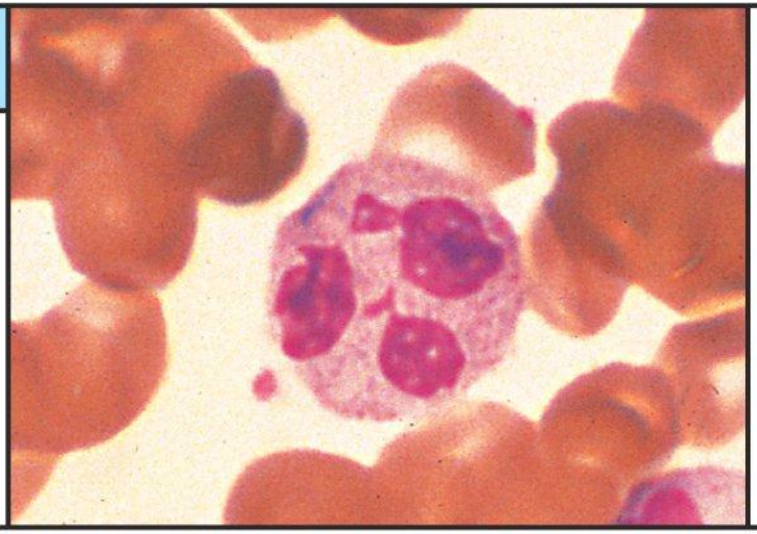
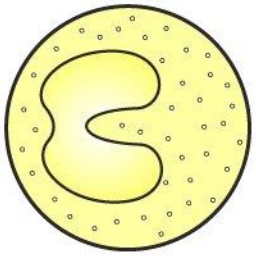
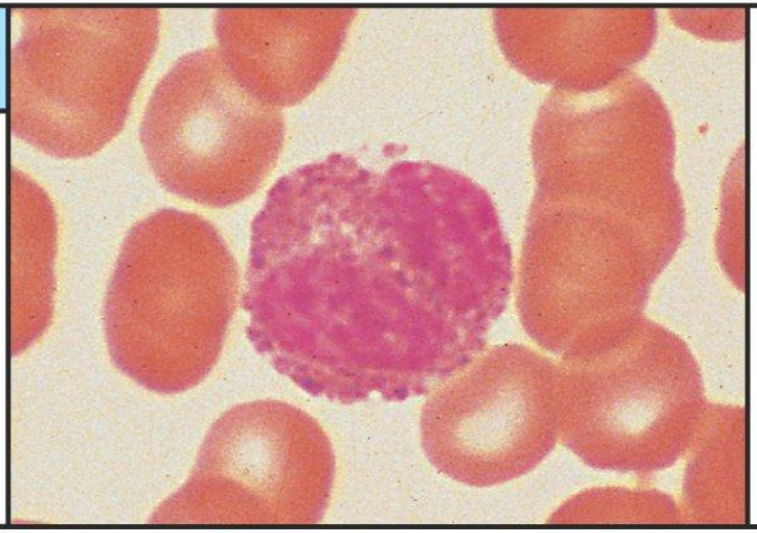
Cell		Activated function
Neutrophil 		Phagocytosis and activation of bactericidal mechanisms
Eosinophil 		Killing of antibody-coated parasites

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

Neutrophils (PMNs)

- Circulate for 7-10 h prior to migration to tissue; live 2-4 days in tissue.
- BM production of PMNs is upregulated rapidly in response to infection
- *Often the first cell to arrive to an infection*
- PMNs move into tissue in a process called extravasation which involves adhering to the vascular endothelium, penetrating the gap between endothelial cells, penetrating the vascular basement membrane and then moving into tissue
- PMNs are recruited by chemokines (IL-8) and complement components (C5a) to sites of infection
- Phagocytic and bactericidal

Neutrophil Granules Release Substances to Kill Pathogens Intracellularly or Extracellularly

- azurophilic granules (or "primary granules") release myeloperoxidase, bactericidal/permeability increasing protein (BPI), Defensins and the serine proteases neutrophil elastase and cathepsin G
- specific granules (or "secondary granules") release Lactoferrin and Cathelicidin
- tertiary granules release cathepsin and gelatinase

NETs

- Activation of neutrophils causes the release of web-like structures of DNA, in addition to the more traditional mechanisms for killing bacteria, such as phagocytosis.(*Science* **303** (5663): 1532–15)
- These neutrophil extracellular traps (NETs) comprise a web of fibers composed of chromatin and serine proteases that trap and kill microbes extracellularly.
- It is suggested that NETs provide a high local concentration of antimicrobial components and bind, disarm, and kill microbes independent of phagocytic uptake.
- In addition, NETs may serve as a physical barrier that prevents further spread of pathogens.
- Trapping of bacteria may be a partcularly important role for NETs in sepsis, where NET are formed within blood vessels

PMNs and lung disease

- Neutropenia post-HSCT is a major risk factor for pneumonia (particularly *P. aeruginosa* and *Aspergillus* species)
- In alpha 1-antitrypsin deficiency, the important neutrophil enzyme elastase is not adequately inhibited by alpha 1-antitrypsin, leading to excessive tissue damage in the presence of inflammation -
  - most prominently pulmonary emphysema.

Eosinophils

- Motile phagocytic cells, but their phagocytic ability is much less than PMNs
- Important in anti-parasite defenses
- Have been shown to present Ag to T cells in humans
- Release of contents in eosinophilic granules can damage the parasite membrane
  - Eosinophils degranulate to release an array of cytotoxic granule cationic proteins including:
  - major basic protein (MBP)
  - eosinophil cationic protein (ECP)
  - eosinophil peroxidase (EPO)
  - eosinophil-derived neurotoxin (EDN)

- In industrialized countries where parasite infections are rare, eosinophils are associated with allergic diseases
- The inappropriate release of their granule content can cause host cell damage leading to airway remodeling (fibrosis) in many cases

Eos and Disease

- An increase in eosinophils, i.e., more than 500 eosinophils/microlitre of blood is called an eosinophilia, and is typically seen in people with
  - Allergy and asthma!
  - a parasitic infestation,
  - Sometimes in collagen vascular disease (such as rheumatoid arthritis),
  - Sometimes in malignant diseases such as Hodgkin's disease,
  - extensive skin diseases (such as exfoliative dermatitis),
  - And in the squamous epithelium of the esophagus in the case of reflux esophagitis, eosinophilic esophagitis, and with the use of certain drugs such as penicillin.

