Immune Cells and Organs

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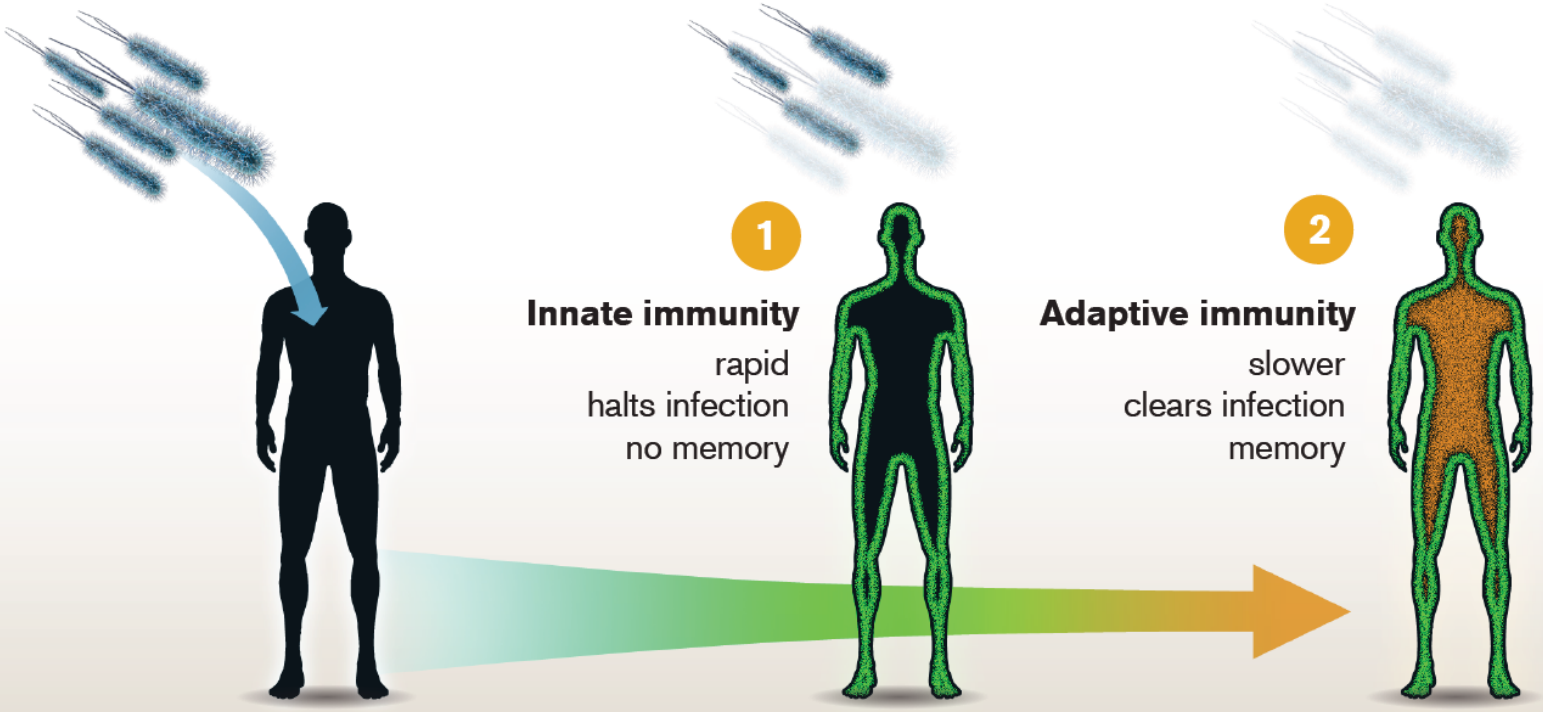
Immune system Purpose/function?

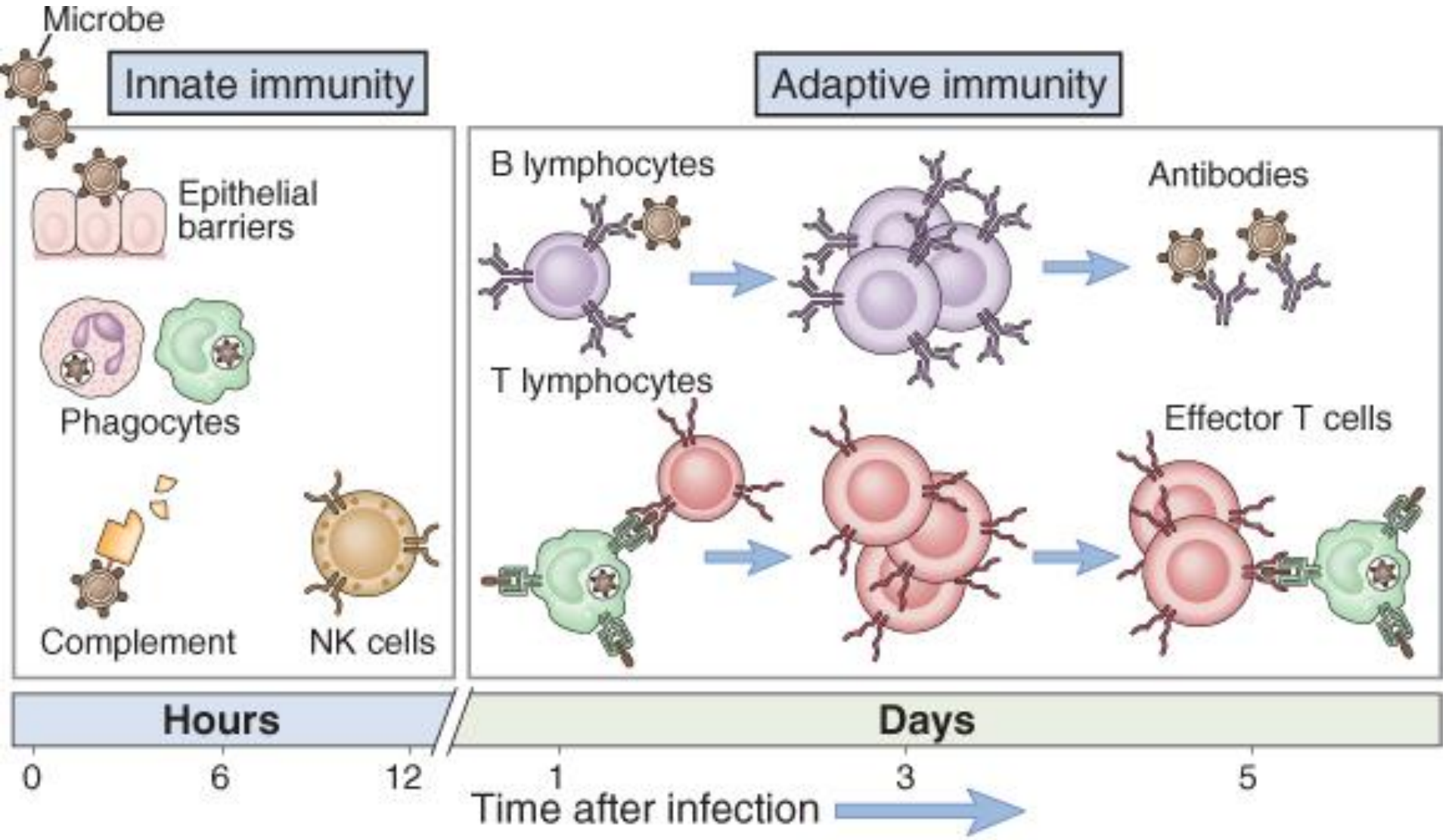
- First line of defense= epithelial integrity= skin, mucosal surfaces
- Defense against pathogens
  - Inside cells= kill the infected cell (Viruses)
  - Systemic= kill- Bacteria, Fungi, Parasites
- Two phases of response
  - Handle the acute infection, keep it from spreading
  - Prevent future infections

The Nobel Prize in Physiology or Medicine 2011



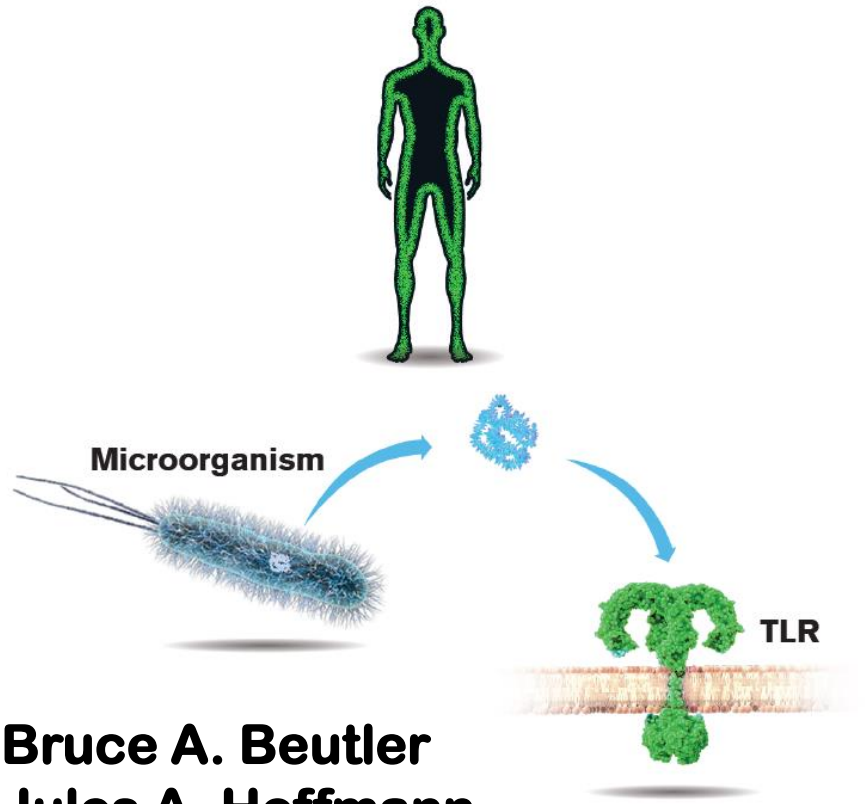
The immune system

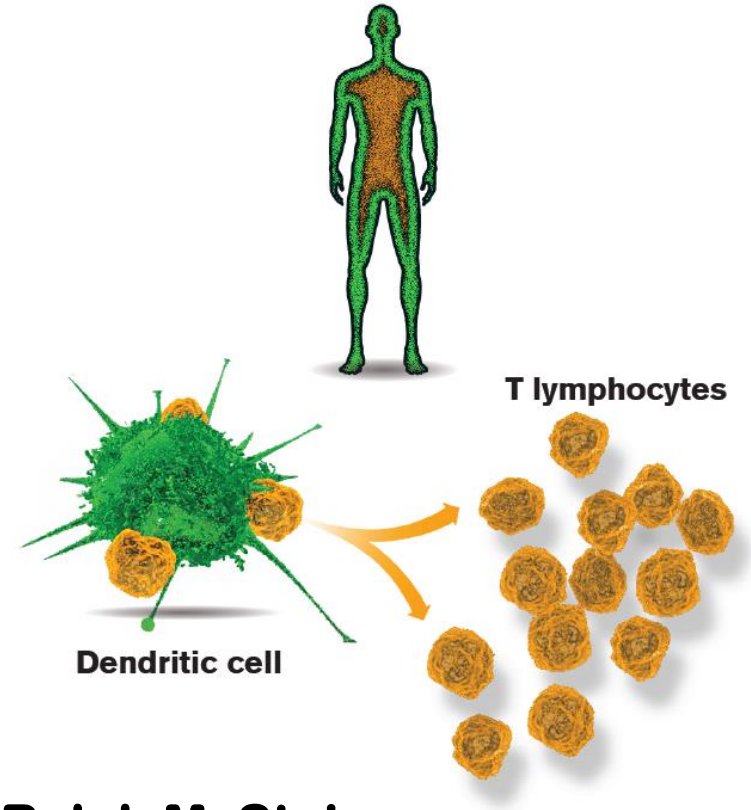
Infection of the human body by pathogenic microorganisms such as bacteria, viruses, parasites or fungi triggers the immune response. It occurs in a two-step process: innate immunity halts the infection, and adaptive immunity subsequently clears it.



We didn’t know….

- What triggers innate immunity-
- What mediates communication between innate and adaptive immunity-





Bruce A. Beutler
Jules A. Hoffmann

Ralph M. Steinman

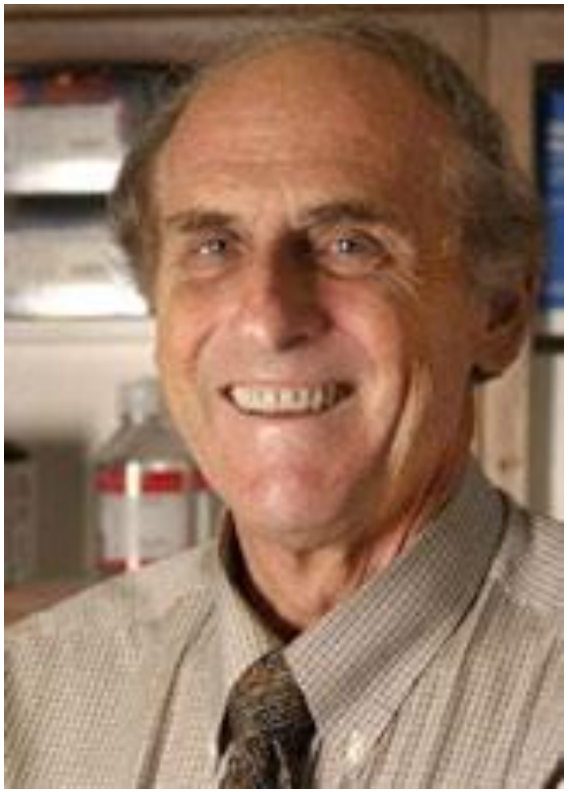
1 Innate immunity

Components of microorganisms bind to Toll-like receptors located on many cells in the body. This activates innate immunity, which leads to inflammation and to the destruction of invading microorganisms.

2 Adaptive immunity

Dendritic cells activate T lymphocytes, which initiates adaptive immunity. A cascade of immune reactions follows, with formation of antibodies and killer cells.

Illustration: Mattias Karlén



Jules A. Hoffmann — 1996 (fruit flies)

Bruce A. Beutler — 1998 (mice)

Ralph M. Steinman — 1973

Discovered receptor proteins that can recognize bacteria and other microorganisms as they enter the body, and activate the first line of defense in the immune system, known as innate immunity.

Discovered dendritic cells "the conductors of the immune system". DC's activate T-cells

The Immune System

"Although the lymphoid system consists of various separate tissues and organs, it functions as a single entity. This is mainly because its principal cellular constituents, lymphocytes, are intrinsically mobile and continuously recirculate in large number between the blood and the lymph by way of the secondary lymphoid tissues… where antigens and antigen-presenting cells are selectively localized."

-Masayuki, Nat Rev Immuno. May 2004

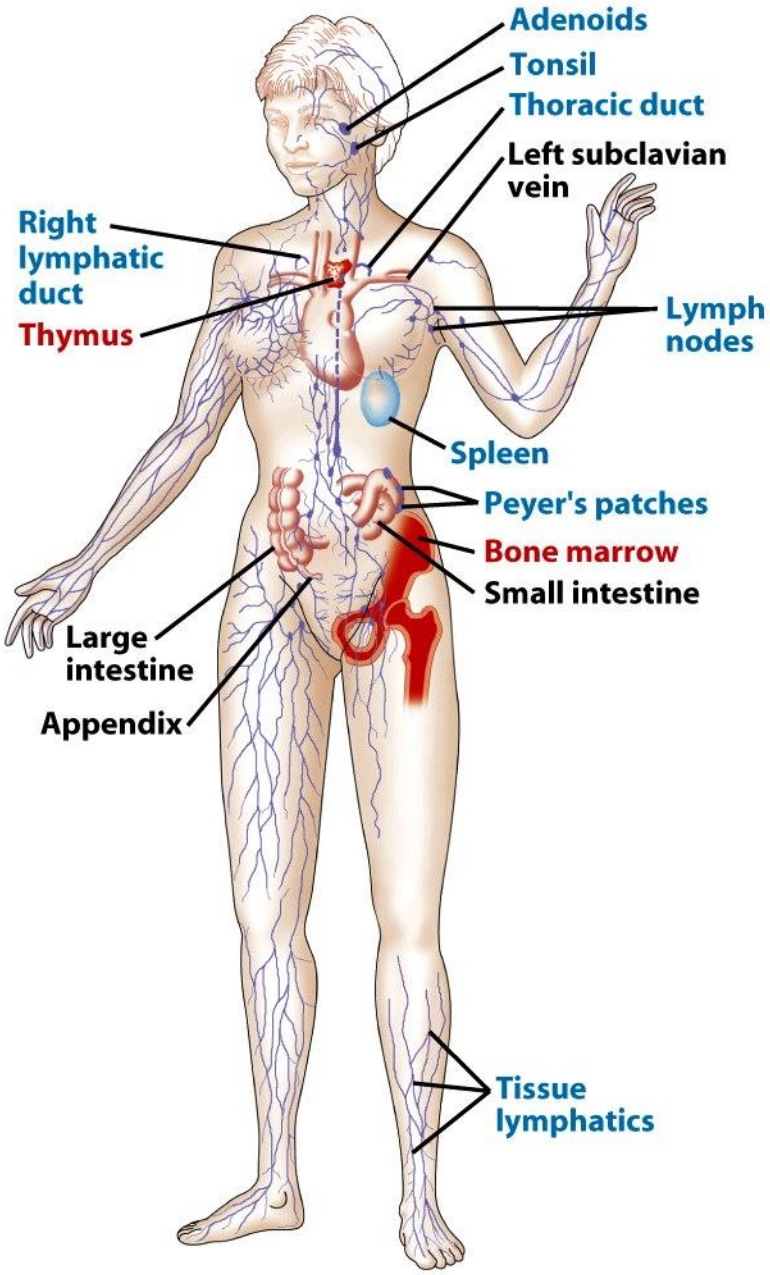
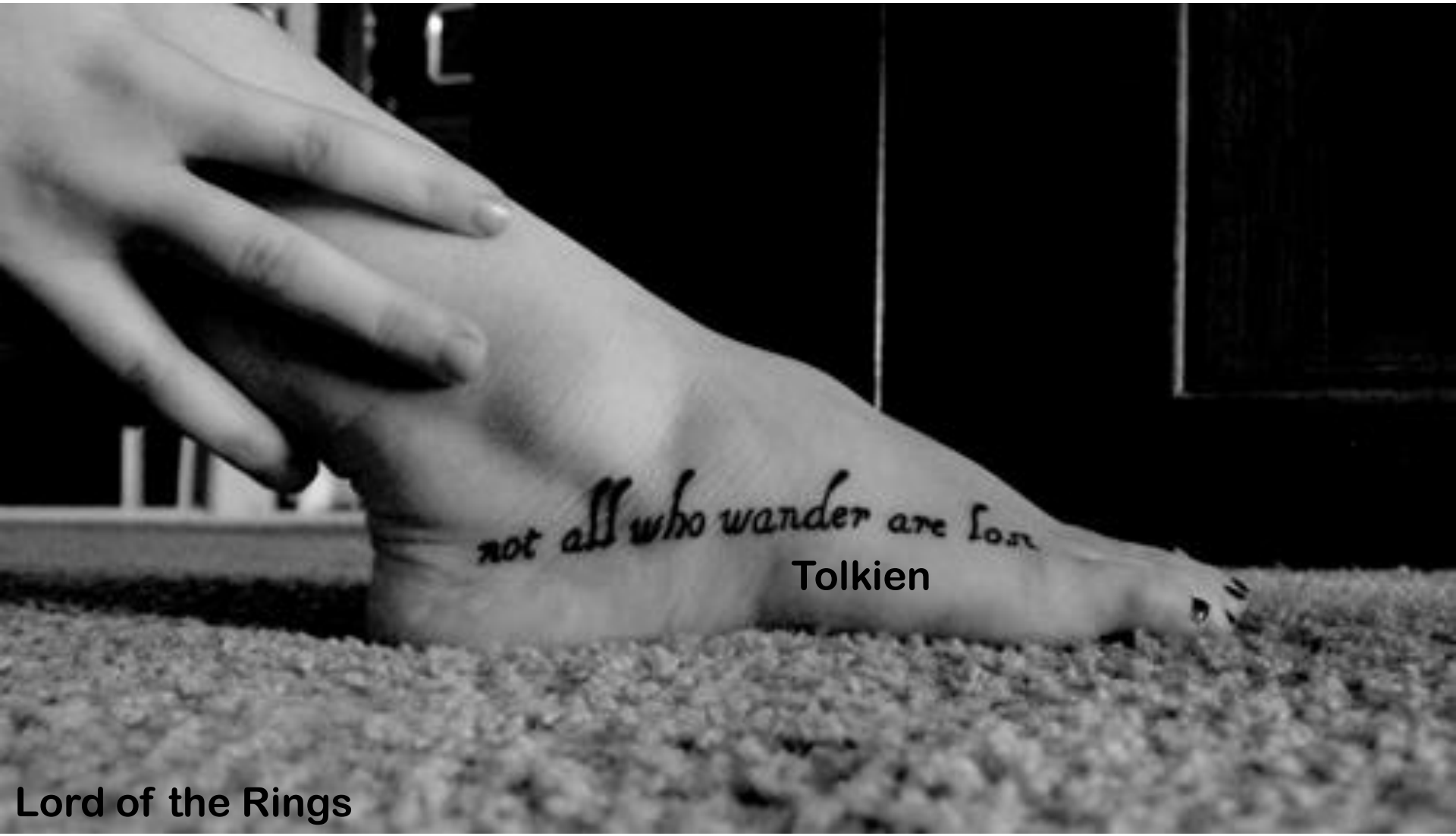


Figure 2-11
Kuby IMMUNOLOGY, Sixth Edition

Not all who wander are lost…..