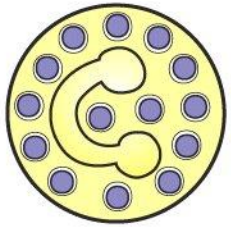
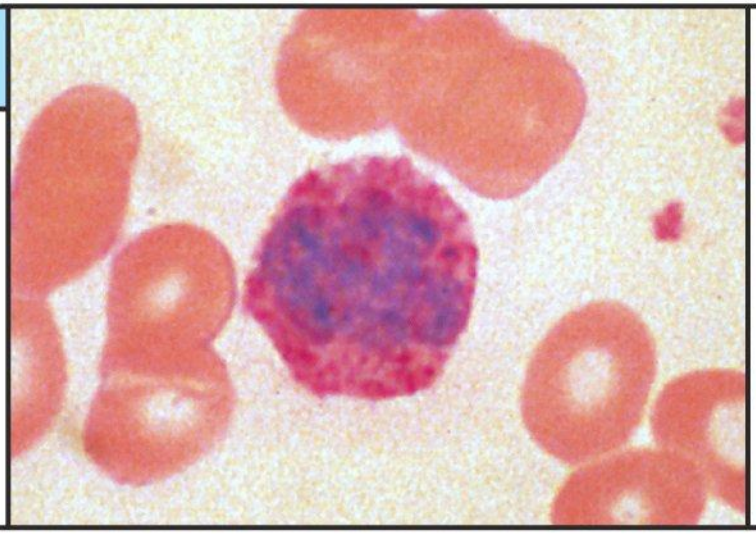
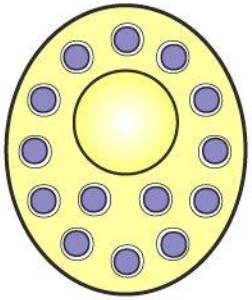
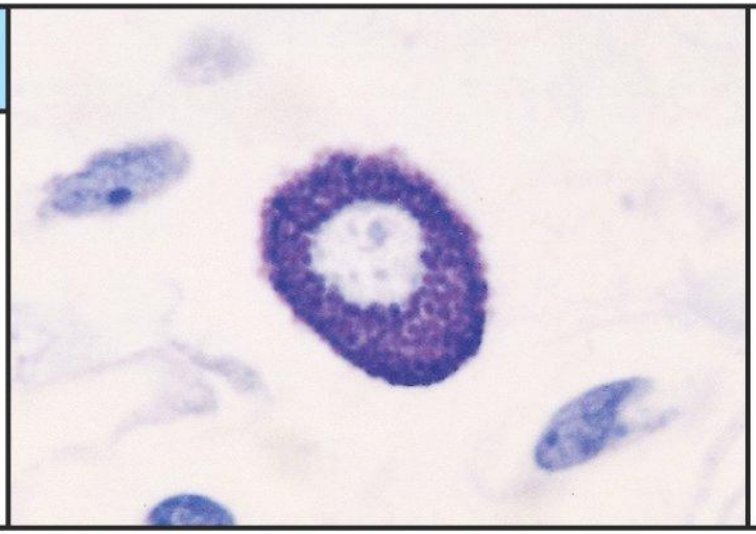
Cell		Activated function
Basophil 		Unknown
Mast cell 		Release of granules containing histamine and other active agents

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

Basophils and Mast Cells

- Basophils are nonphagocytic, but can release toxic substances from their granules
- Increased in allergic diseases; more prominent in the human than the mouse

- Mast cell precursors do not appear to differentiate until they enter the tissue
- Mast cells are widely distributed in skin, epithelium, respiratory tract, GI and digestive tract
- Granules contain histamine, serotonin and prostaglandins and leukotrienes
- Mast cells are important in allergy and seen in fibrosis

Dendritic Cell Functions

Cell	Activated function

DCs can arise from either lymphoid or myeloid stem cells. DCs are present In the interstitum of virtually all tissues except the brain. In general, DCs can be characterized as myeloid (monocyte-derived) or plasmacytoid (likely lymphoid-derived). Some tissues have names for specialized DCs, like Langerhans cells in the skin. Note follicular dendritic cells in lymph nodes are not BM-derived, are not APCs and are not related to the other DCs we are discussing.

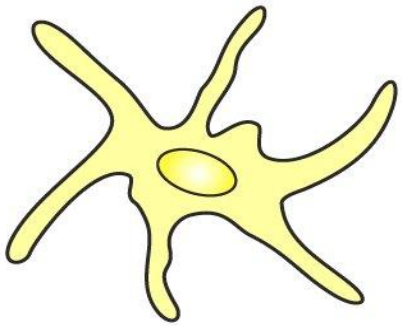
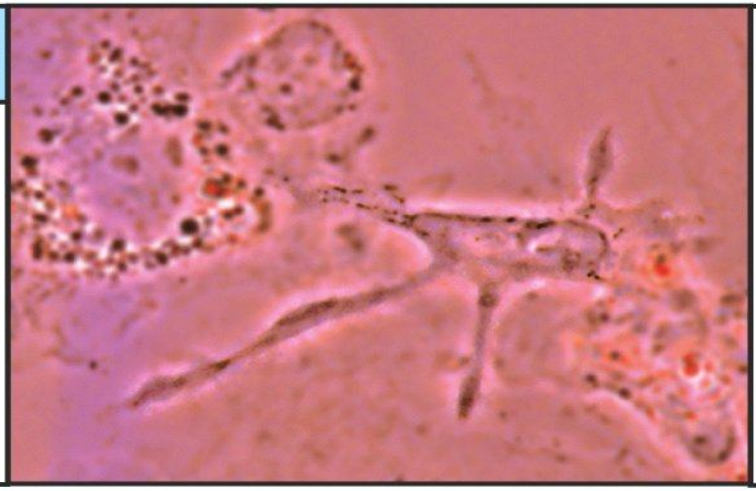
Dendritic cell		
		Antigen uptake in peripheral sites Antigen presentation in lymph nodes

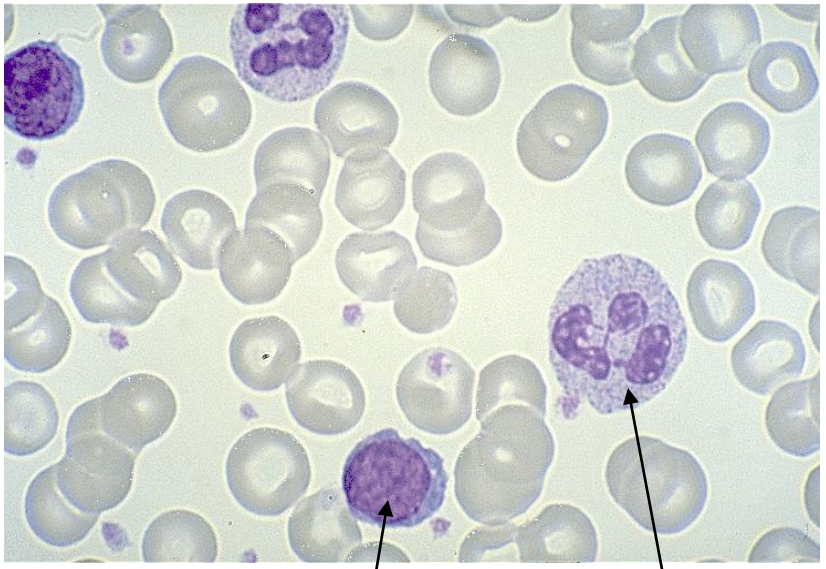
Figure 1-4 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Features of DCs