…..some are searching

Immune System

- Cells
  - Innate response- several cell types
  - Adaptive (specific) response- lymphocytes
- Organs
  - Primary where lymphocytes develop/mature
  - Secondary where mature lymphocytes and antigen presenting cells interact to initiate a specific immune response
- Circulatory system- blood
- Lymphatic system- lymph

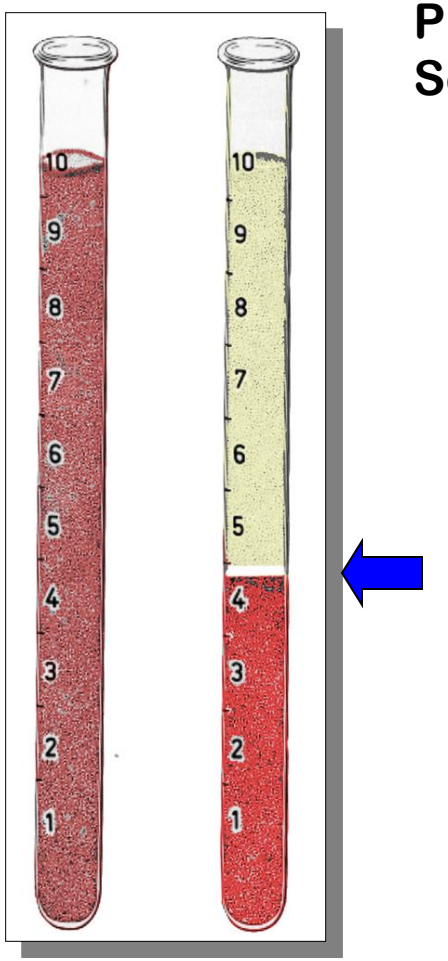
Cells= Leukocytes= white blood cells

Granulocytes

1. neutrophils
2. eosinophils
3. basophils

Non-granulocytes

4. monocytes
5. lymphocytes



Plasma- with anticoagulant
Serum- after coagulation

Plasma (56%)

After centrifugation in Ficoll, leukocytes are found in the "buffy coat" 1%

RBCs

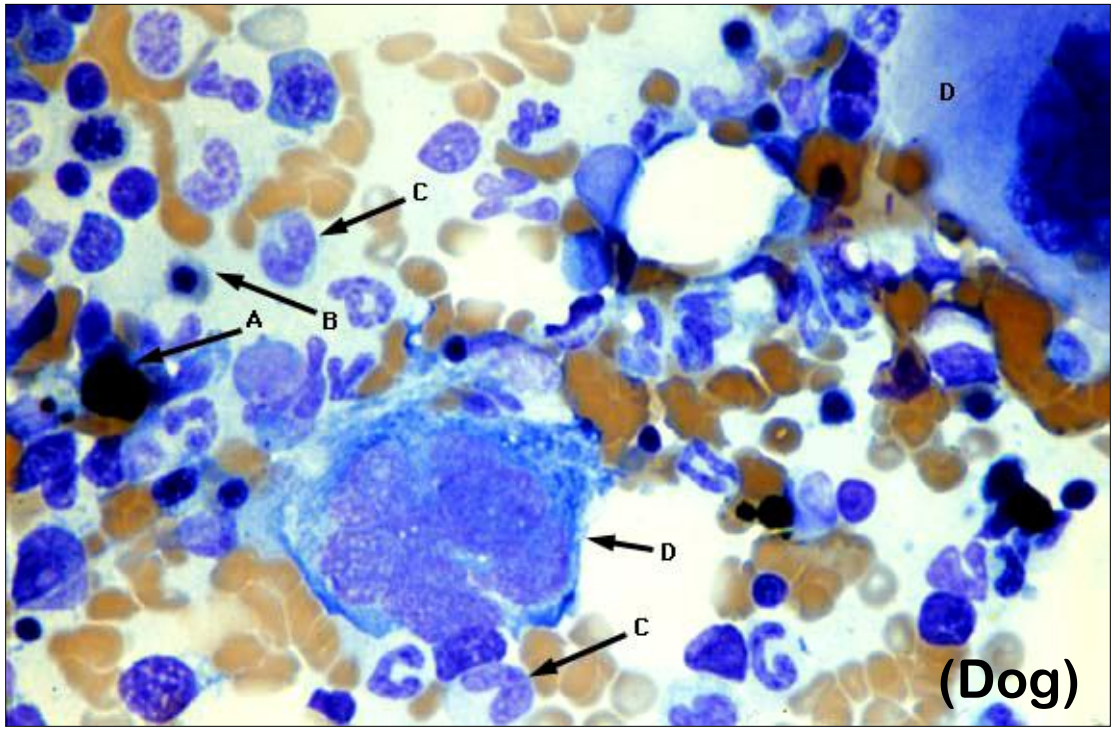
Where do all these cells come from?

The cells of the immune system arise from pluripotent hematopoeitic stem cells (HSC) through two main lines of differentiation

- **Myeloid** lineage produces phagocytes (neutrophils..) and other cells
- **Lymphoid** lineage produces lymphocytes

Hematopoeisis

• Pleuripotent Hematopoeitic Stem Cells give rise to second generation stem cells with restricted lineage potential= progenitors



A. Hemosiderin: A protein that stores iron in the body, derived chiefly from the hemoglobin released during hemolysis
B. Erythroid precursor
C. Band cells
   - Neutrophil
D. Megakaryocytes
   - platelets

Univ Penn, Vet School, http://cal.nbc.upenn.edu/histo

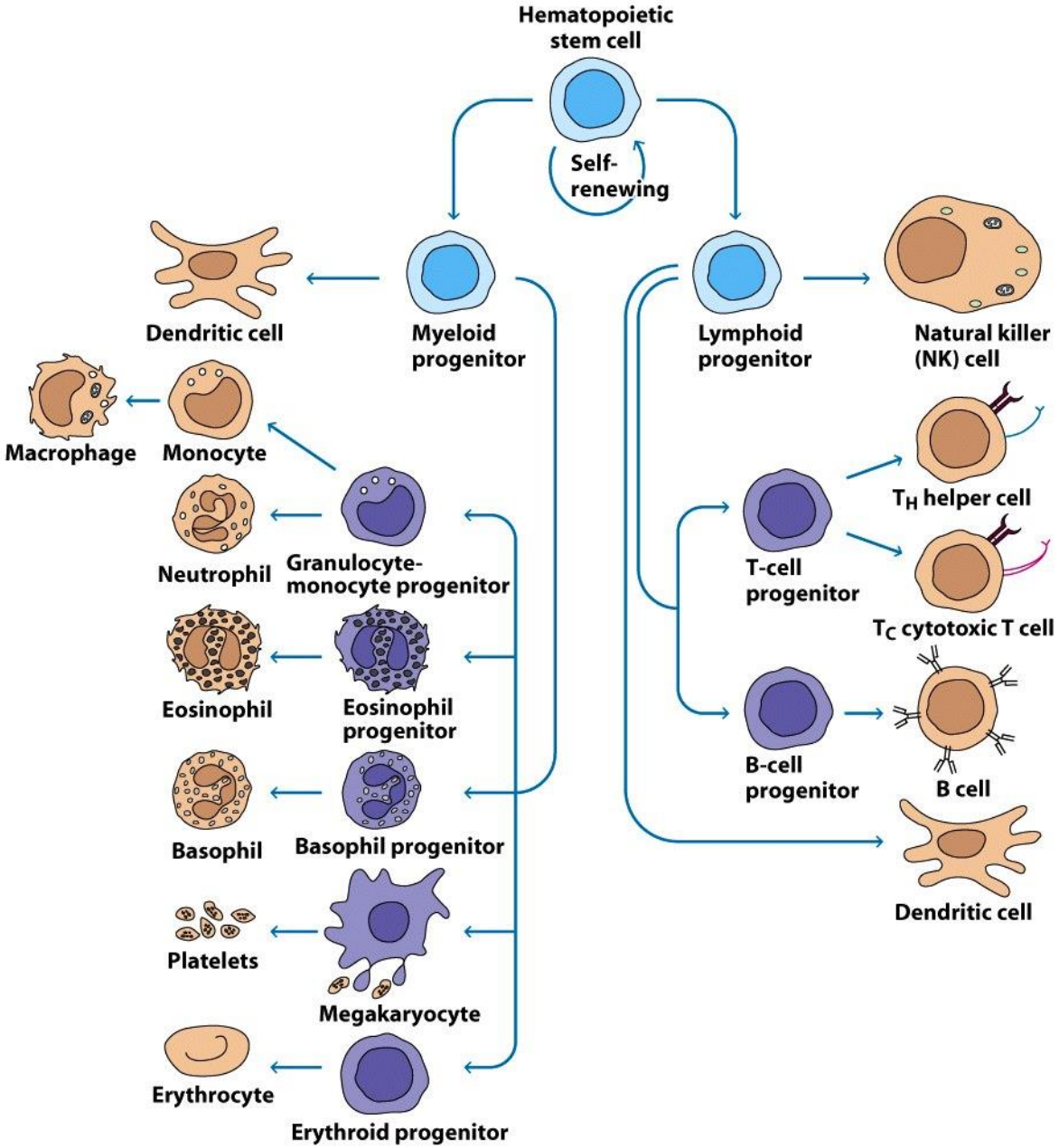


Figure 2-2
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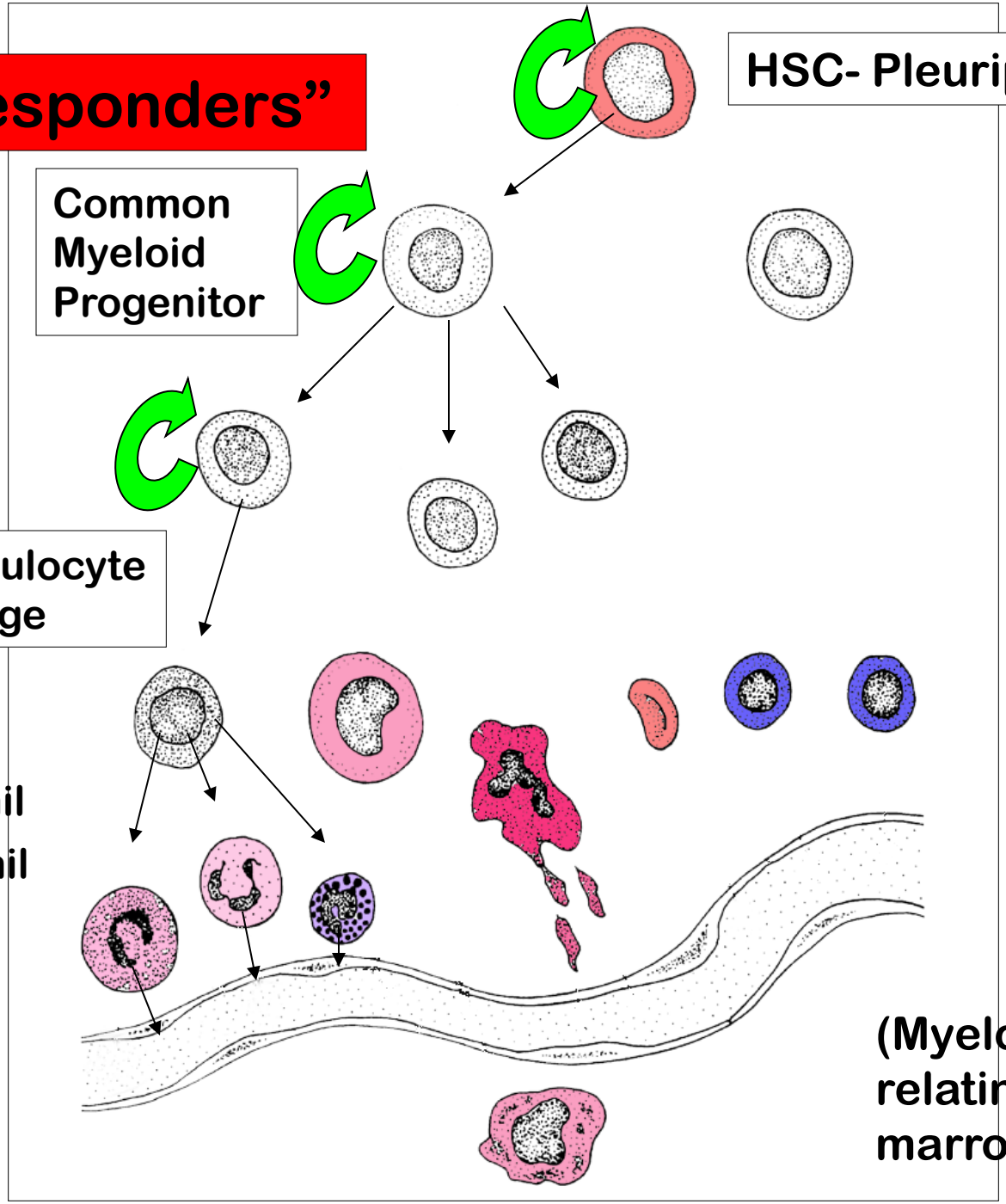
"First Responders"



(Myeloid = of or relating to the bone marrow)

Granulocytes

- Front line of attack during immune response~ part of innate immune response
- Identified by characteristic staining patterns of “granules”
  - Released in contact with pathogens
  - Proteins with distinct functions: killing, regulation of other cells, tissue remodeling
- All have multilobed nuclei

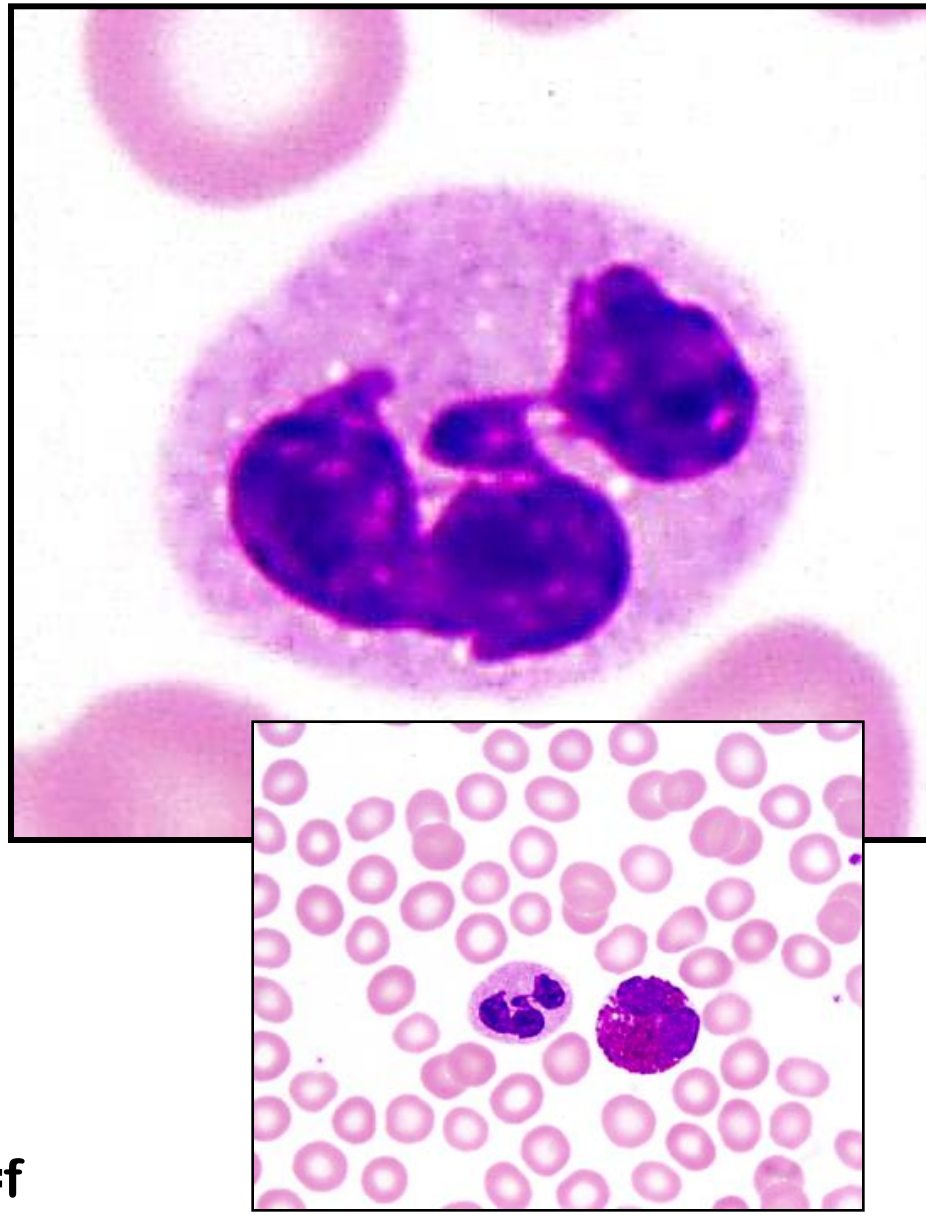
Neutrophils

- One of the main effector cells in the innate immune system
- 50-70% of white blood cells
- Released from bone marrow, circulate 7-10 hrs, enter tissues, live only a few days
- Numbers & recruitment increase during infections~ “leukocytosis”~ diagnostic
- shown to kill microorganisms by phagocytosis 100 years ago
- Main cellular component of pus

Neutrophil

- Named based on staining qualities of granules
- Multilobed nucleus= polymorphonuclear leukocyte= PMN
- Neutrophilic granules stain lightly blue to pink
- 7-10 hrs in blood, then migrates into tissues
- First responders- Motile & phagocytic
- "Leukocytosis" indicates infection
- Extracellular "traps"

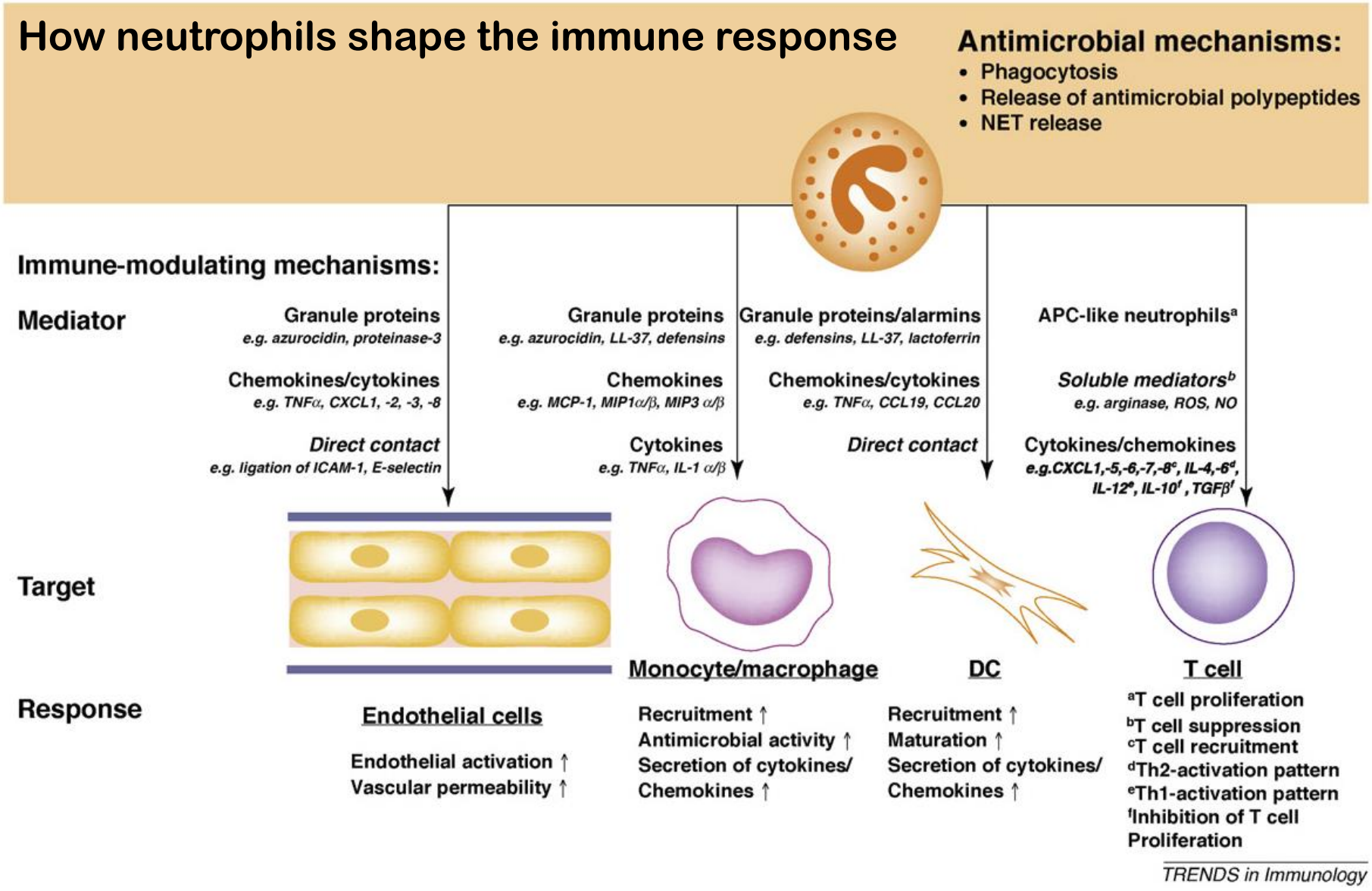
http://www.youtube.com/watch?v=fpOxgAU5fFQ



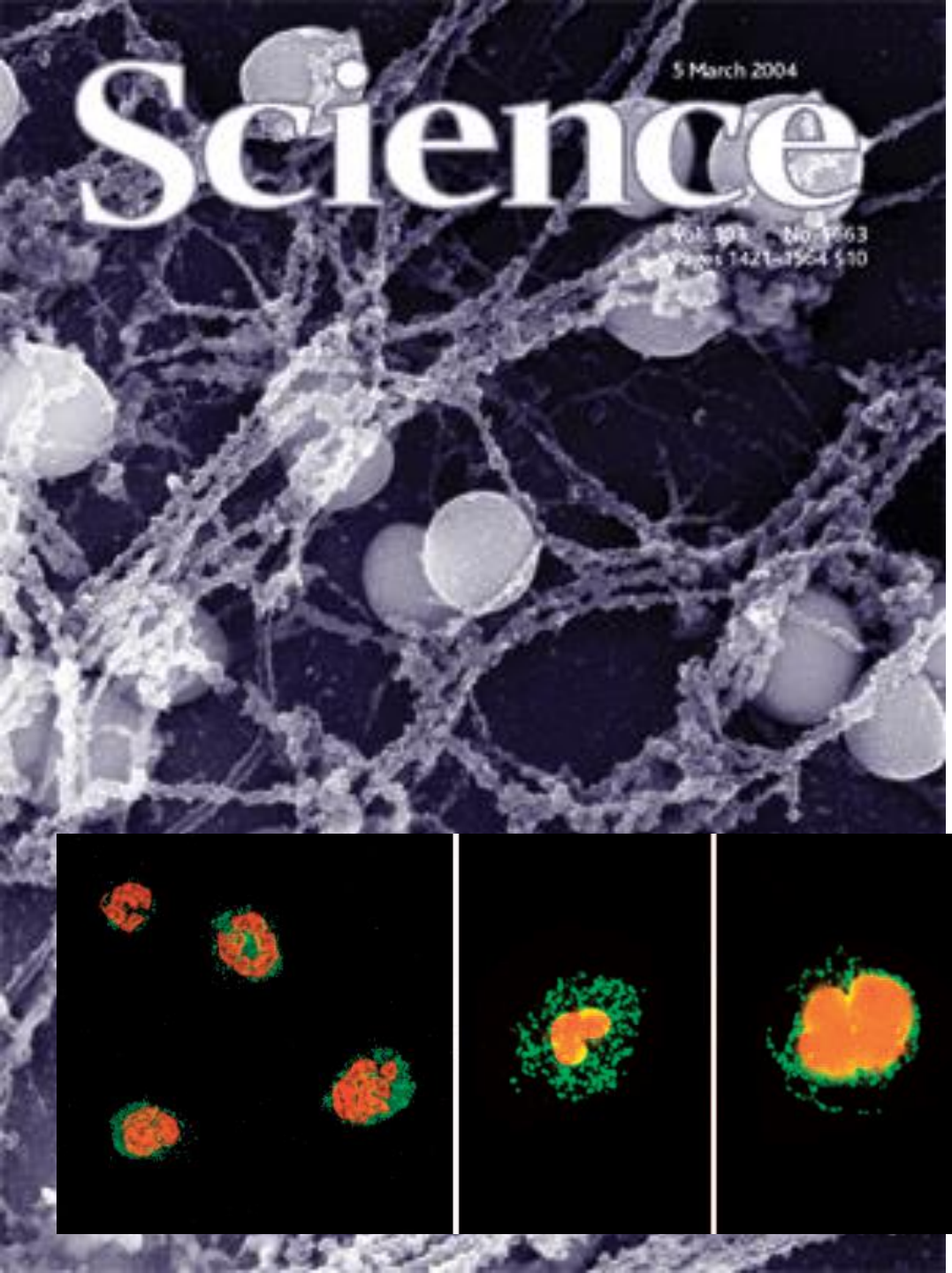
Neutrophil movie

https://www.youtube.com/watch?v=VAhM9OxZDkU

How neutrophils shape the immune response

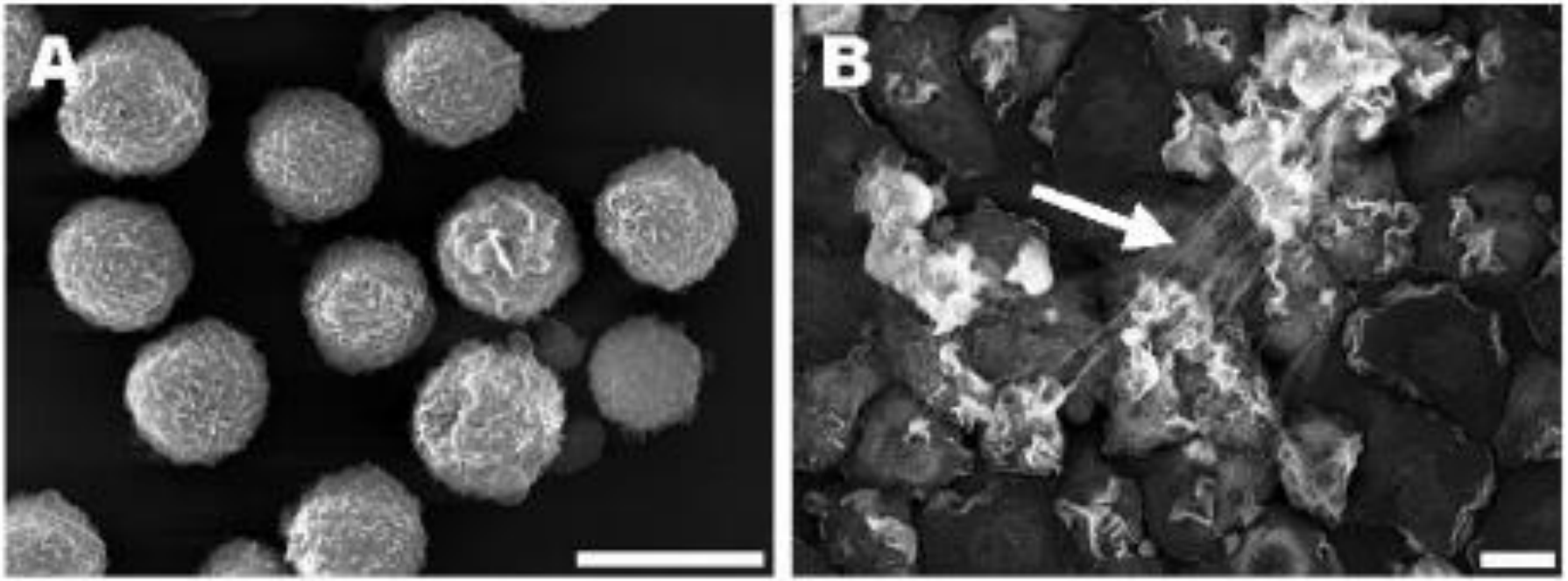


Soehniein, Trends in Immunol 2009



COVER
Scanning electron micrograph of *Staphylococcus aureus* bound to neutrophil extracellular traps (NETs). These novel structures formed by activated neutrophils can disarm and kill bacteria before they reach host cells

NETS

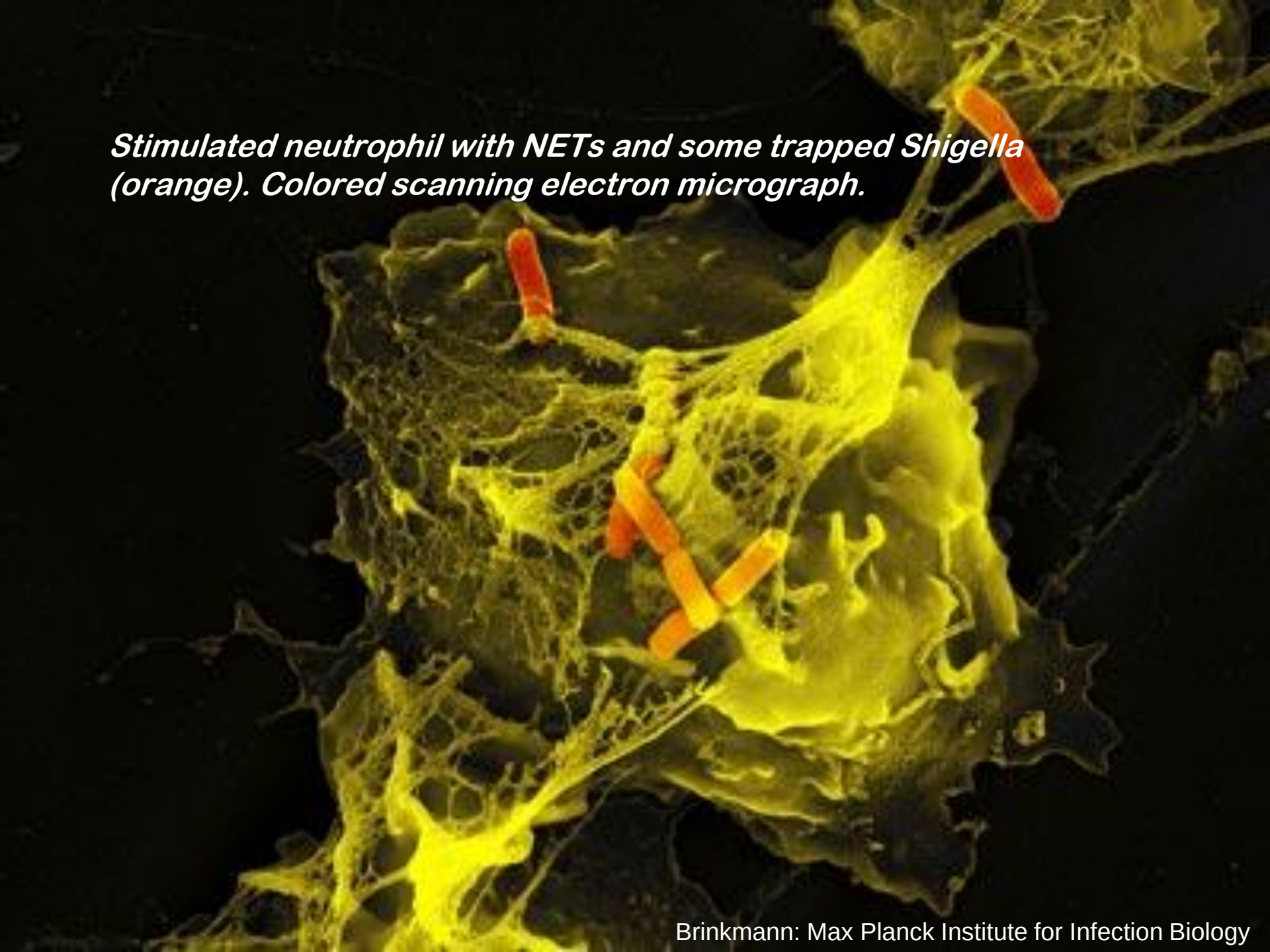


neutrophils resting

neutrophils activated

Brinkman/Zychlinsky Nat Rev Micro 5: 2007
“Beneficial suicide: why neutrophils die to make NETS”

Brinkmann et al, Science 303, 2004

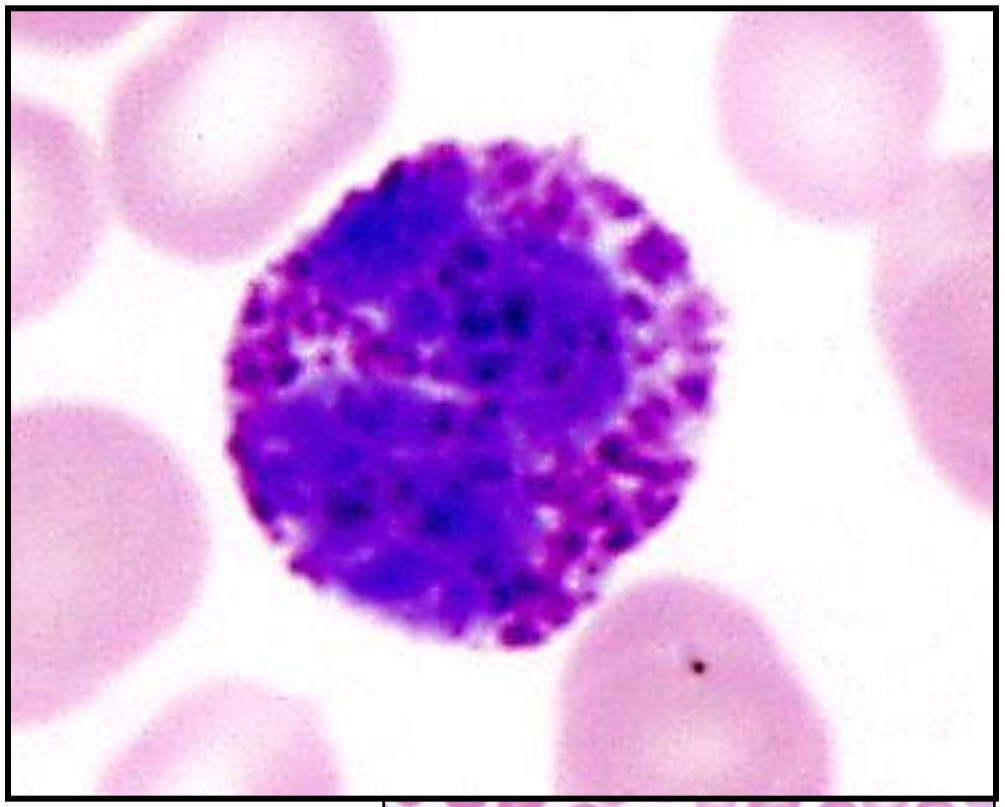


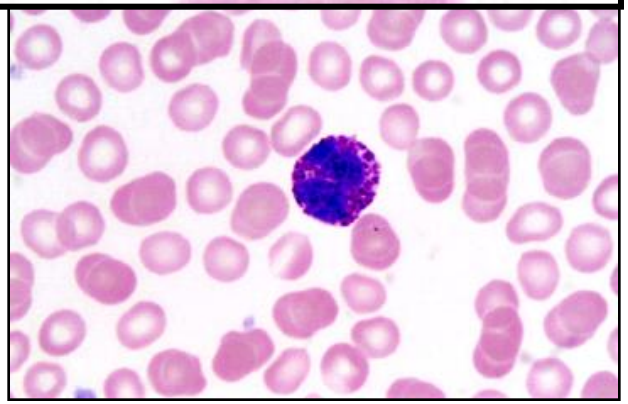
Stimulated neutrophil with NETs and some trapped Shigella (orange). Colored scanning electron micrograph.

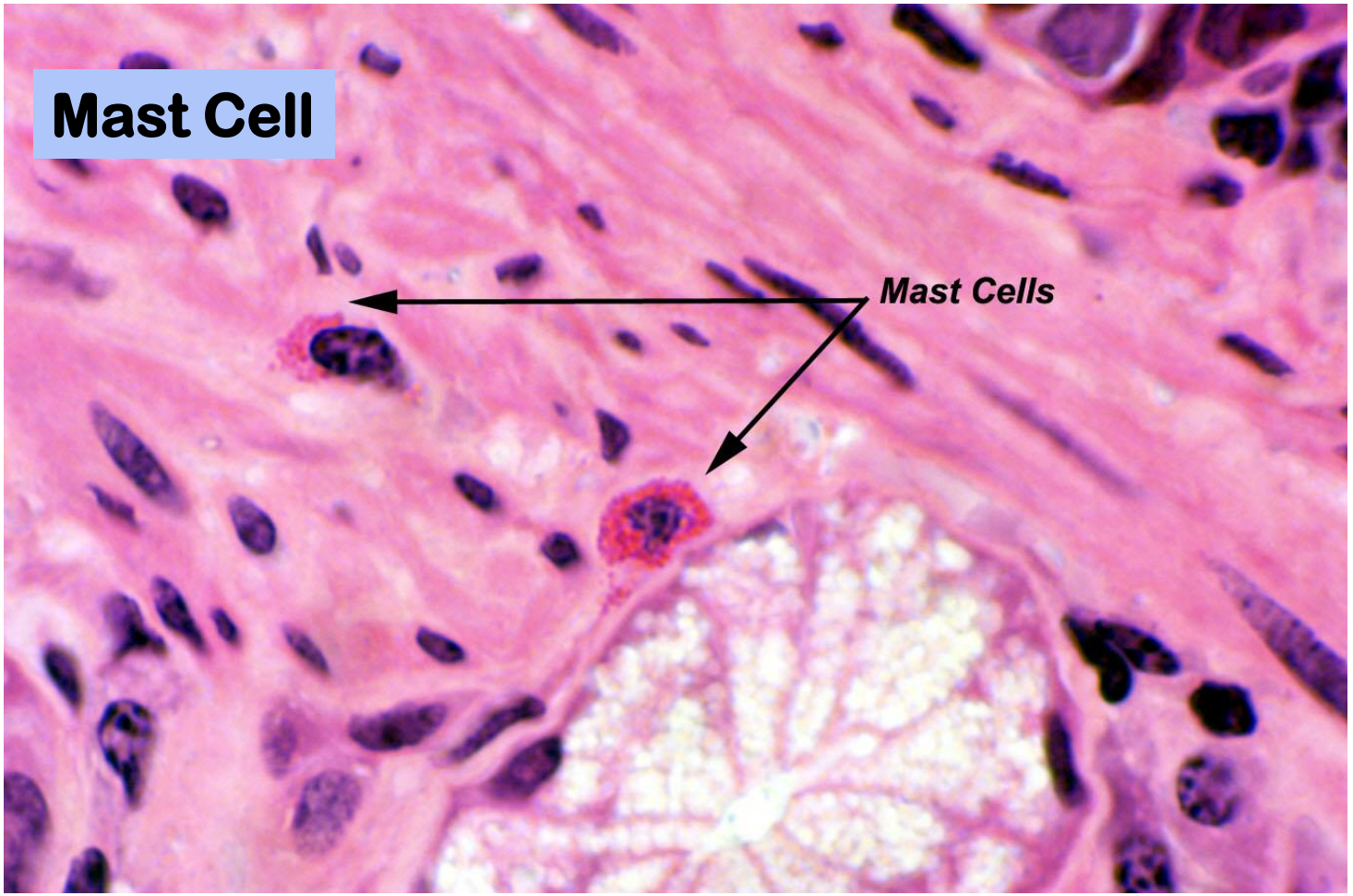
Brinkmann: Max Planck Institute for Infection Biology

Basophil

- <1% all leukocytes
- Non-phagocytic
- Nucleus obscured by coarse blue (H&E) granules
- Important in some allergic responses
- Critical to response to parasites
- Bind circulating Abs and release histamine- increasing permeability of blood vessels







- Leave bone marrow as undifferentiated cells and mature in tissues; histamine
- May be related to basophils (?)