- Express both MHC I and II
- Phagocytic—uptake of particles activates them to migrate to lymph nodes and mature
- Express CD80 and CD86 which are co-stimulatory molecules for Th cell activation
- By virtue of where the DC came from and what cytokines it secretes, they can “direct” the T cell response

Lymphoid Functions

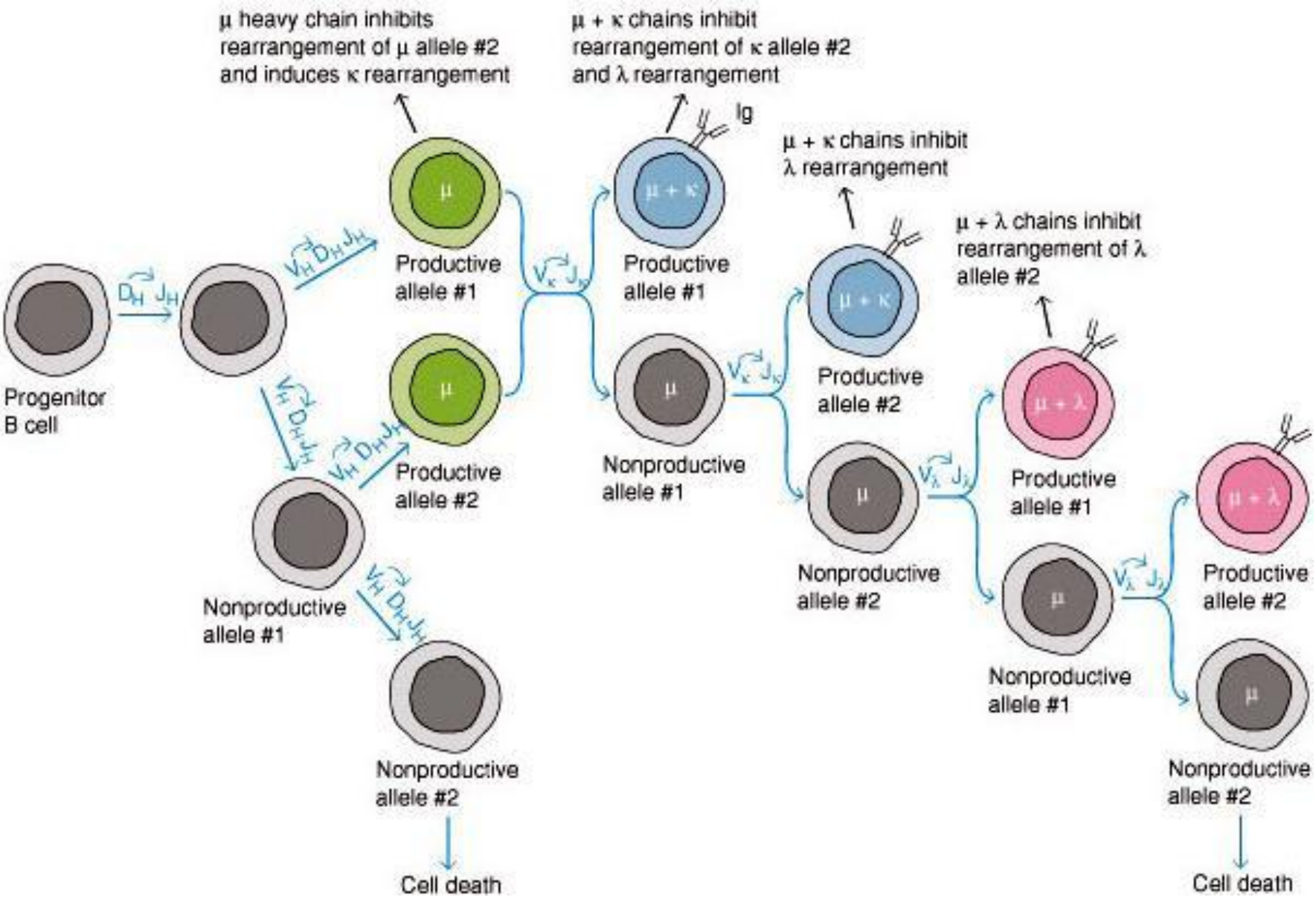
- B cells, T cells and NK cells
- In general lymphocytes are smaller than myeloid cells
- However, activated lymphocytes can increase in size
- An activated lymphocyte and a monocyte are a similar size



B cells

- B cells are responsible for Ig synthesis
- They mature in the BM
- Naïve and memory B cells have surface Ig
- Plasma cells have almost no surface Ig as they are specialized for secreting Ig
- Ig=Ab
- They must productively rearrange a heavy and light chain for Ig to survive and mature
- All Ig from a single B cell have identical Ag specificity, but the isotype of Ab produced can change via class switching processes

Gene rearrangements in B cell maturation



B cell functions

- B cells primarily are responsible for secreting Abs or developing long-lived memory cells
- Immunization strategies are often aimed at developing good memory B cells
- B cells are professional APCs as well—they can engulf the pathogen via recognition with their cell surface Ig-and present Ag on MHC II to Th cells
- Agammaglobulinemias are related to B cell defects
- They are the most common reservoir for EBV latent virus

T cells

- T cells exit the BM and mature in the thymus
- Th, Tc and Tr cells are the main phenotypes of $\alpha\beta$ TcR expressing T cells
- In addition, there are $\gamma\delta$ T cells
- CD4+ T cells are generally helper cells
- CD8+ T cells are generally cytotoxic T cells
- In normal human peripheral blood the ratio of CD4:CD8 is approximately 2:1
- All of the receptors on a given T cell are identical
- Thus all progeny are clonal as well

Th functions

- Th cells are involved in activating and directing other immune cells
- They are essential in determining B cell antibody class switching (by virtue of which cytokines they produce)
- Th cells activate cytotoxic T cells by secreting IL-2
- IFNgamma made by Th cells maximizes bactericidal activity of phagocytes such as macrophages.
- It is this diversity in function and their role in influencing other cells that gives T helper cells their name.
- Based on cytokines secreted, can be classified as Th0, Th1, Th2 or Th17