Eosinophil

- Bilobed nuclei
- Motile, phagocytic
- Killing of antibody coated parasites
- Degranulation of substances that kill parasites, worms

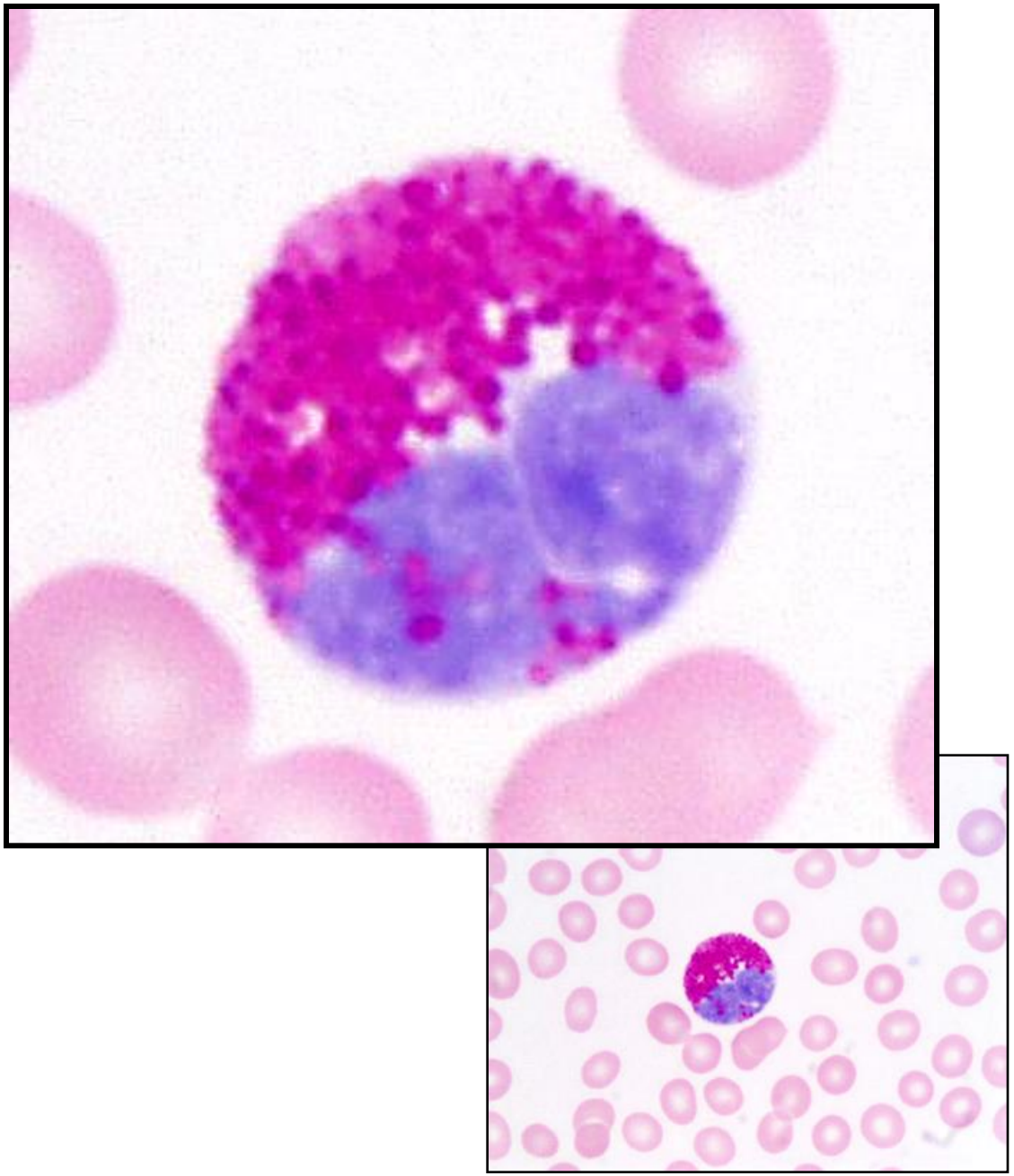


TABLE 2-2 Examples of proteins contained in neutrophil, eosinophil, and basophil granules

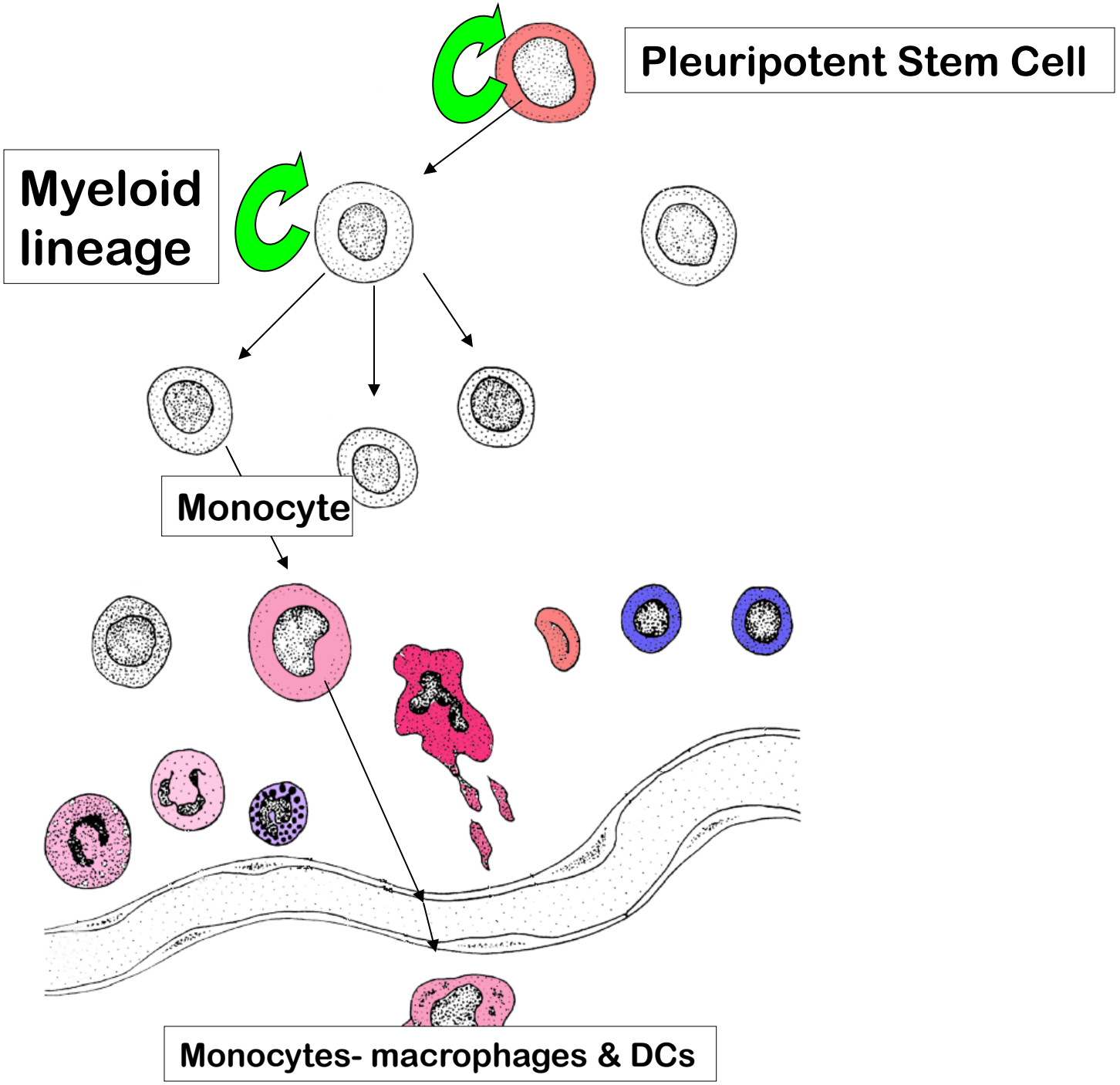
Cell type	Molecule in granule	Examples	Function
Neutrophil	Proteases	*Elastase, Collagenase*	Tissue remodeling
	Antimicrobial proteins	*Defensins, lysozyme*	Direct harm to pathogens
	Protease inhibitors	*α1-anti-trypsin*	Regulation of proteases
	Histamine		Vasodilation, inflammation
Eosinophil	Cationic proteins	*EPO*	Induces formation of ROS
	Ribonucleases	*MBP*	Vasodilation, basophil degranulation
	Cytokines	*ECP, EDN*	Antiviral activity
	Chemokines	*IL-4, IL-10, IL-13, TNFα*	Modulation of adaptive immune responses
		RANTES, MIP-1α	Attract leukocytes
Basophil/Mast Cell	Cytokines	*IL-4, IL-13*	Modulation of adaptive immune response
	Lipid mediators	*Leukotrienes*	Regulation of inflammation
	Histamine		Vasodilation, smooth muscle activation

Table 2-2
Kuby Immunology, Seventh Edition

Myeloid antigen presenting cells:

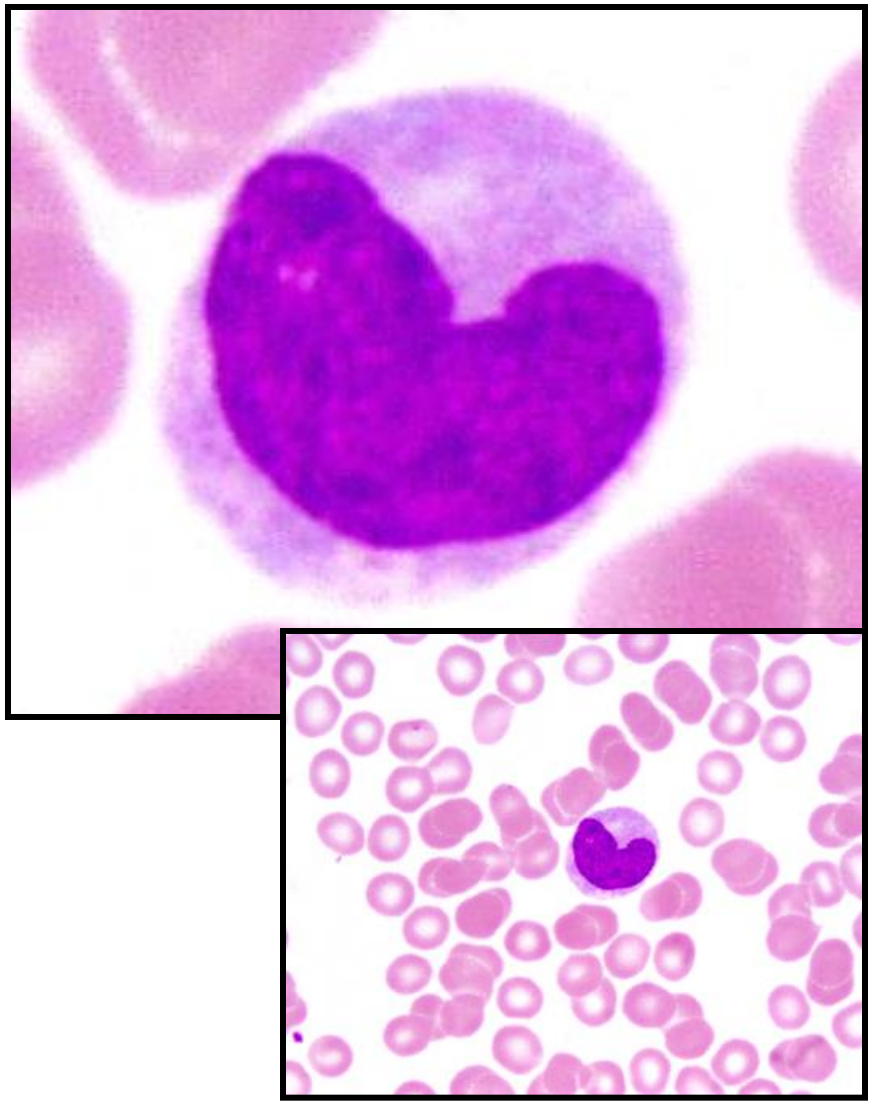
Monocytes, macrophages, dendritic cells

- Phagocytic
- Ingest, digest into peptides, present on cell surface
- Bridge between innate and adaptive immune responses
- Make contact with antigens in periphery and then interact with lymphocytes in lymph node
- Secrete proteins that attract and activate other immune cells


Pleuripotent Stem Cell
Myeloid lineage
Monocyte
Monocytes- macrophages & DCs

Monocyte

- Mononuclear
- Circulate in blood~ 8 hrs
- Bean-shaped nucleus



Macrophage

- Monocytes enter tissues and become fully mature macrophages or dendritic cells
  - Enlarge
  - Become phagocytic
- Free vs fixed tissue mΦ
  - Special names in different organs- Kupffer cells-liver
- Digest and/or *present* Ag
- Surface receptors for Abs (opsinized Ags)

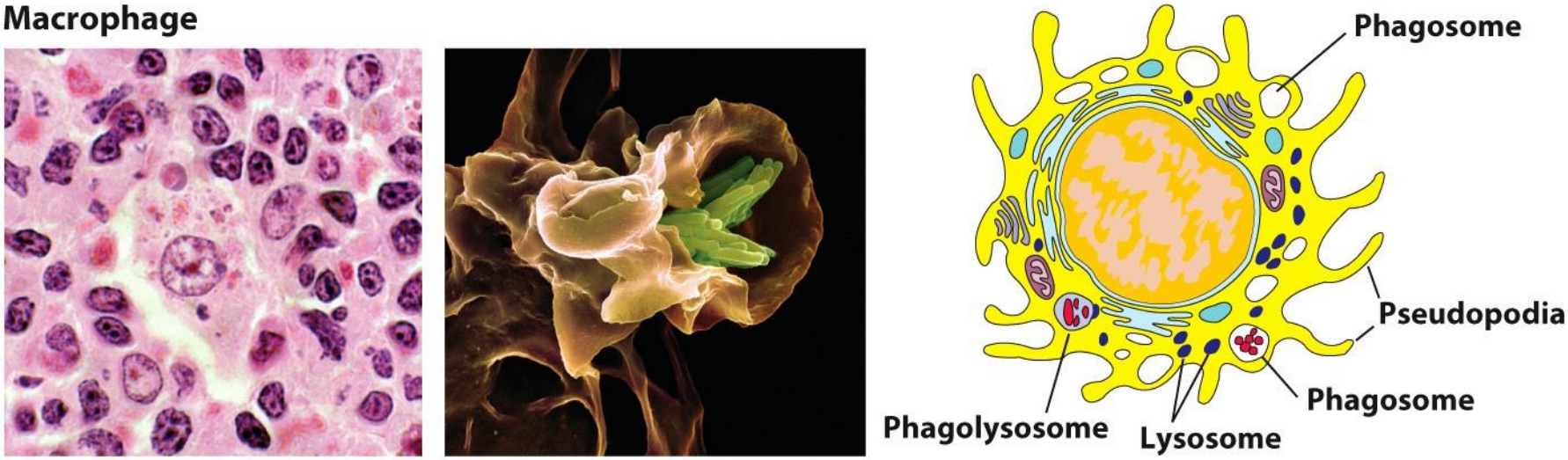


Figure 2-3b
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Dendritic cells:

heterogeneous myeloid & lymphoid origins

- Best APC for presenting to naïve T-cells
- Ralph Steinman discovered them in mid 1970's; just received Nobel Prize 2011
- Critical
- Named for long processes; actively extend and retract sampling Ags & examining T cells
- Capture Ag in one place- then migrate- present Ag in another place (eg. LN)
- Immature to mature; change in functionality from Ag capture to Ag presentation

Dendritic cell

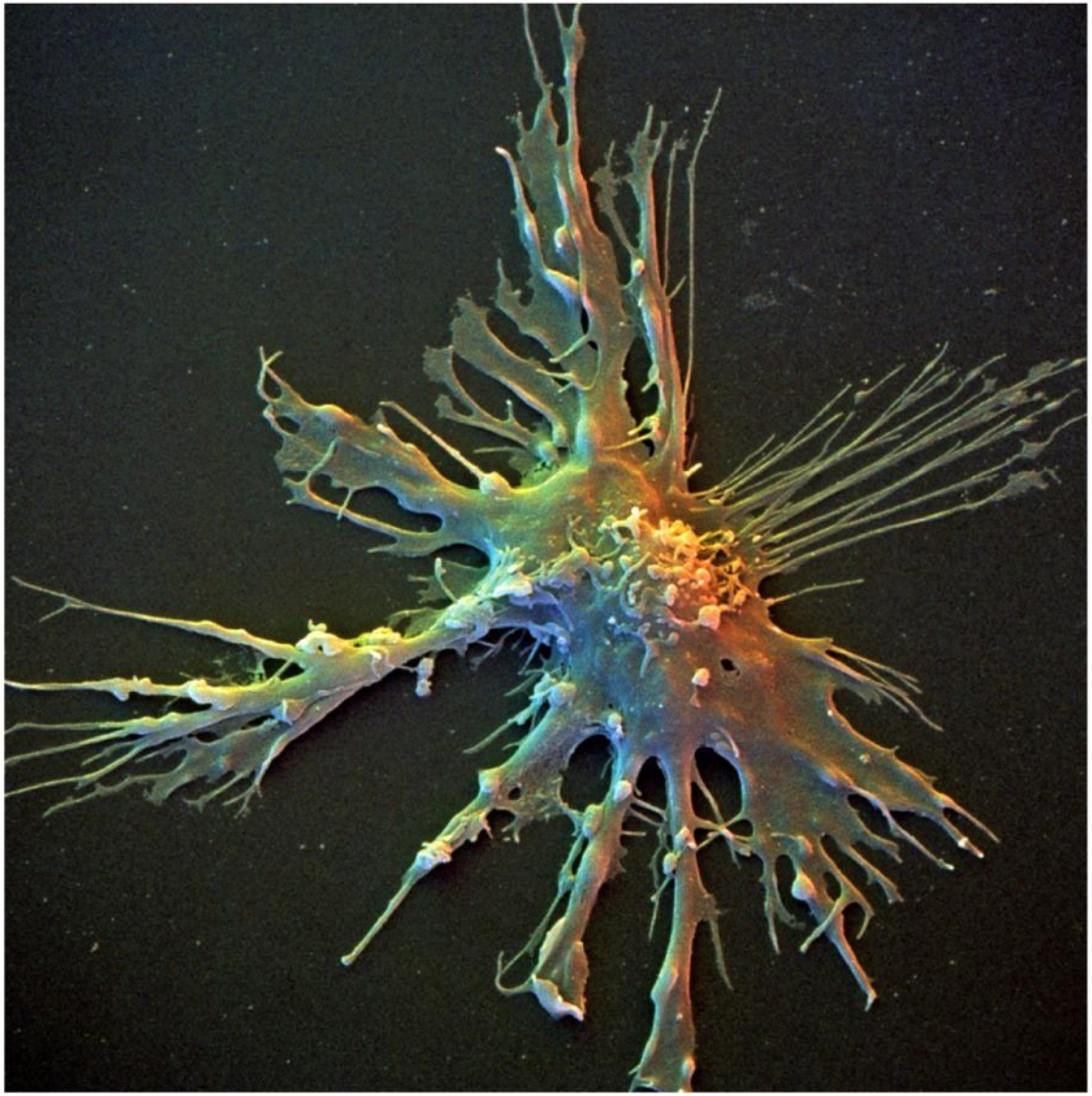

Figure 2-3c part 1
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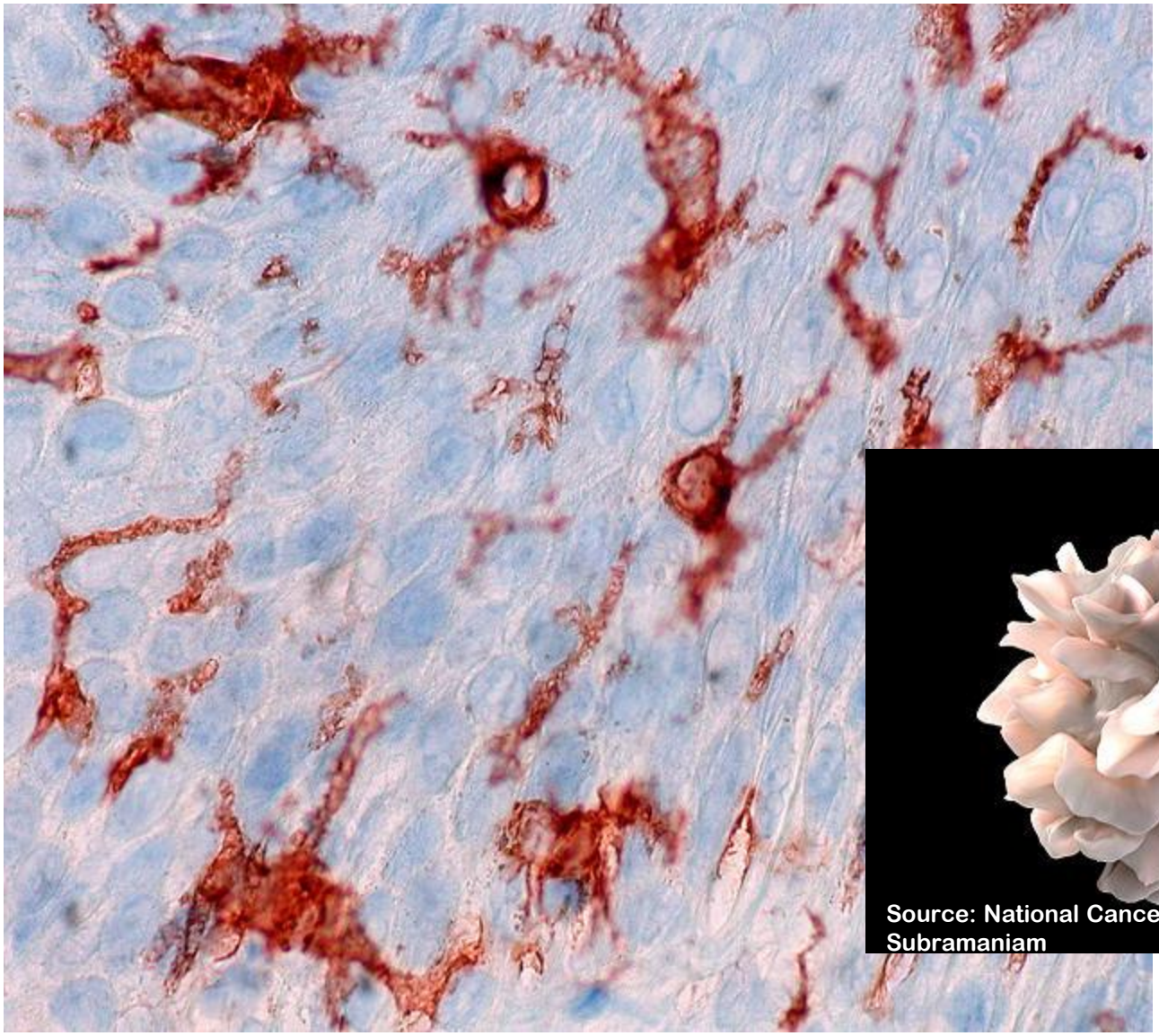
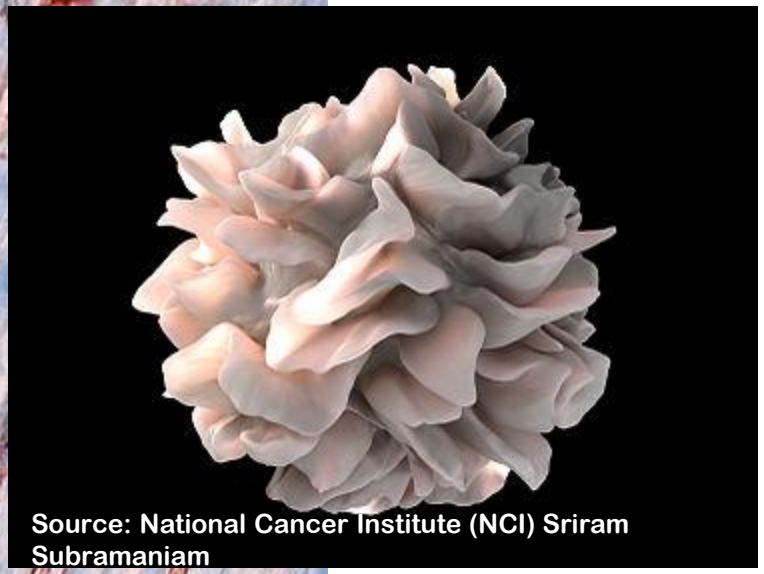
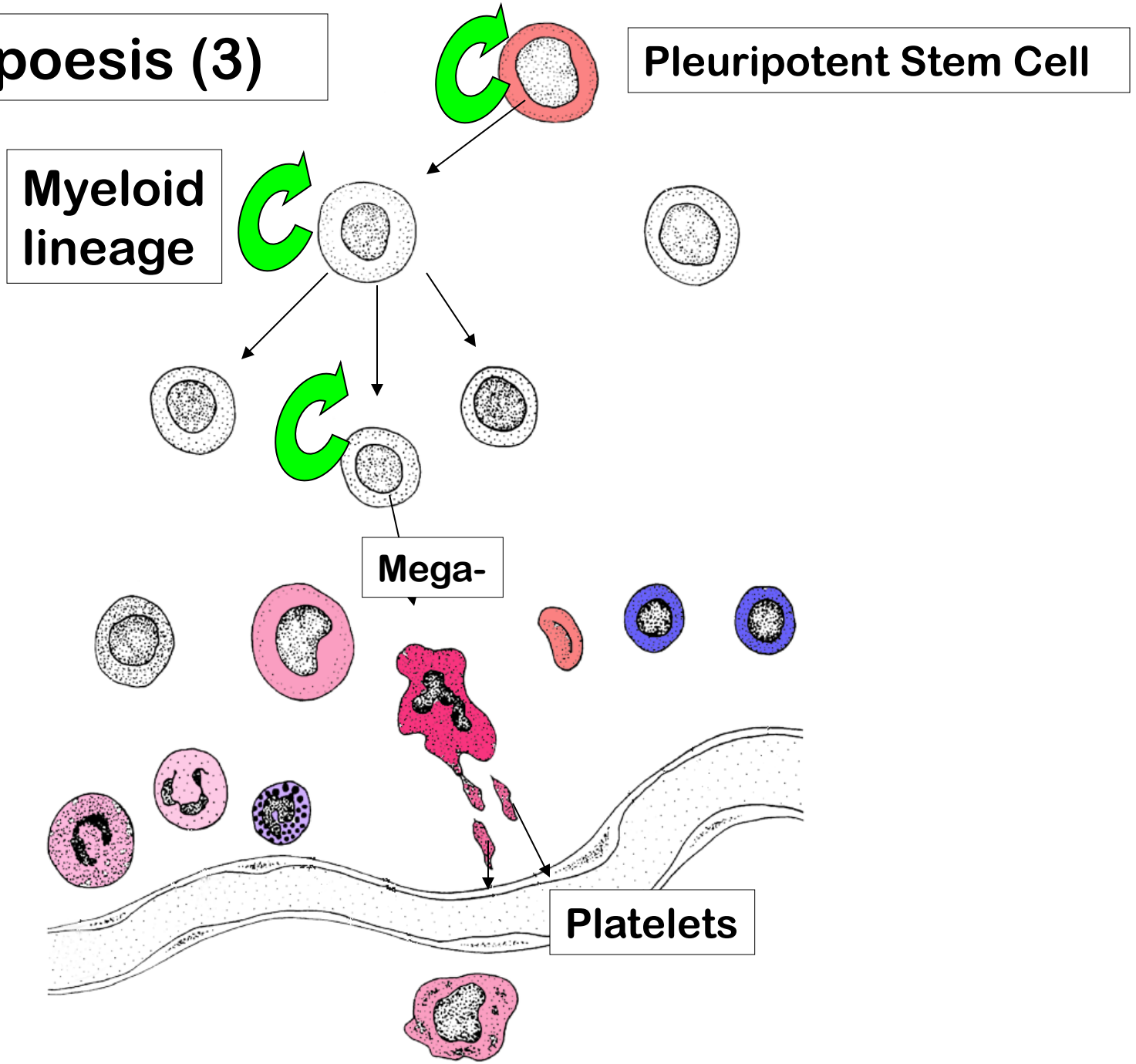
Dendritic cells



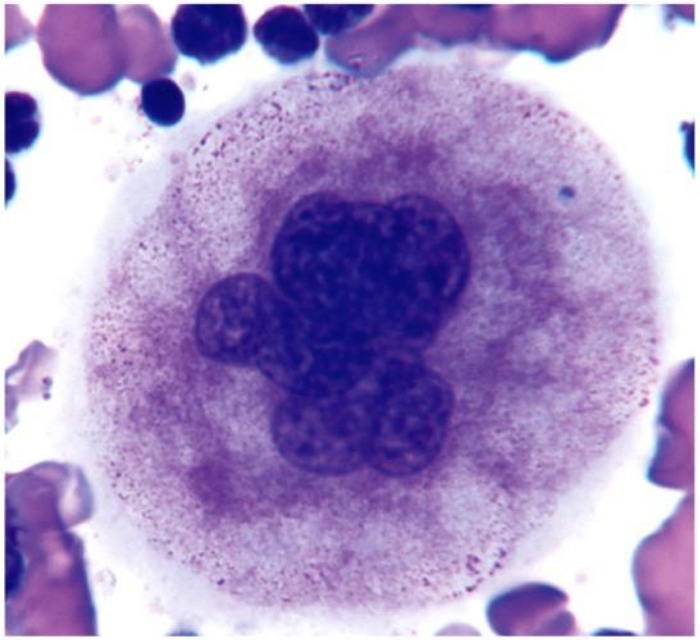


Source: National Cancer Institute (NCI) Sriram Subramaniam

Hematopoesis (3)



Megakaryocyte



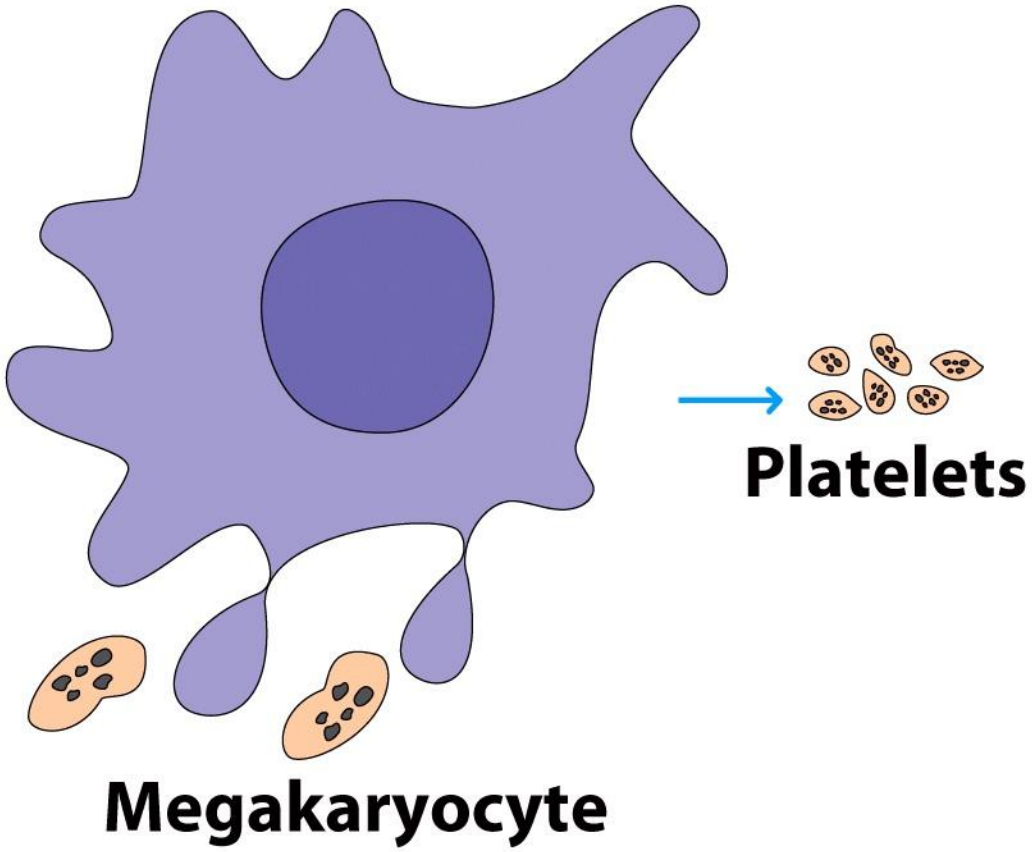


Figure 2-3d
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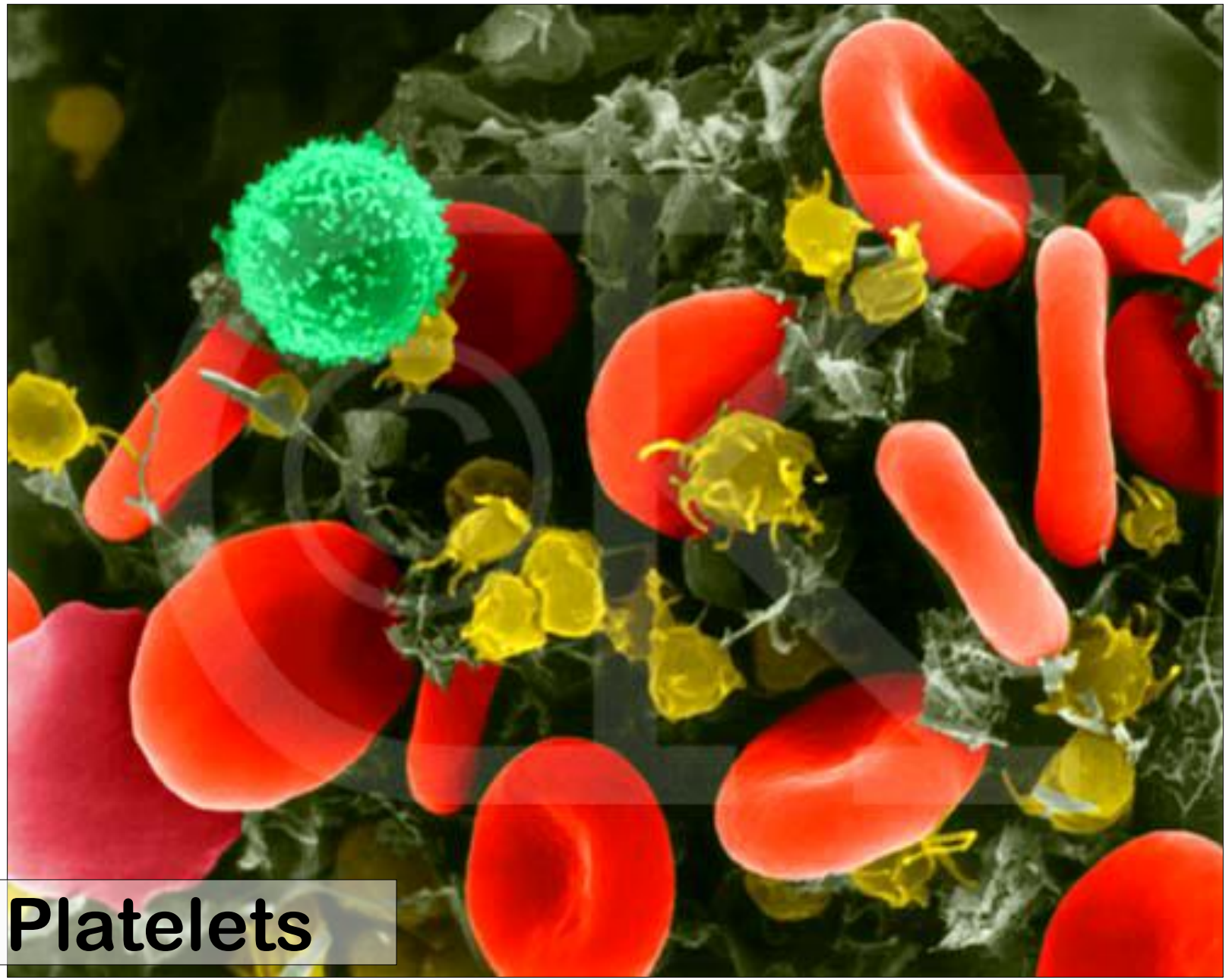
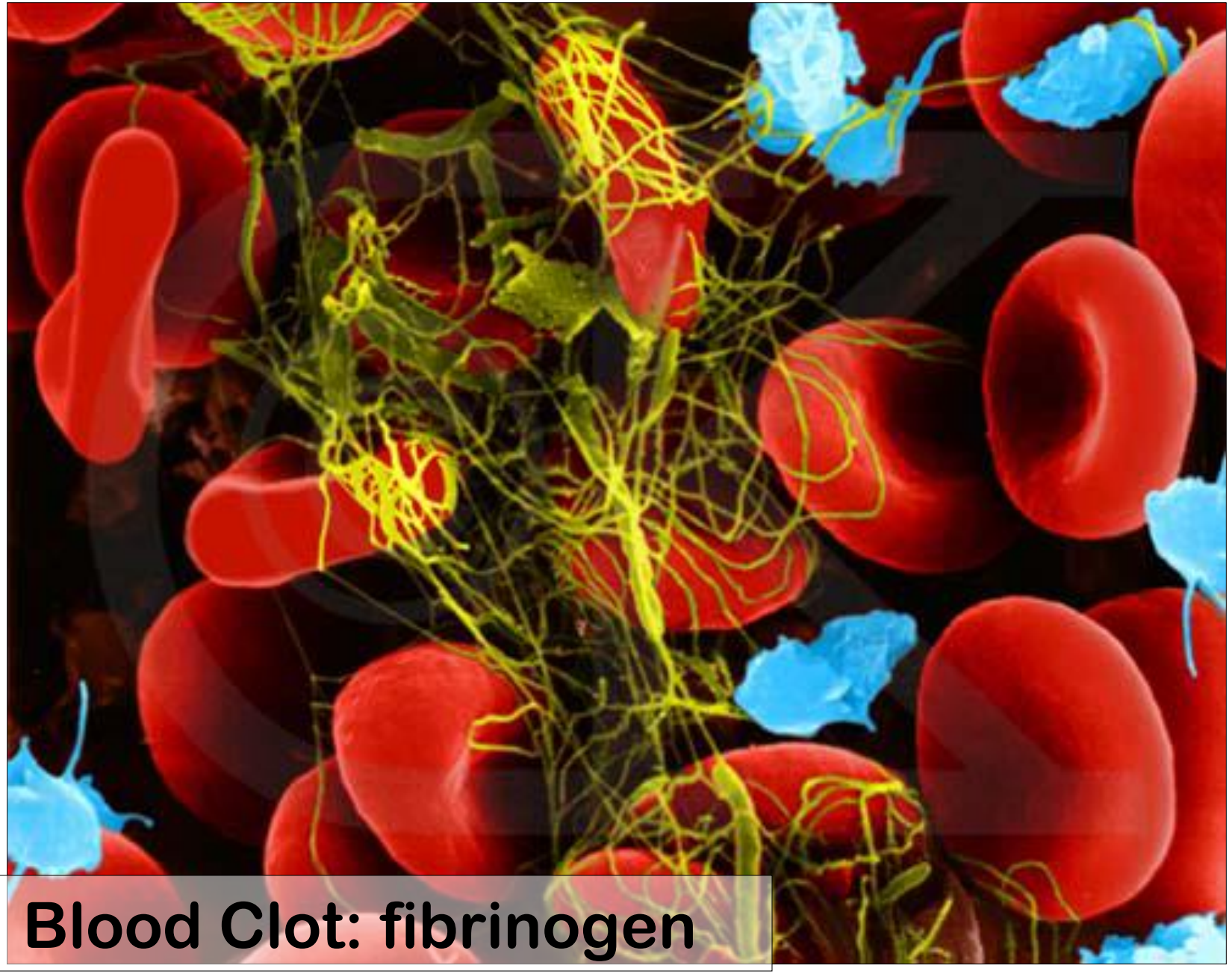
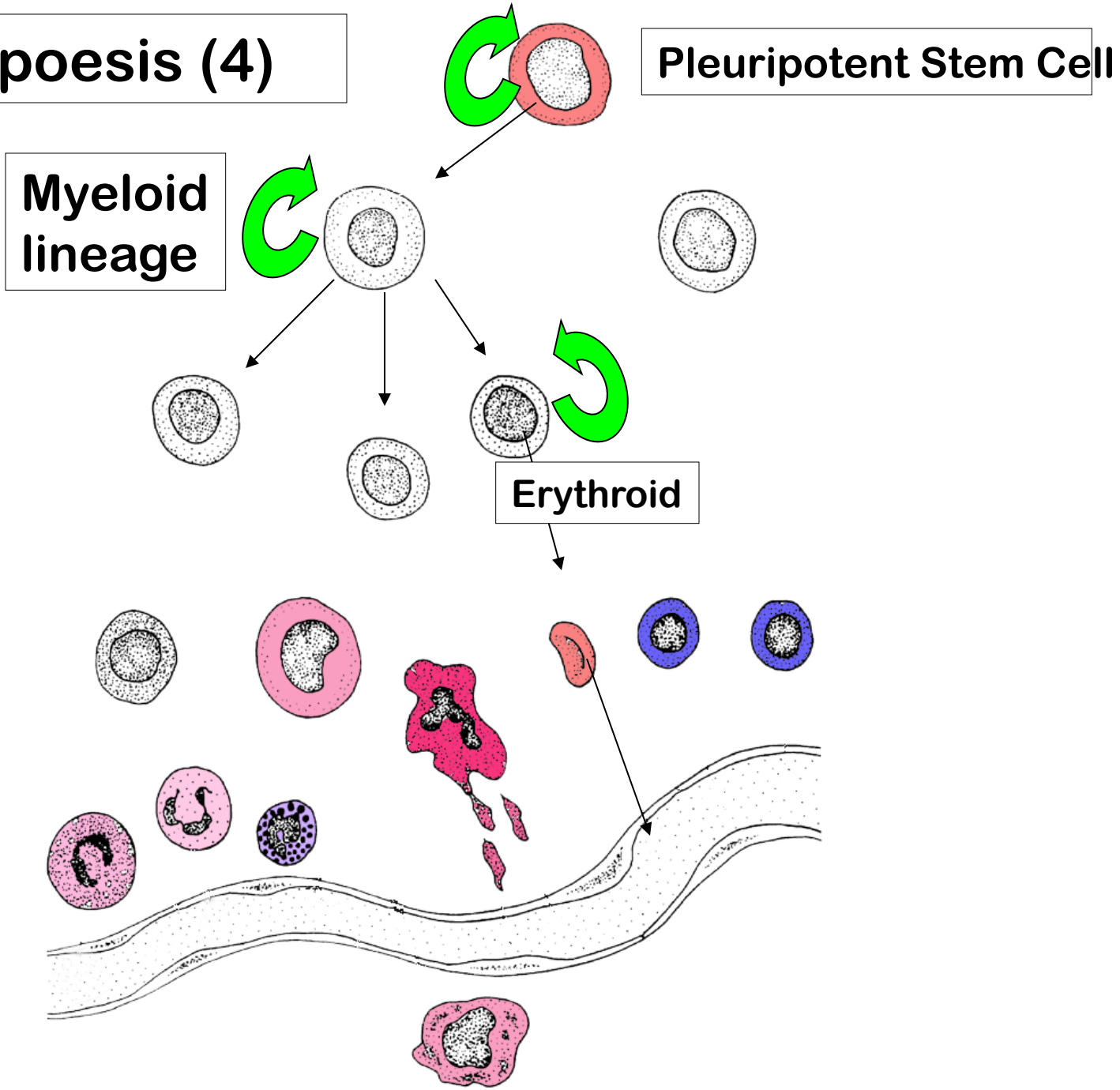