T cell subsets

- Th0 cells are uncommitted and may be capable of secreting many kinds of cytokines
- Th1 cells in general secrete IFNγ and IL-12—these cytokines classically activate macrophages and cytotoxic T cells
  - Anti-viral defense, anti-tumor, graft rejection
- Th2 cells in general secrete IL-4, IL-13 and IL-10
  - Anti-bacterial, anti-parasite (asthma and allergy)
- Th17 cells secrete IL-17
  - Host defense functions unclear—pathogenic in autoimmune diseases like arthritis

Th cells and disease

- CD4+ Th cells are the cells destroyed by HIV leaving patients open to opportunistic infections.
- Also involved in delayed type hypersensitivity responses, allergy and asthma

Tc cell functions

- Tc cells release the cytotoxins perforin and granulysin.
- Perforin forms pores in the target cell's plasma membrane allowing granzymes to enter the target cell, which then activate the caspase cascade, that eventually lead to apoptosis (programed cell death).
- A second way to induce apoptosis is when a Tc is activated it starts to express the surface protein *FAS ligand* (FasL), which can bind to *Fas* molecules expressed on the target cell.

γδ T cells

- Found at their highest abundance in the gut mucosa, within a population of lymphocytes known as intraepithelial lymphocytes (IELs).
- γδ T cells are believed to have a prominent role in recognition of lipid antigens.
- There also exists a γδ T cell sub-population within the epidermal compartment of the skin.
  - Dendritic Epidermal γδ T cells

T regs

- Generally CD4+ foxP3+ CD35+
- specialized subpopulation of T cells that act to suppress activation of the immune system and maintain immune system homeostasis and tolerance to self-antigens
- Can work via contact-dependent or independent mechanisms
- Often secrete inhibitory cytokines like IL-10 or TGFβ1

T reg dysfunction

- Humans with mutations in Foxp3 suffer from a severe and rapidly fatal autoimmune disorder known as
- **I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy **X**-linked (**IPEX**) syndrome.
- The IPEX syndrome is characterized by the development of overwhelming systemic autoimmunity in the first year of life

NK cells

- Comprise 5-10% of lymphocytes in human blood
- Have no Ag-specific receptors
- Involved in recognition of missing MHC molecules (seen cancer and viral infections)
- Can recognize targets via NK receptors or via recognition of Ab bound to target (ADCC)
- Have characteristic granules which secrete toxins to allow NK cells to kill without previous activation
- NK-T cells do express a TcR that recognizes Ag in the context of the CD1 MHC-like molecule
- Potent source of cytokines such as IFNγ

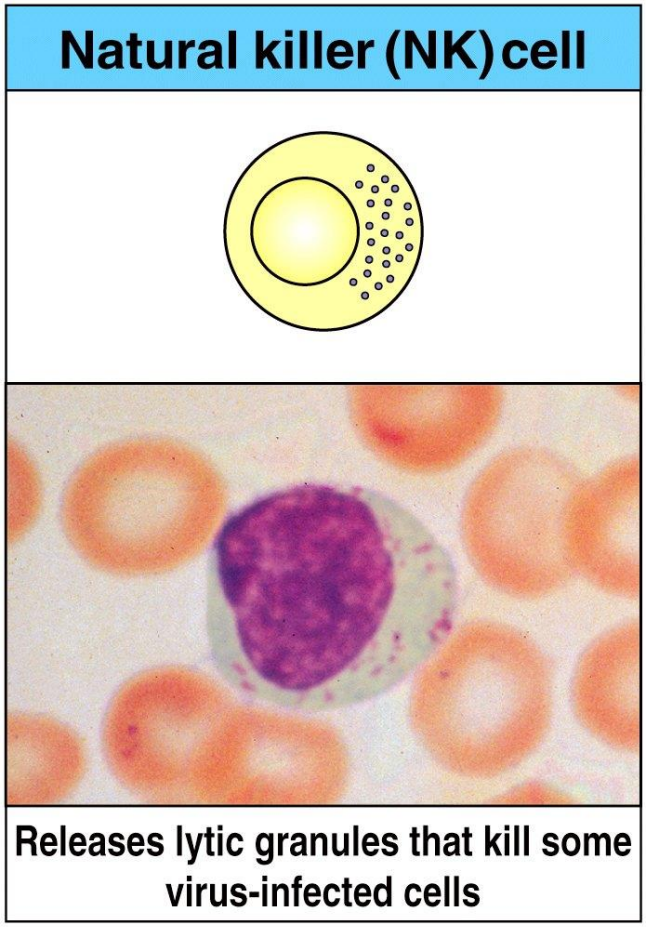
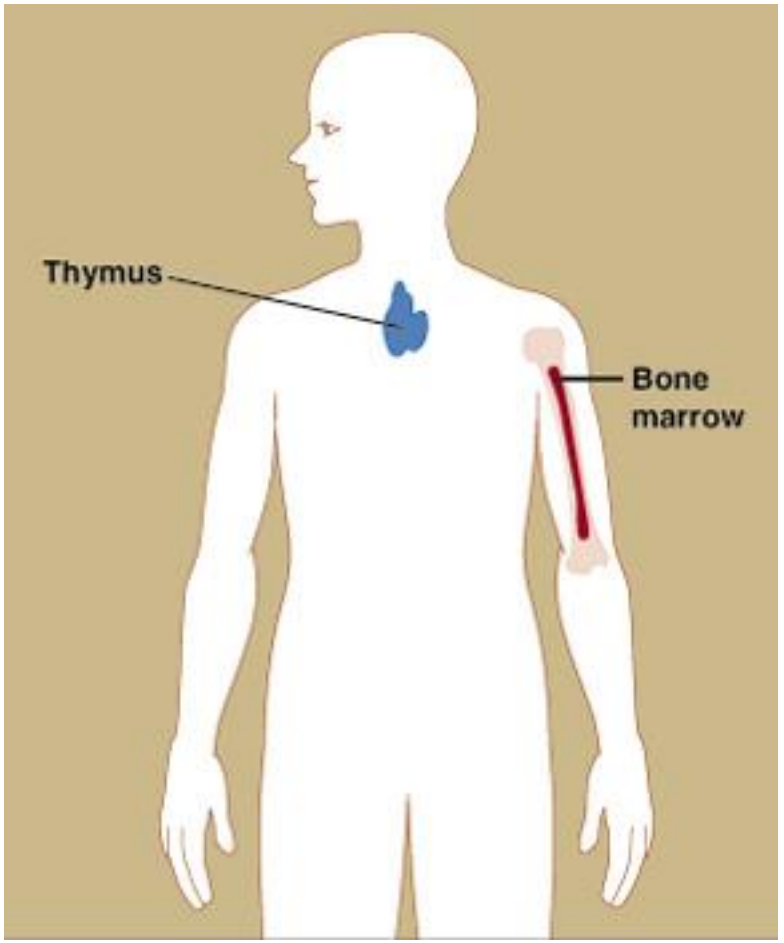