Platelets

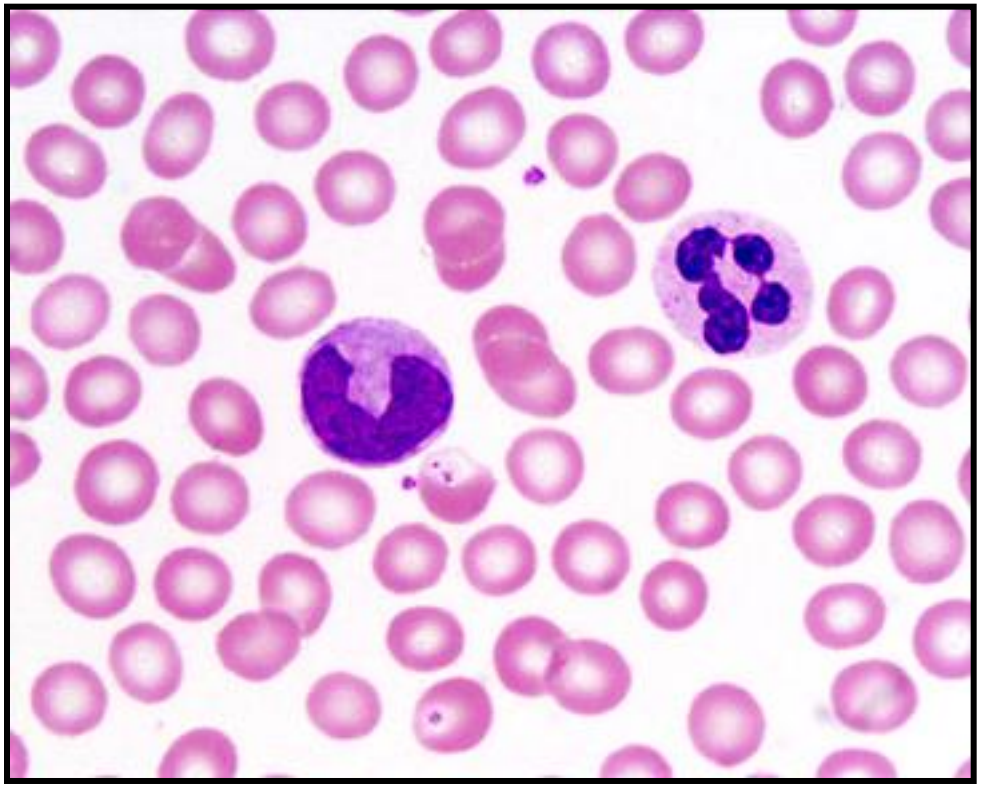


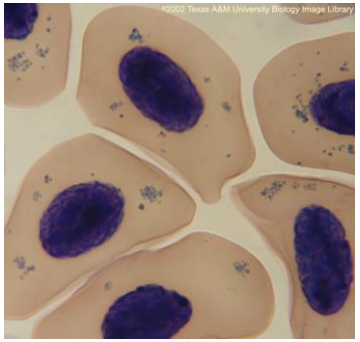
Blood Clot: fibrinogen

Hematopoesis (4)



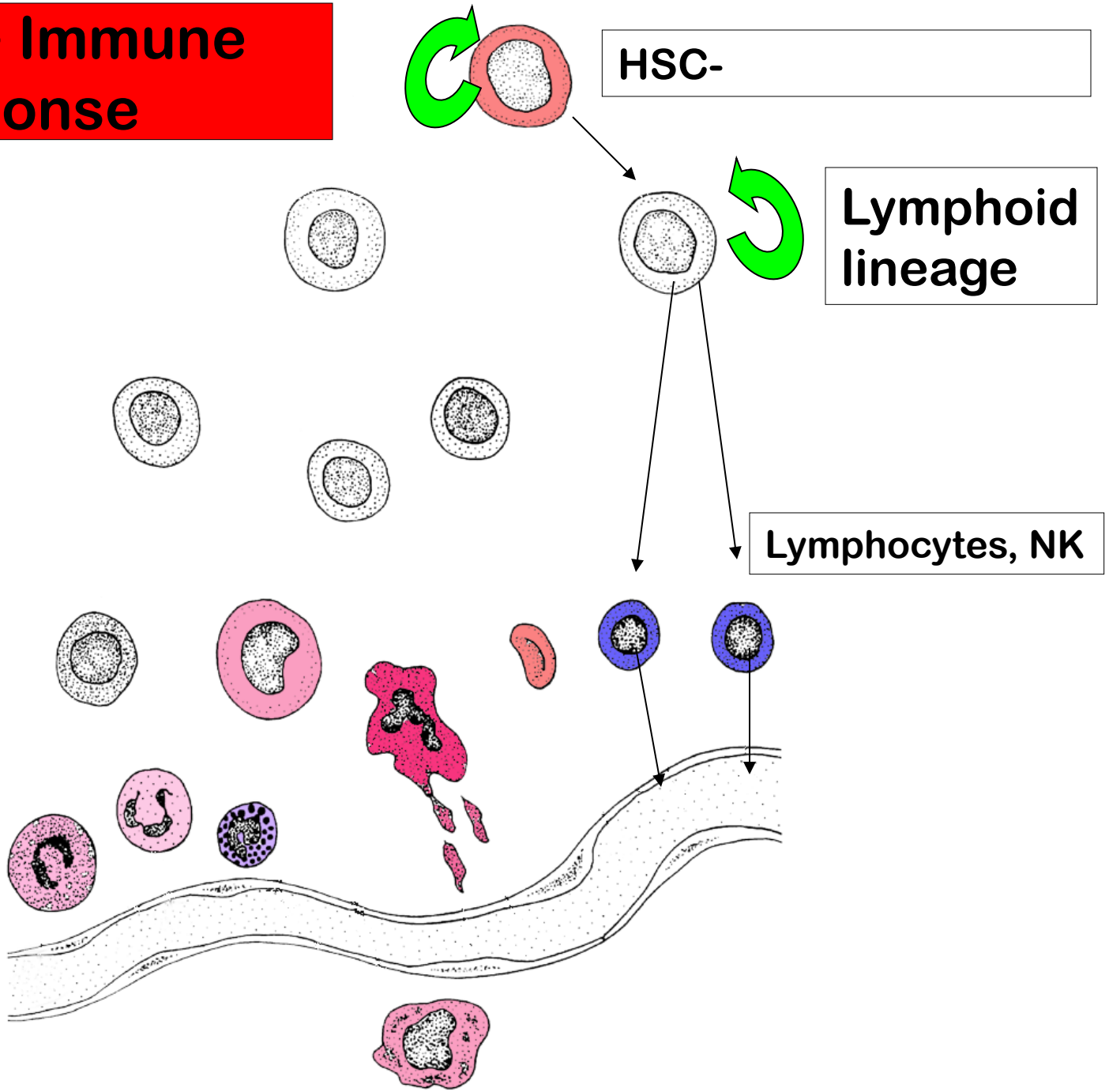
Mature human and mouse RBCs have no nuclei





Salamander RBCs

Adaptive Immune Response

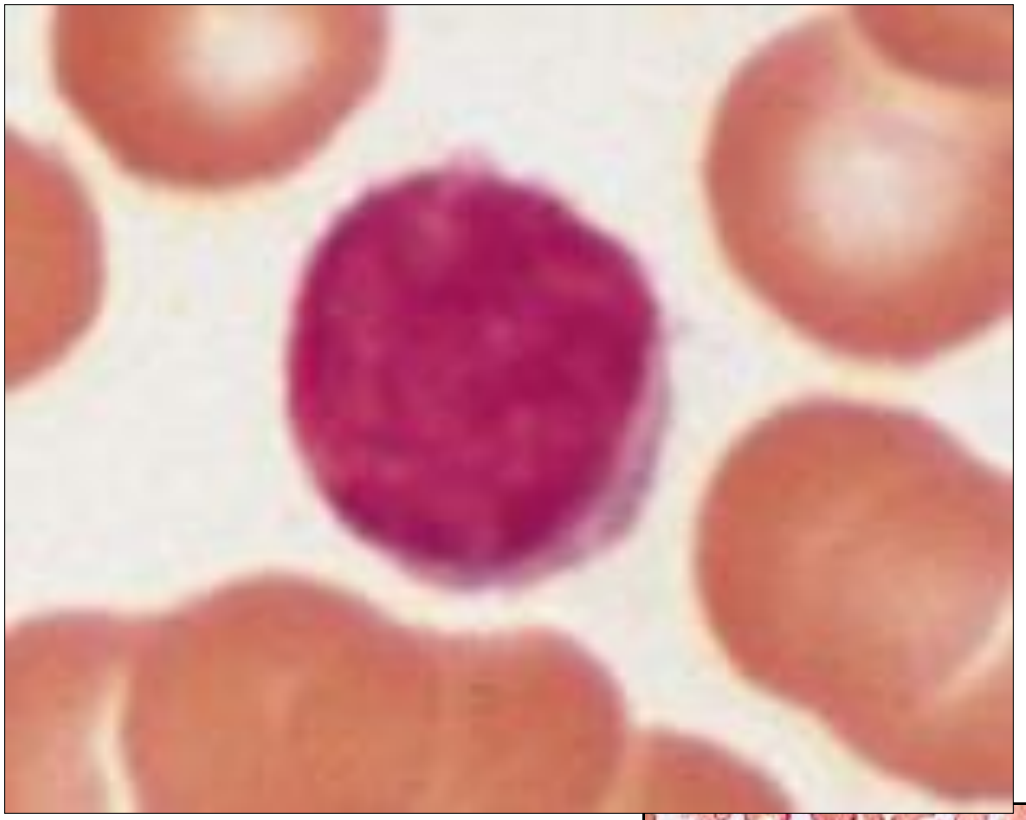


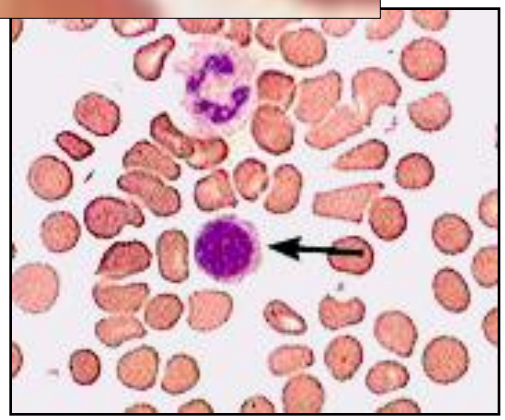
Lymphocytes: 3 types

- 20-40% of WBC
- Cannot be distinguished morphologically
- T-cells
  - helper CD4+ recognize Ag in context of MHCII
  - cytotoxic CD8+ recognize Ab in MHCI
- B-cells
  - become antibody producing plasma cells
- NK cells
  - part of the innate immune response

T and B Lymphocytes

- Large nucleus with dense heterochromatin
- Thin rim of cytoplasm
- Recognizes specific antigenic determinants
- Therefore are responsible for specificity and memory of the adaptive immune response





Examples of lymphocytes:

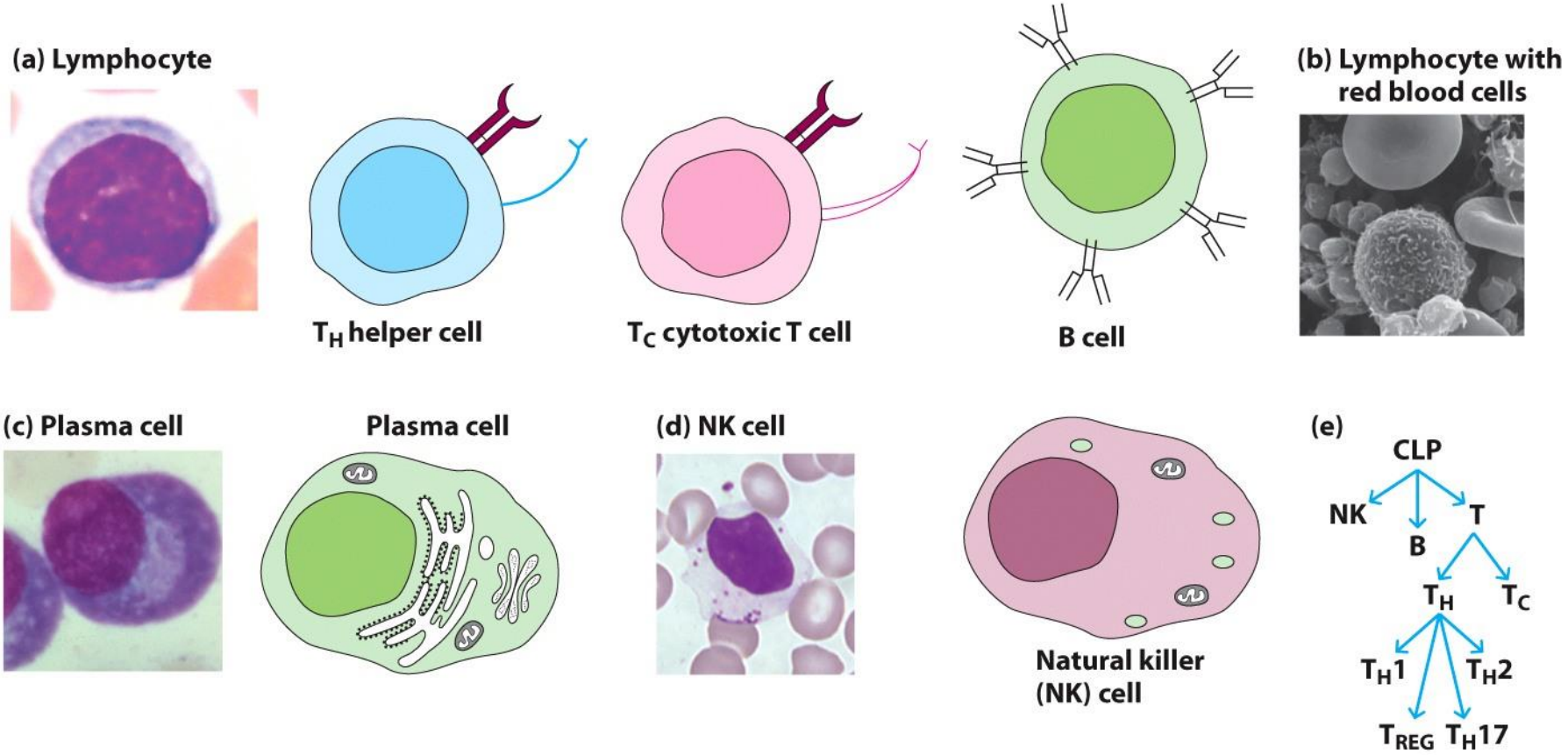


Figure 2-4
Kuby Immunology, Seventh Edition

TABLE 2-5 Common CD markers used to distinguish functional lymphocyte subpopulations

CD designation*	Function	B cell	T cell		NK cell
			T_H	T_C	
CD2	Adhesion molecule; signal transduction	−	+	+	+
CD3	Signal transduction element of T-cell receptor	−	+	+	−
CD4	Adhesion molecule that binds to class II MHC molecules; signal transduction	−	+ (usually)	− (usually)	−
CD5	Unknown (subset)	−	−	+	+
CD8	Adhesion molecule that binds to class I MHC molecules; signal transduction	−	− (usually)	+ (usually)	+ (variable)
CD16 (FcγRIII)	Low-affinity receptor for Fc region of IgG	−	−	−	+
CD21 (CR2)	Receptor for complement (C3d) and Epstein-Barr virus	+	−	−	−
CD28	Receptor for costimulatory B7 molecule on antigen-presenting cells	−	+	+	−
CD32 (FcγRII)	Receptor for Fc region of IgG	+	−	−	−
CD35 (CR1)	Receptor for complement (C3b)	+	−	−	−
CD40	Signal transduction	+	−	−	−
CD45	Signal transduction	+	+	+	+
CD56	Adhesion molecule	−	−	−	+

*Synonyms are shown in parentheses.

Table 2-5
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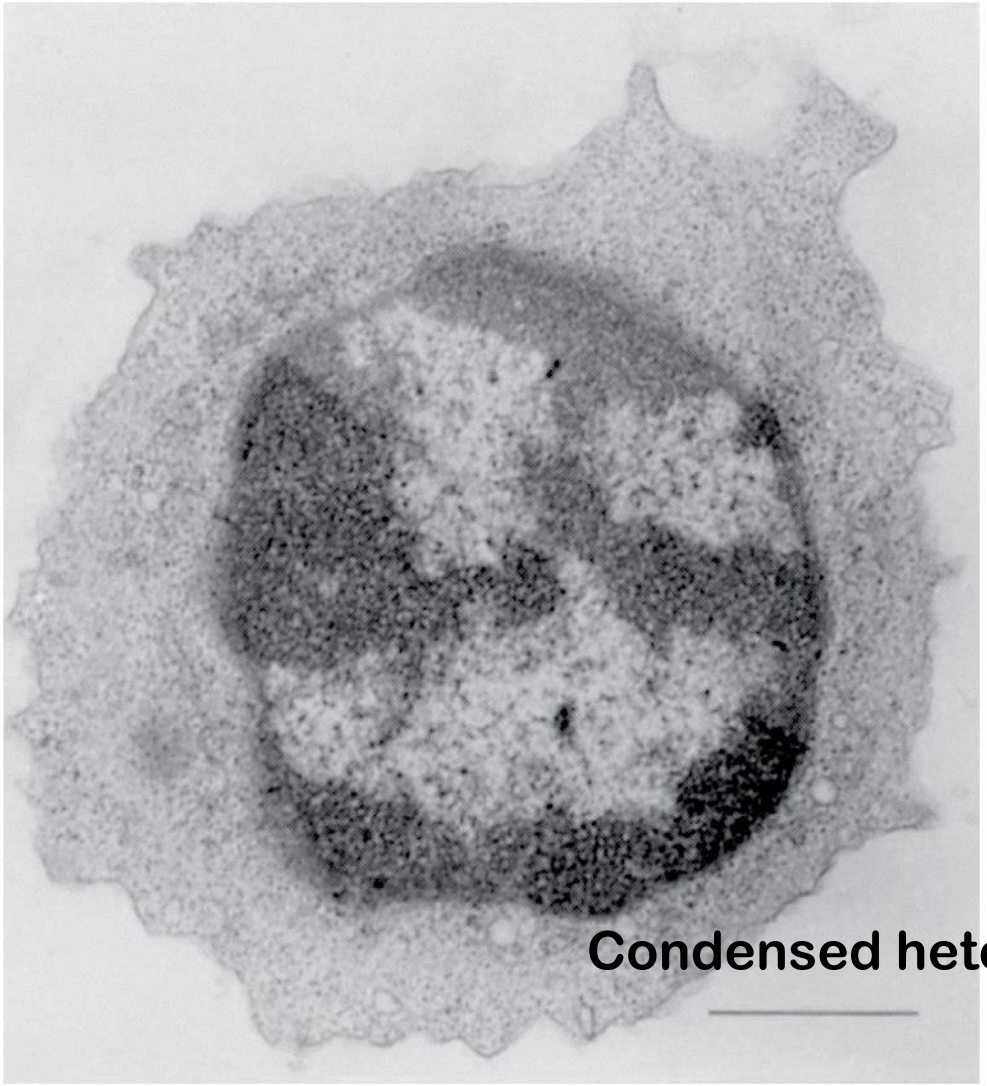

Condensed heterochromatin= resting

Small lymphocyte (T or B)
6 μm diameter

Figure 2-6b part 1
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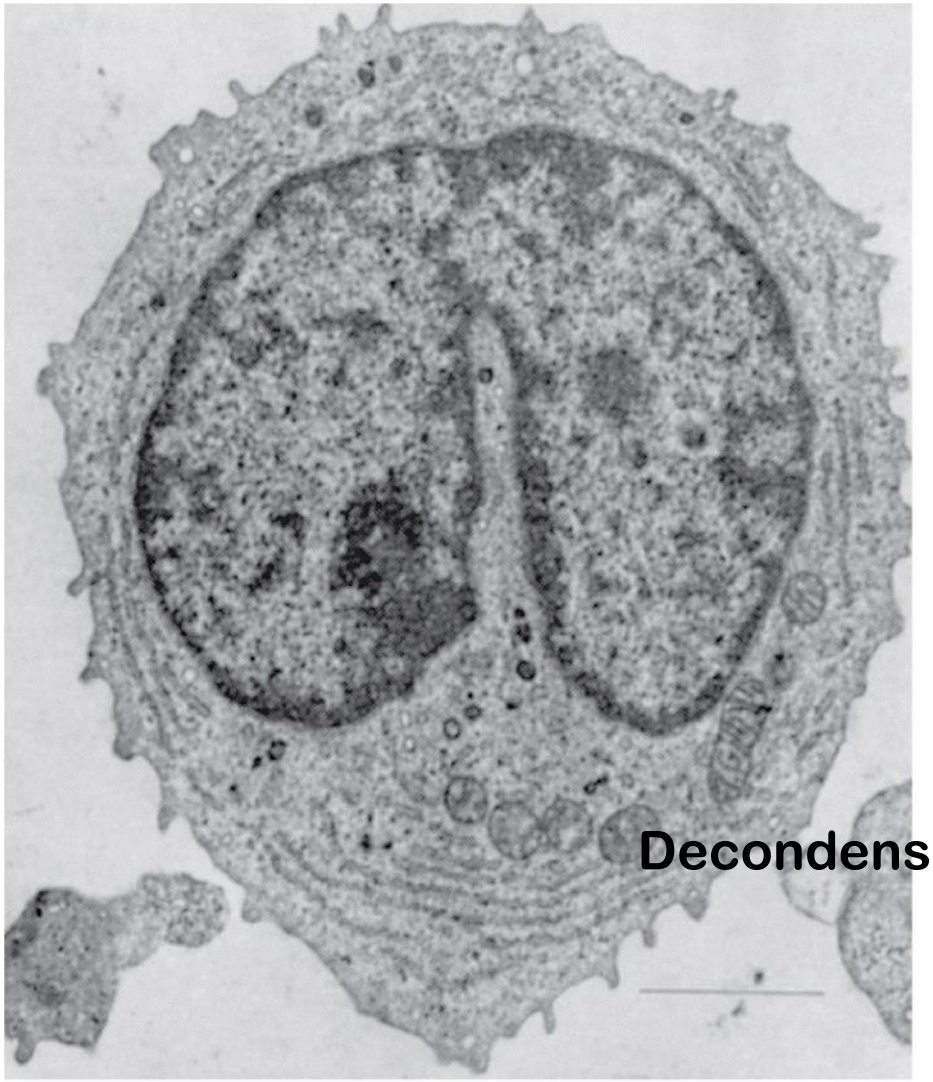

Decondensed chromatin= active

Blast cell (T or B)
15 μm diameter

Figure 2-6b part 2
Kuby IMMUNOLOGY, Sixth Edition

Usually lives 1-2 weeks
Secretes 100's- 1000 Ab molecules/sec

Plasma cell (B)
15 μm diameter

Figure 2-6b part 3
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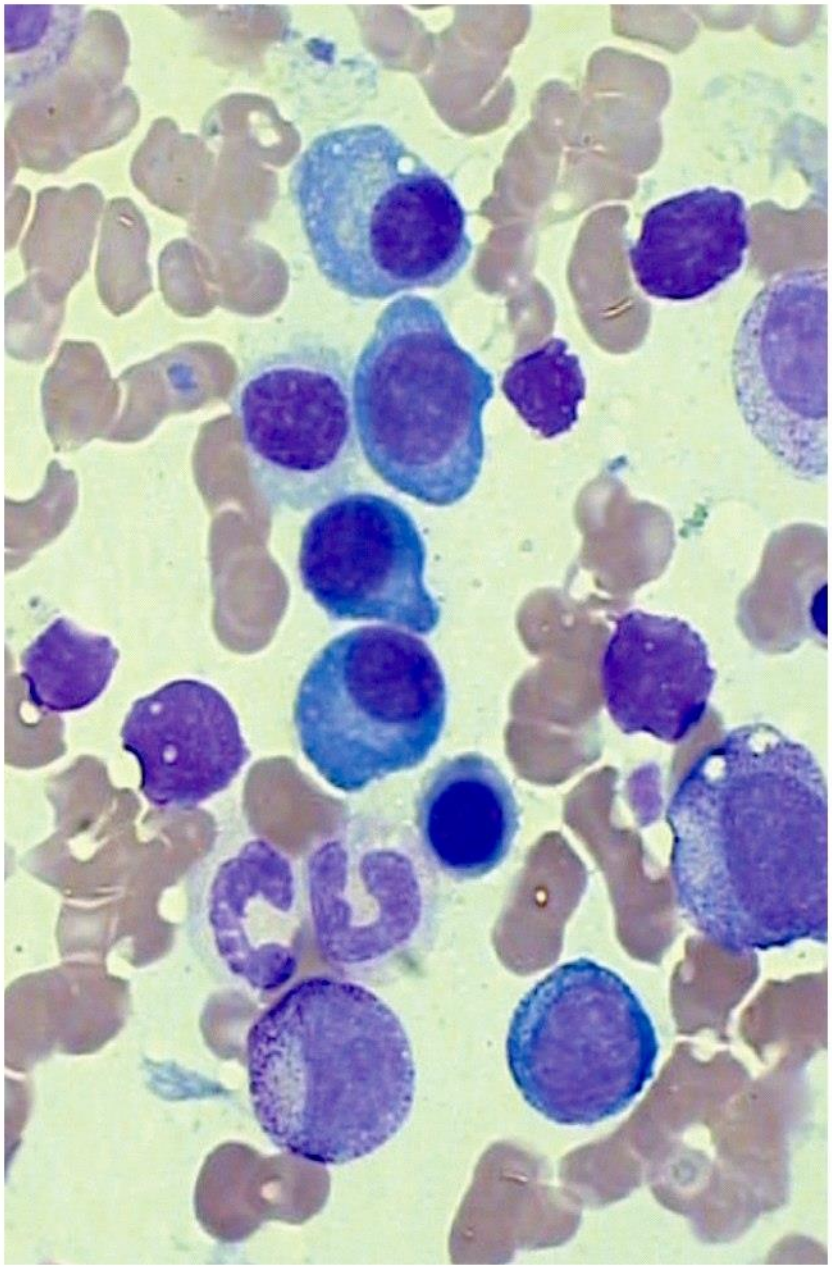


Plasma cell
Perinuclear golgi and abundant layers of endoplasmic reticulum

Figure 2.8e *The Biology of Cancer* (© Garland Science 2007)

Mononucleosis

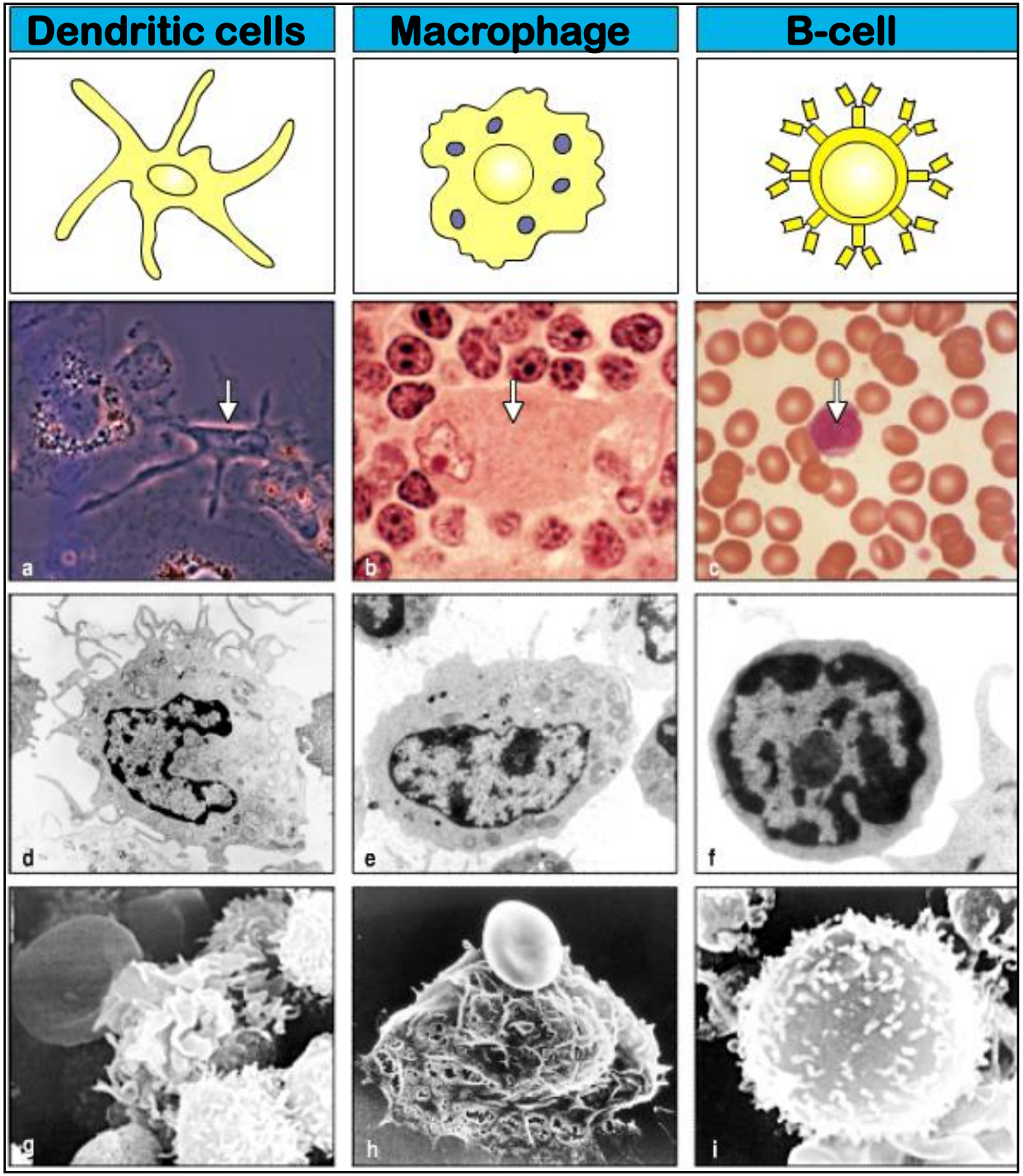
- Caused by Epstein-Barr virus
  - DNA herpes-types virus
- Infects 2 cell types
  - First epithelial cells of salivary gland- virus released in saliva
  - Then B lymphocytes via CD21
- Circulating B cells spread virus
  - to “reticuloendothelial system (liver, spleen, lymph nodes)
- Symptoms
  - Adenopathy, hepatosplenomegaly, fever, pharyngitis
  - Characteristic peripheral blood smear showing reactive lymphocytes

Antigen Presenting Cells

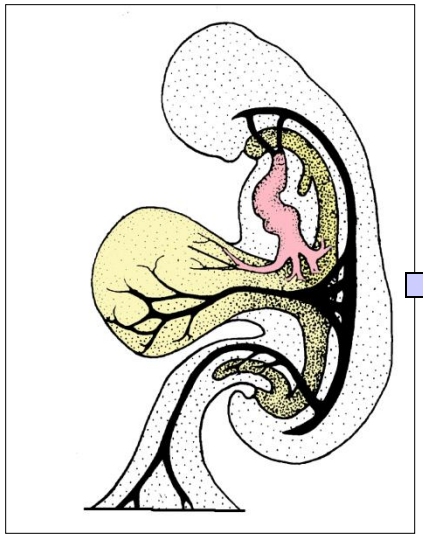
3 kinds of cells present Ag to T-cells

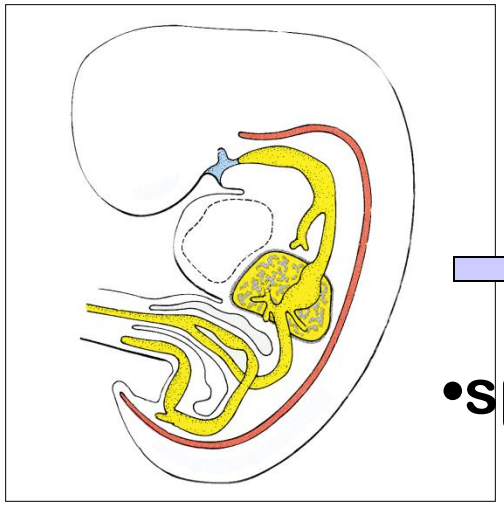
Dendritic cells: Several types

Capture, process, present Ag

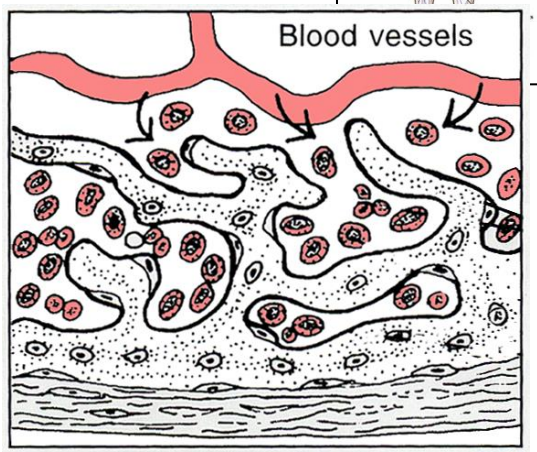


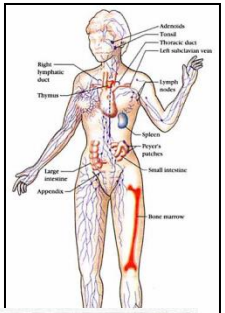
Organs of Hematopoesis…





•spleen





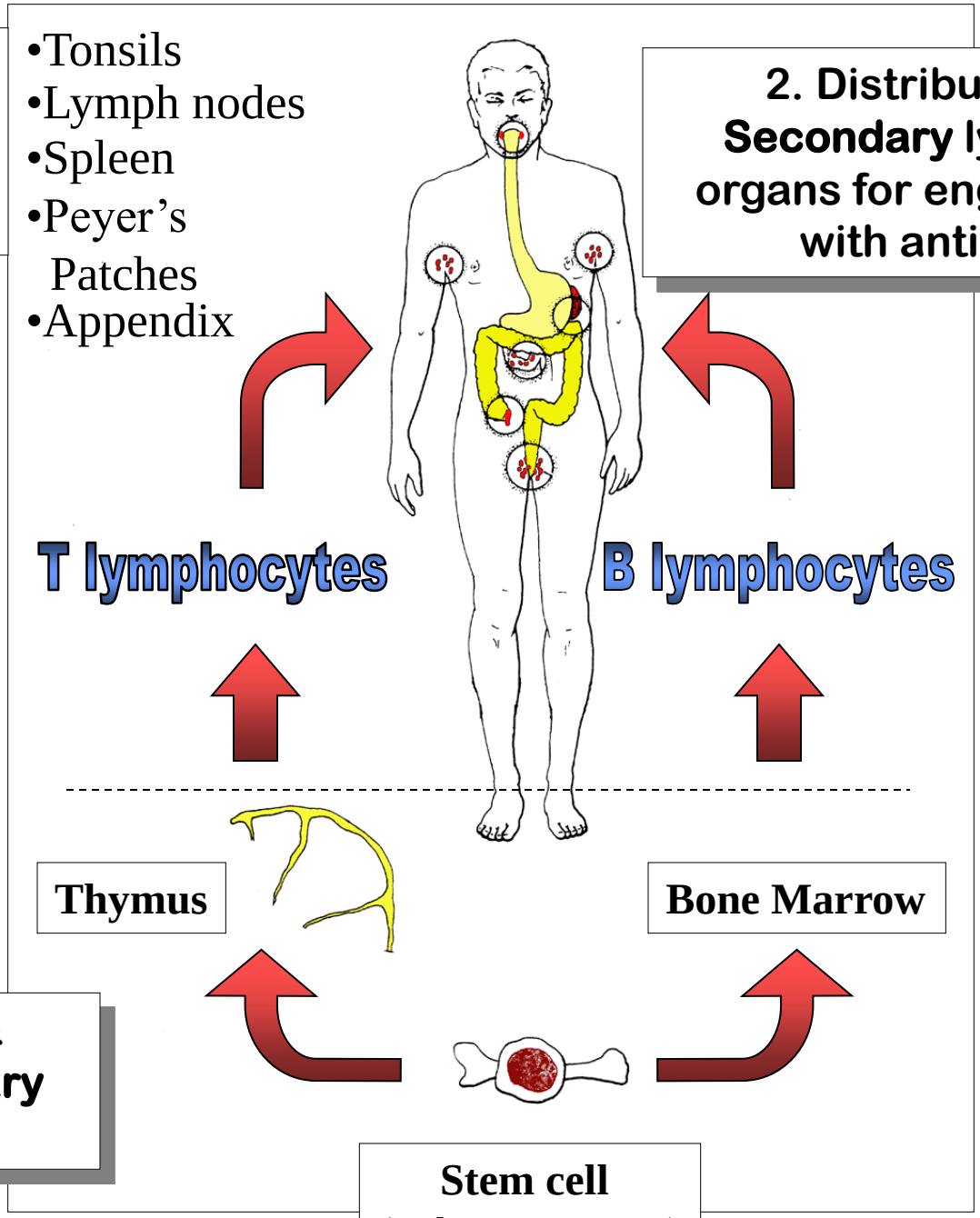
Yolk Sac
- 3 weeks
- Blood islands
- Erythro-myeloid stem cells
- RBC's are large and nucleated=*primitive*
- *Cannot form lymphoid progeny*

Fetal Liver
- 5-6 weeks
- Seeded from both outside sources
- Max 6 mos then declines to neonatal stage

Bone Marrow
- Source of all stem cells in adult
- B-cell maturation
- T-cells to thymus

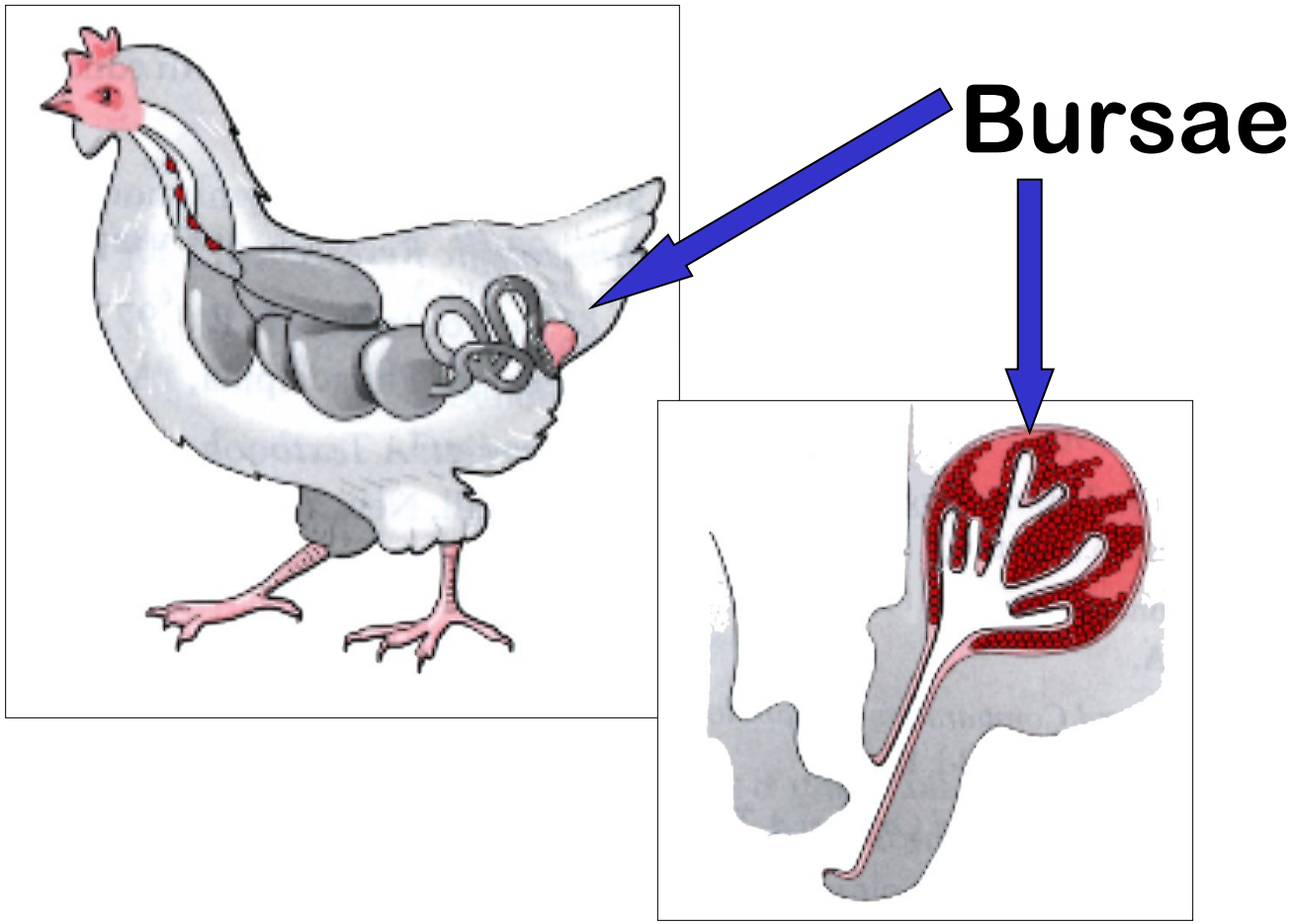
Organs of the Immune System

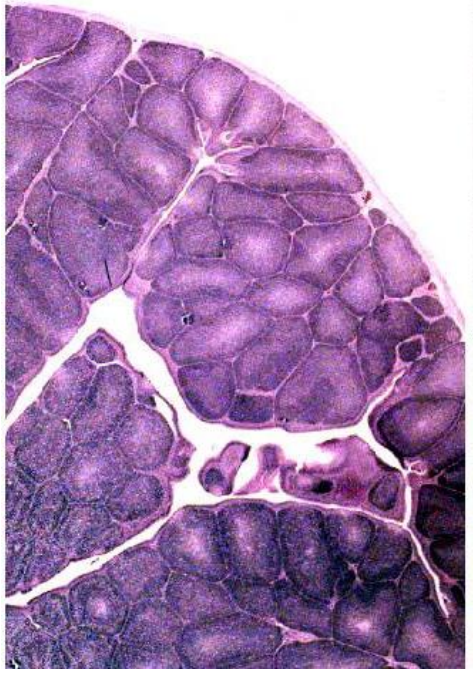
- Tonsils
- Lymph nodes
- Spleen
- Peyer's Patches
- Appendix