Figure 1-6 Immunobiology, 6/e. (© Garland Science 2005)

Where are lymphocytes generated? Primary Lymphoid Organs

- B cells originate in and mature in the bone marrow (unless you are a chicken=bursa)
- T cells are immature when they leave the bone marrow
- T cells must mature in the thymus. This is where they get their name (T=thymus)



Lymphocytes can be activated in Secondary Lymphoid Organs

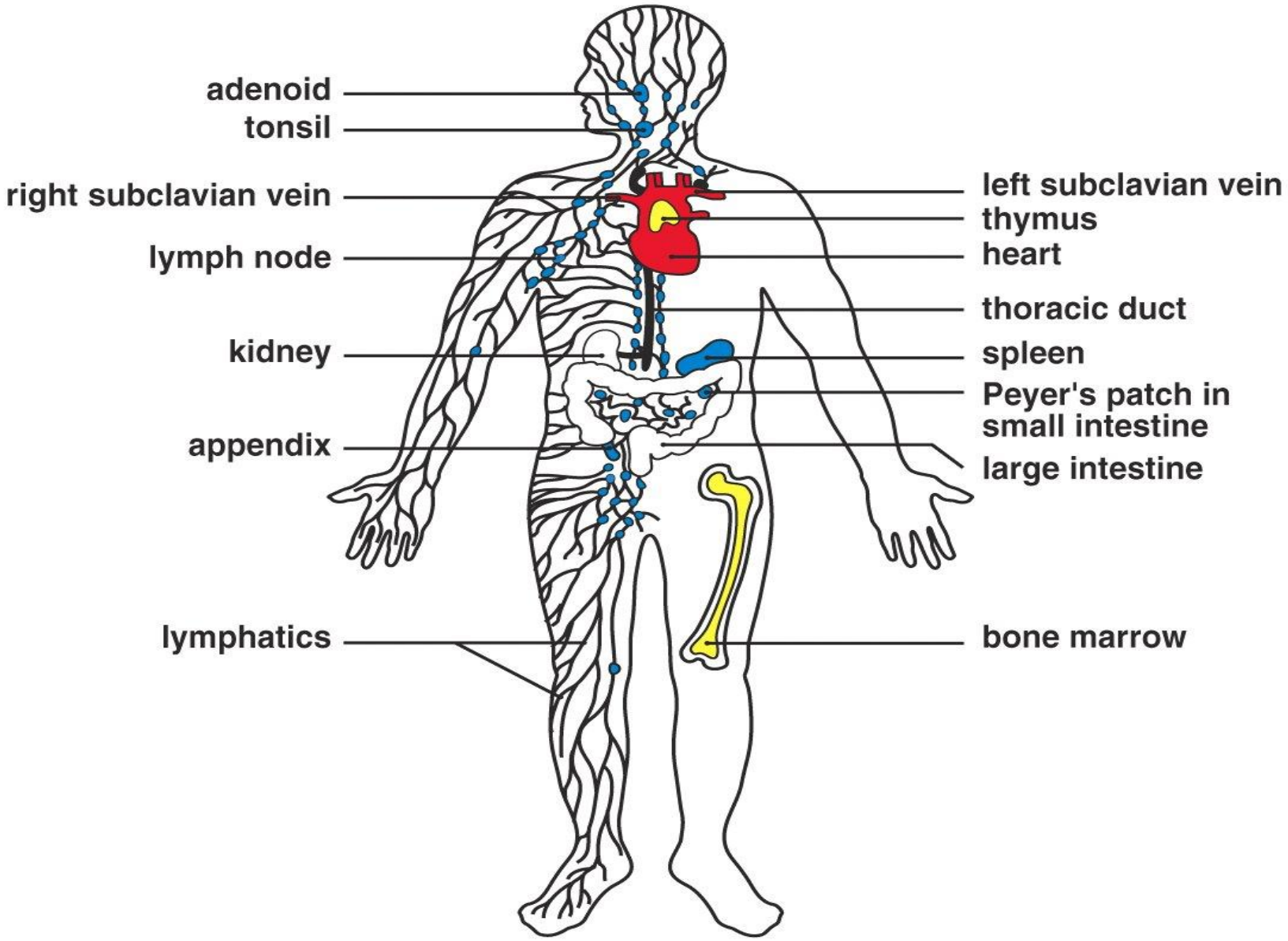
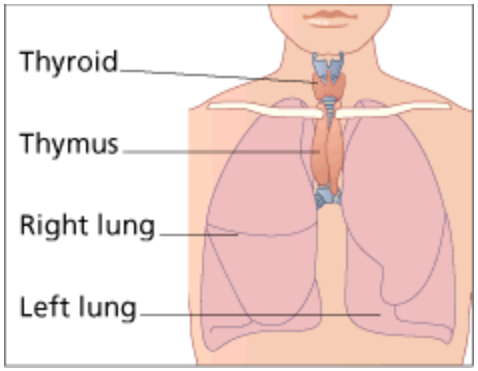


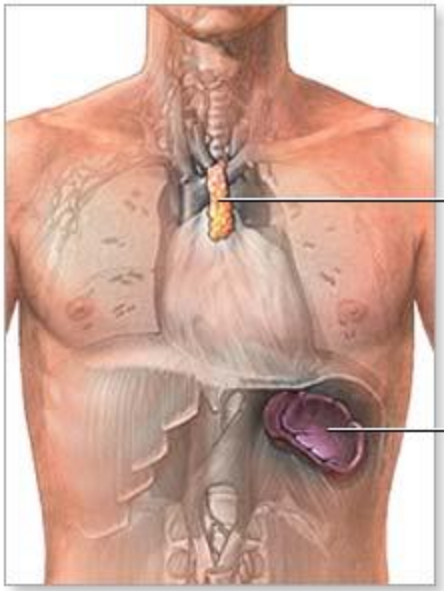
Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

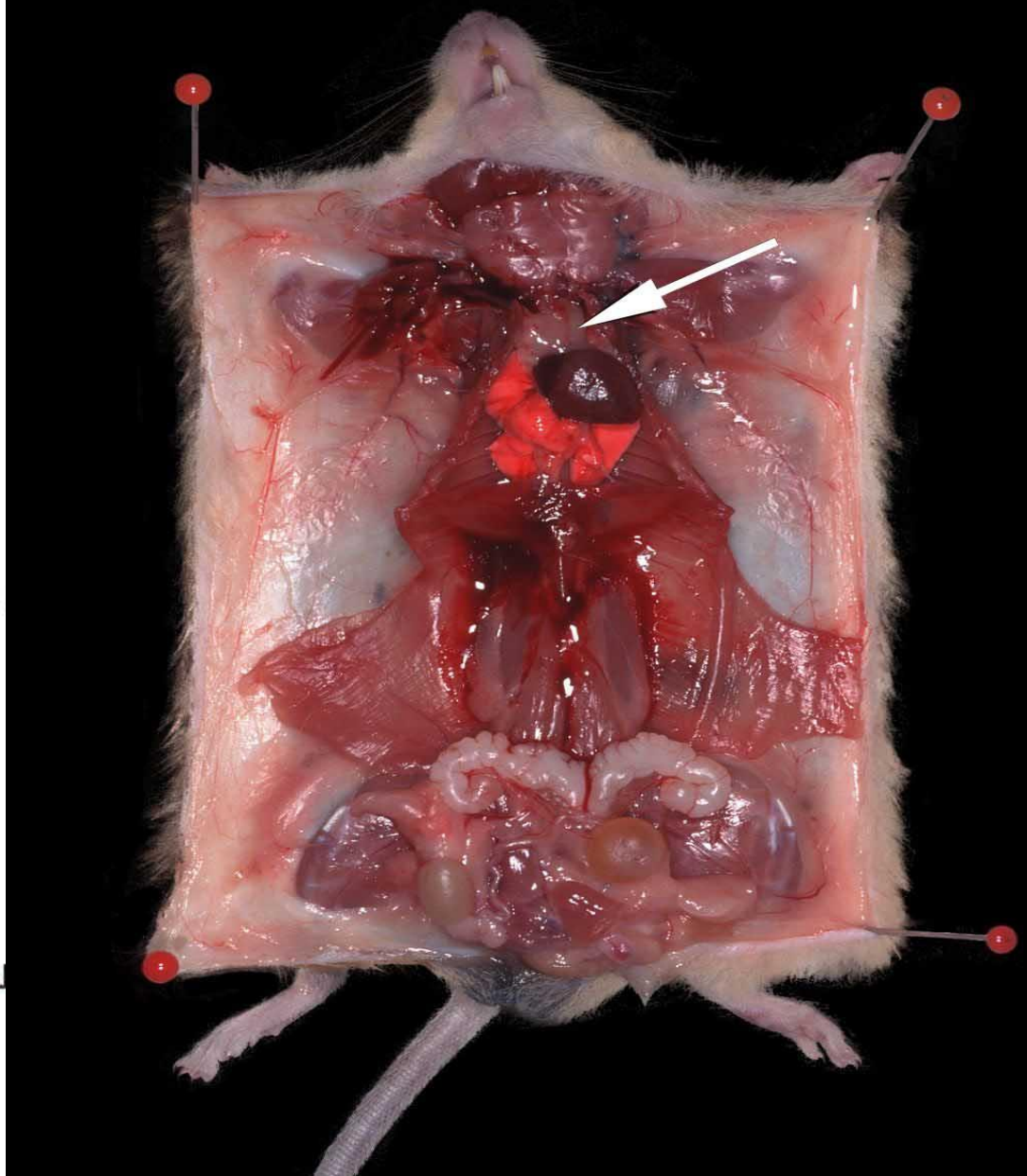
Thymus

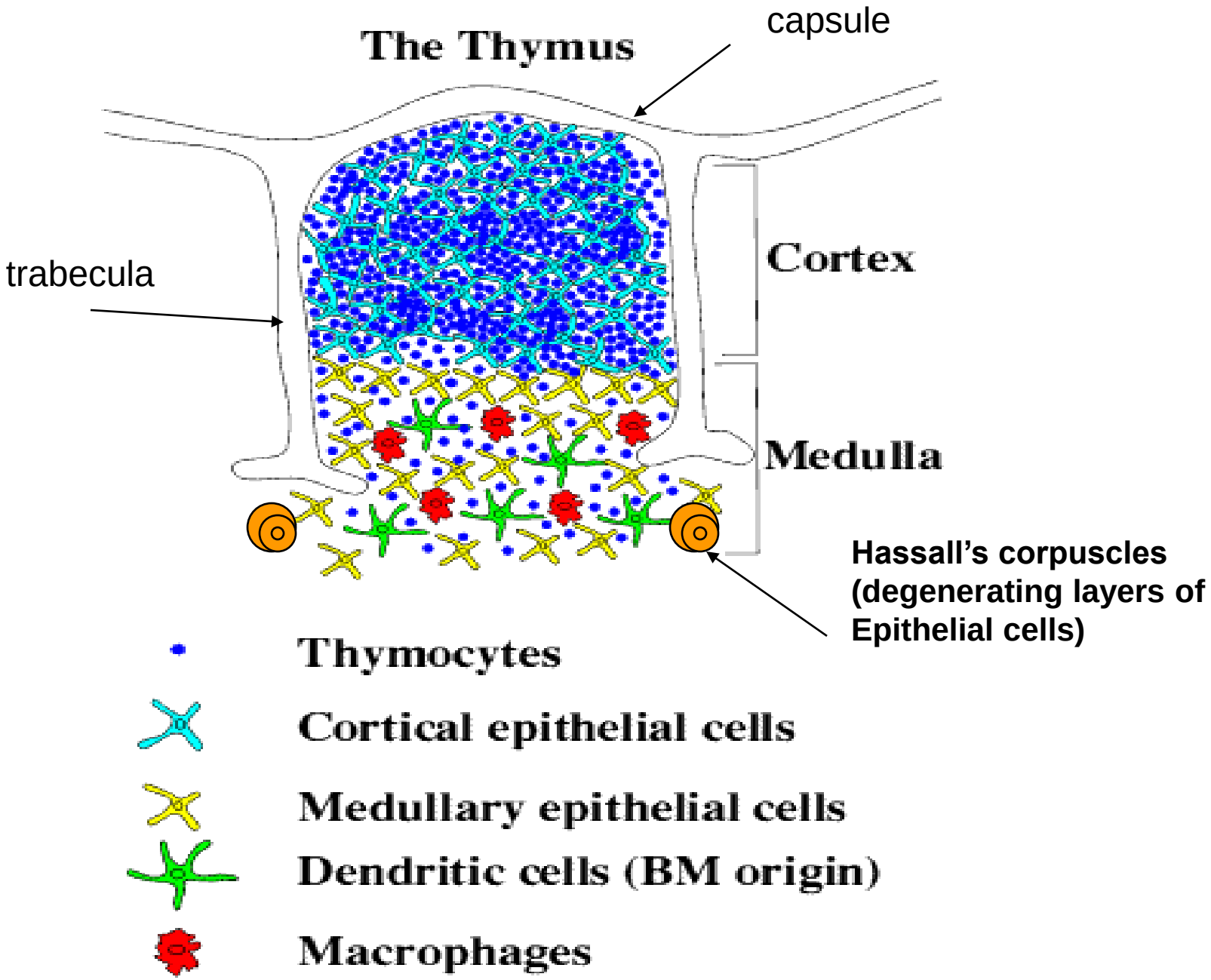
- Bilobed Organ on Top of Heart
- Reaches Max. Size During Puberty
  - 70g infants, 3 g in adults
- 95-99% Of T Cells Die in Thymus
  - self reactivity or no reactivity to Ag
- Consists of Cortex and Medulla
- Rat Thymocytes Sensitive to Glucorticoids

Thymus Location

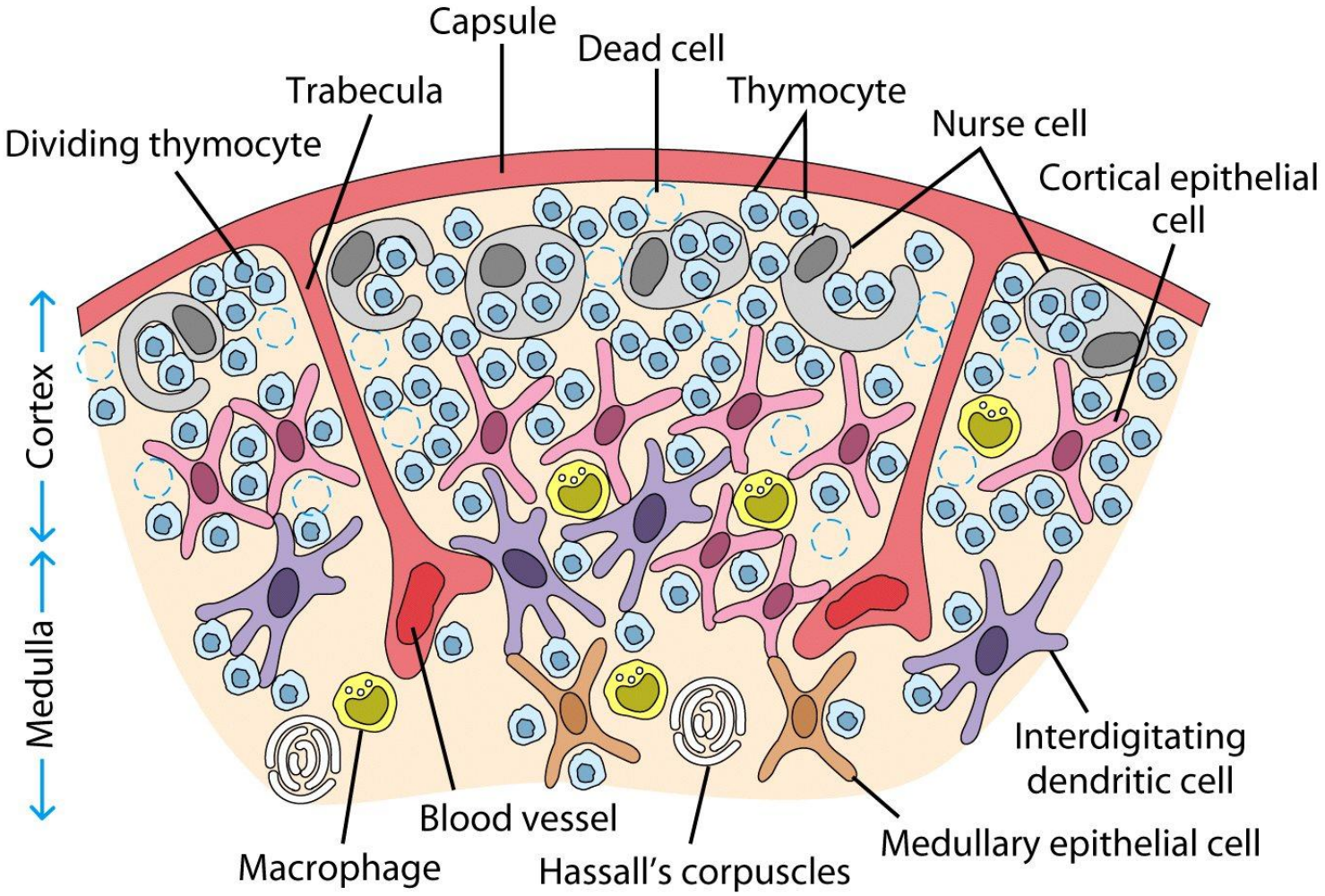







The Thymus
capsule
trabecula
Cortex
Medulla
Hassall's corpuscles
(degenerating layers of
Epithelial cells)
Thymocytes
Cortical epithelial cells
Medullary epithelial cells
Dendritic cells (BM origin)
Macrophages

Thymus


Capsule
Dead cell
Trabecula
Thymocyte
Dividing thymocyte
Nurse cell
Cortical epithelial cell
Cortex
Medulla
Interdigitating dendritic cell
Blood vessel
Medullary epithelial cell
Macrophage
Hassall's corpuscles

CORE

Hematopoiesis

(1) The process to produce immune cells

(2) Stem cells and cytokines

(3) Hematopoiesis in bone marrow is regulated by some cytokines such as stem cell factor, IL-1, IL-3, IL-6, IL-7, GM-CSF, EPO, G-CSF and M-CSF

Hematopoiesis generates immune cells

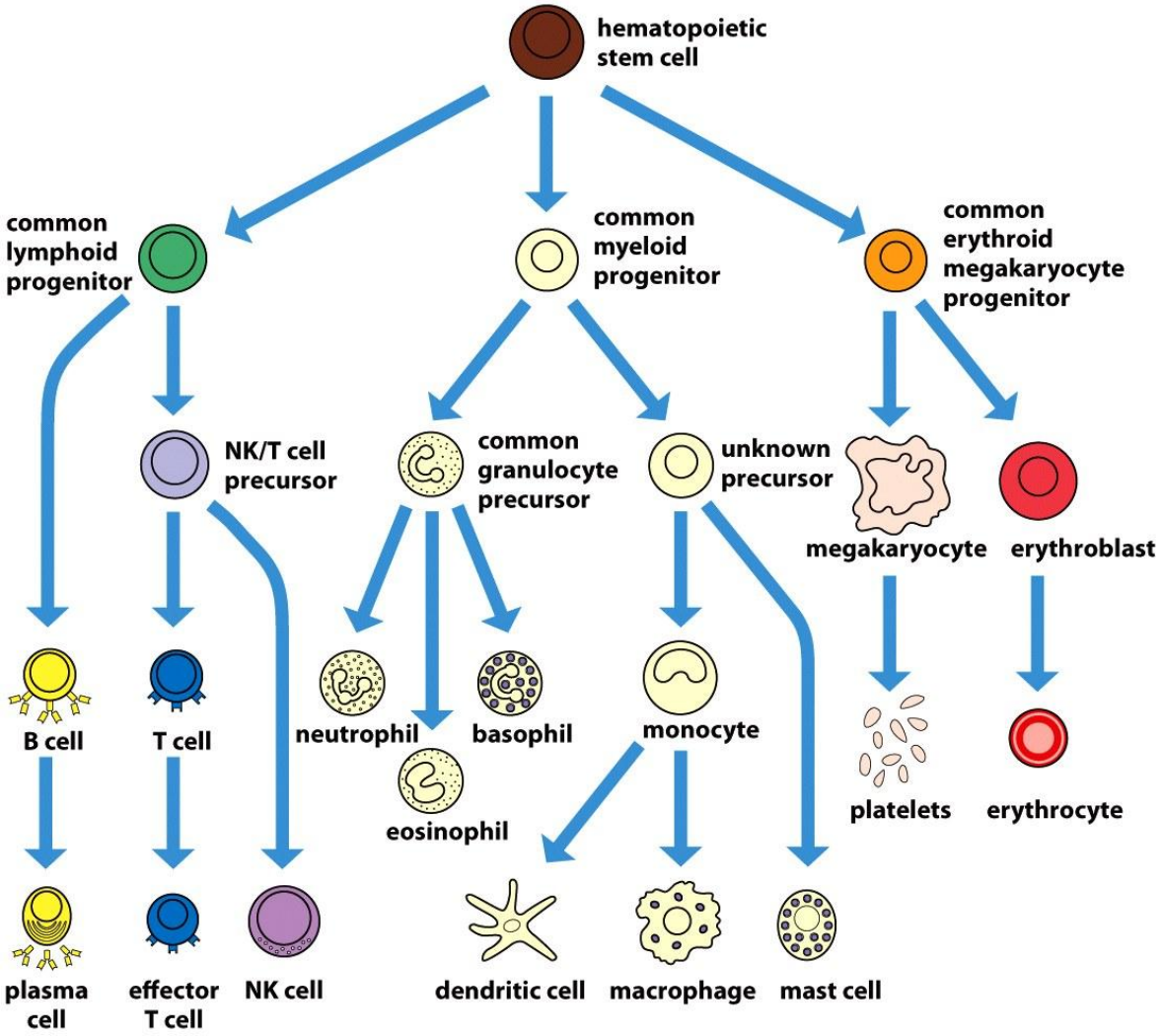


Figure 1.14 The Immune System, 3ed. (© Garland Science 2009)

Hematopoietic stem cells:

1. Self renewal
2. Totipotency

They are in bone marrow after birth

They make immune cells, platelets, and RBCs

T cell progenitors migrate to thymus and generate T cells

B cell progenitors reside in bone marrow to make naïve B cells

Hematopoiesis occurs in the adult bone marrow

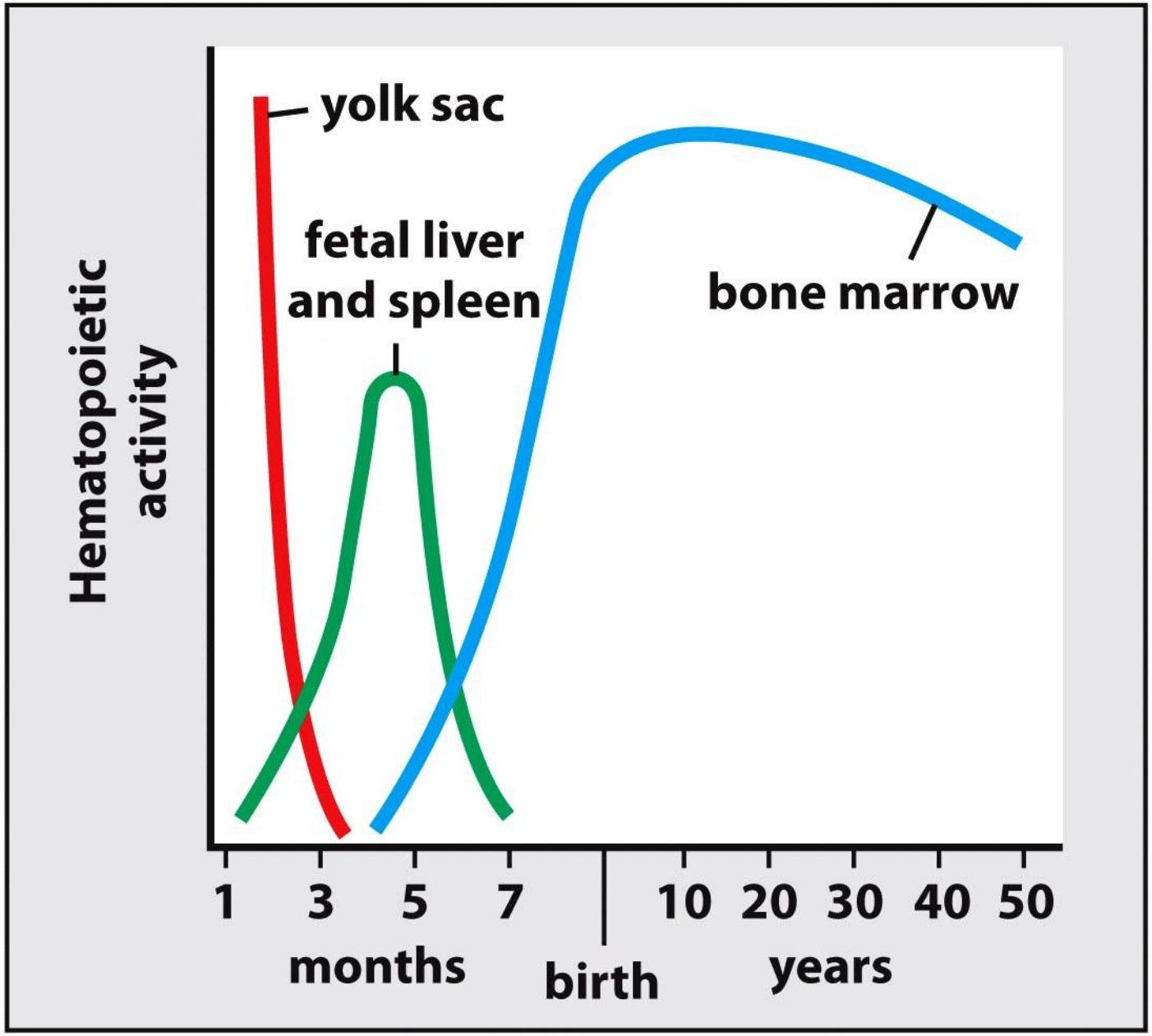


Figure 1.13 The Immune System, 3ed. (© Garland Science 2009)

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

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.