In birds, the *Bursae of Fabricius* is the site of B-cell maturation

- Outpocketing of cloaca day 4-5
- Day 11-12, nodules form from lining: cortex and medulla





Maturation of T cells-

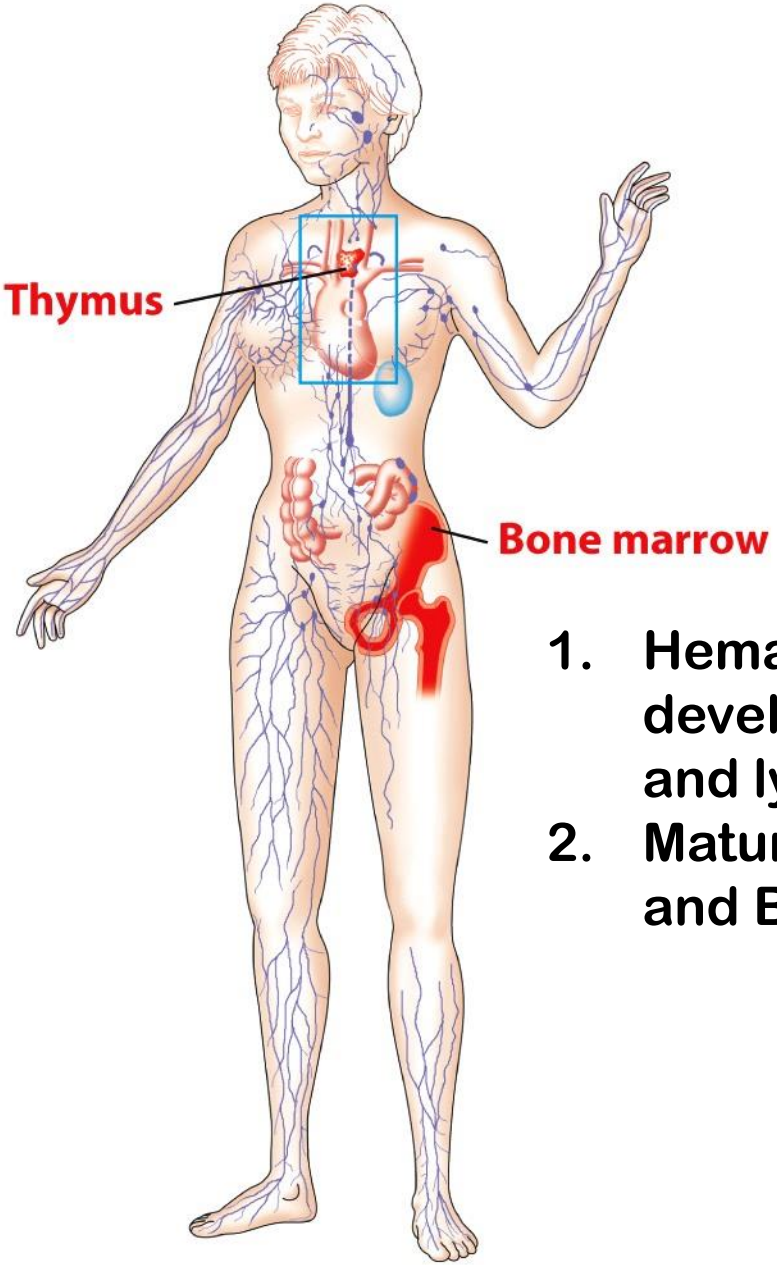


Figure 2-6a
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1. Hematopoesis/ development of myeloid and lymphoid cells
2. Maturation of myeloid and B-cells

The thymus in the adult lies behind the sternum, above the heart

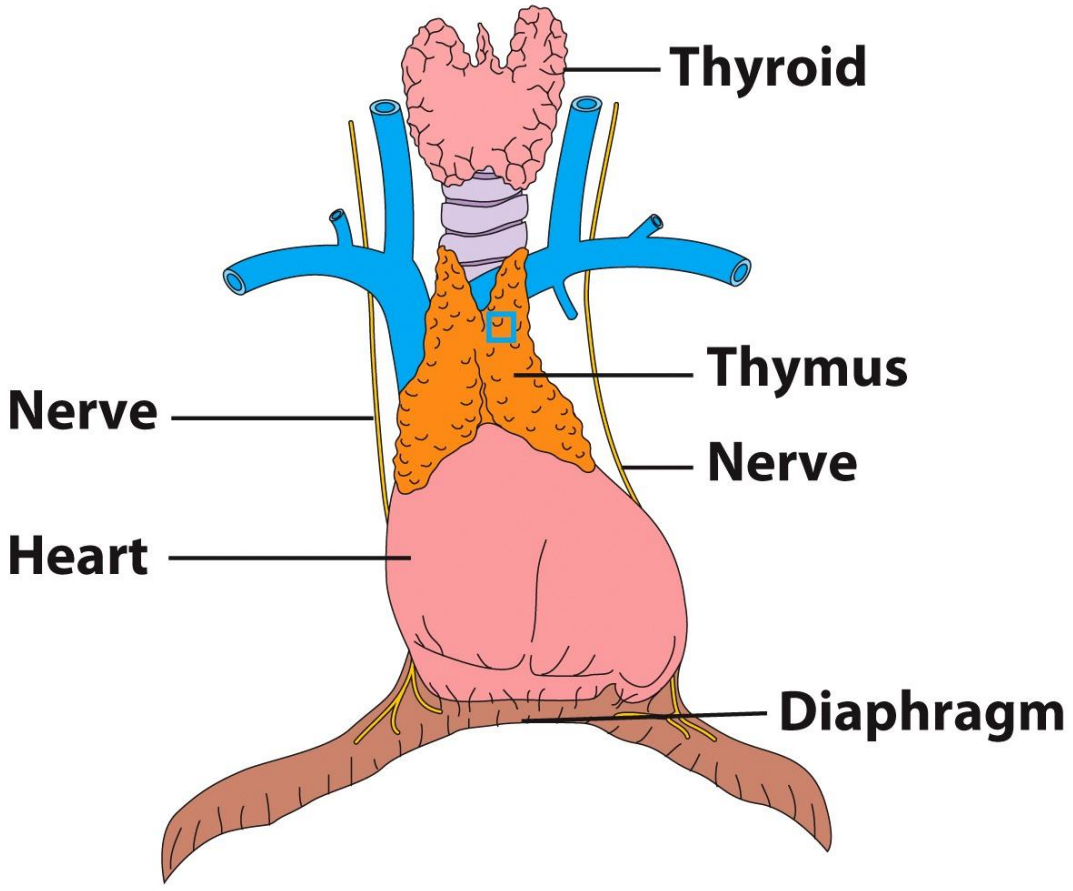

Figure 2-6b
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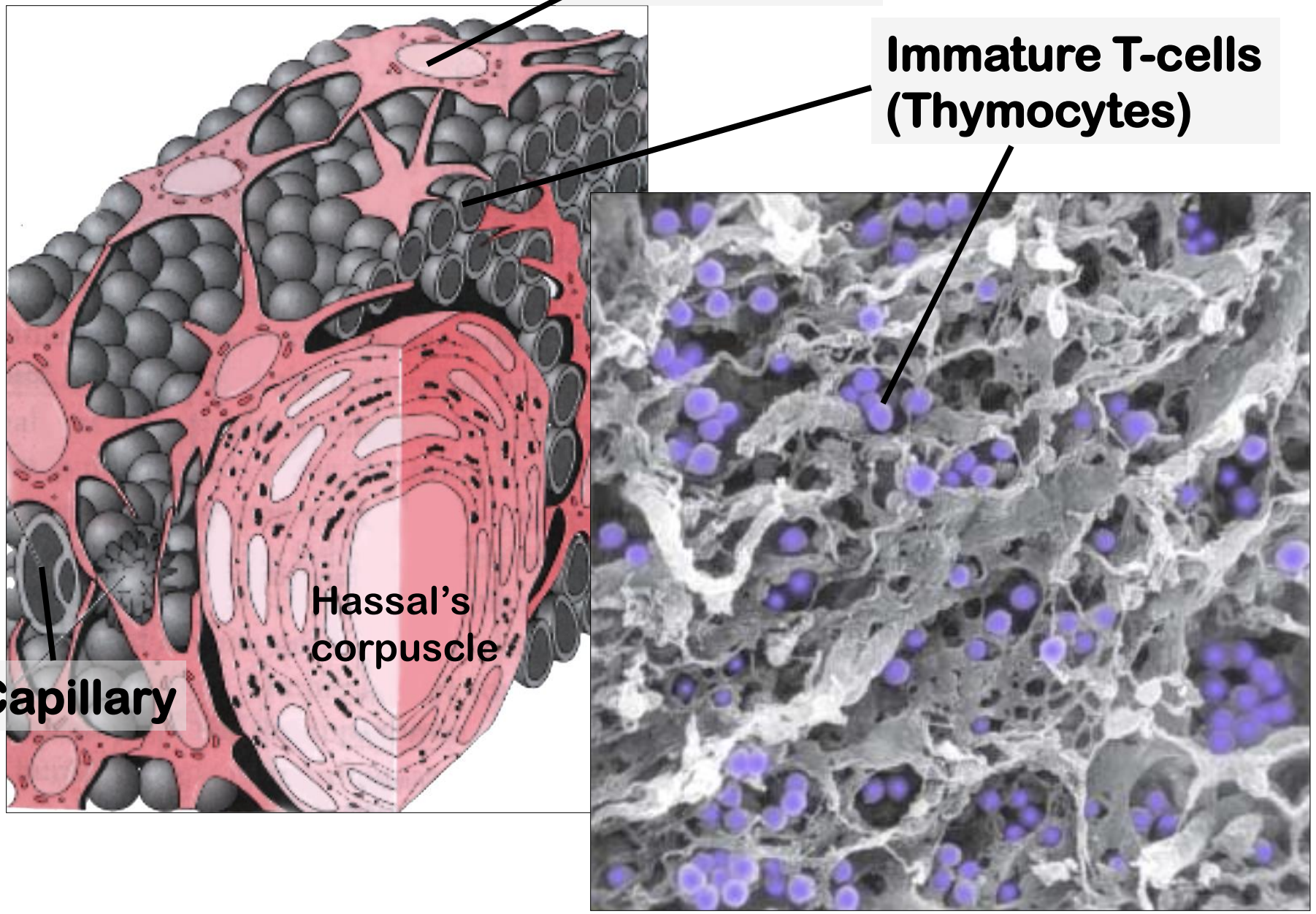
Thymus

- Initially epithelial cells giving rise to thymus are contiguous
- Lymphocytes arriving from yolk sac and liver push the epithelial cells apart, week 10
- Cells remain connected via desmosomes between their processes forming a sponge-like meshwork of epithelial cells= reticular epithelial cells
- Induce lymphocytes to proliferate and distribute into medulla and cortex
- Blood vessels grow in, week 14-15
- Lymphocytes differentiate into T-cells, leave and populate other organs

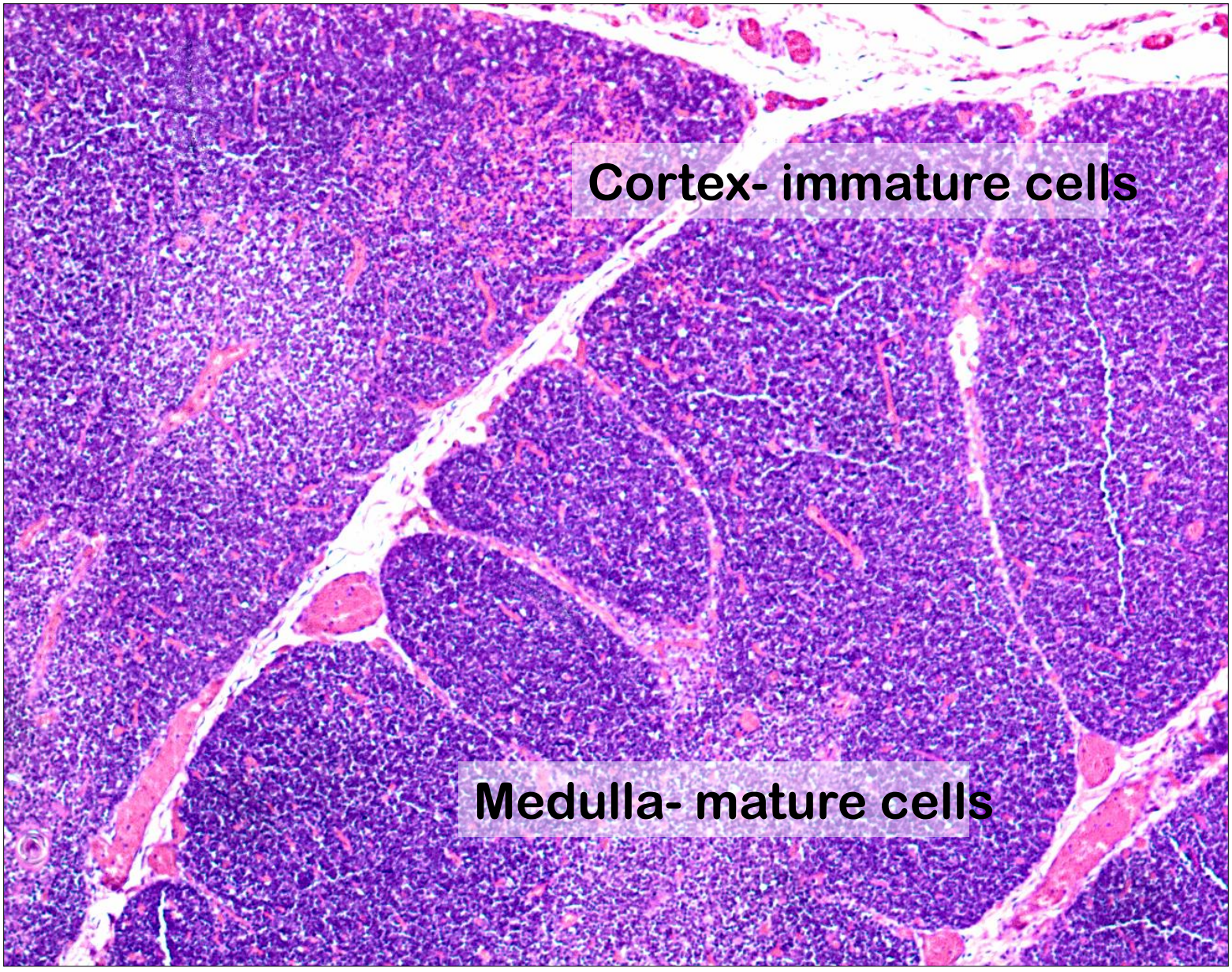
The Thymus is the Site of T-cell Maturation

- Epithelial cells (thymic stroma)
  - forming a sponge-like meshwork of epithelial cells= reticular epithelial cells
- T-cells- Lymphopoiesis (proliferate and mature)
- mature T-lymphocytes leave via venules in the medulla and travel through the blood to populate peripheral organs
- If the thymus fails to form, and T-cells do not develop

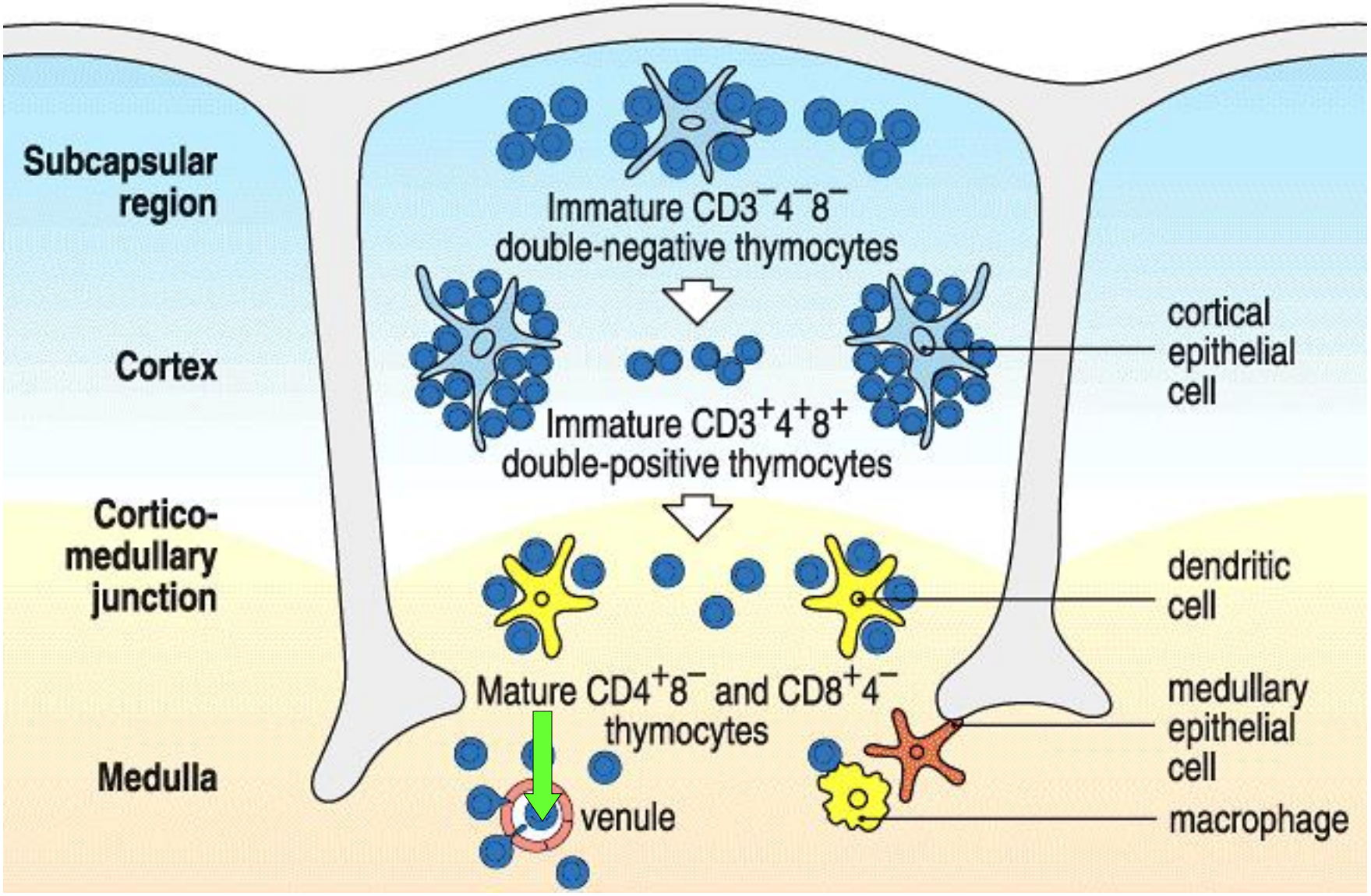
Thymus


Epithelial cell
Immature T-cells
(Thymocytes)
Hassal's
corpuscle
Capillary

Fetal Thymus: **Lobes**



The cortex contains immature thymocytes which move into the medulla as they mature.



Adult thymus

- Rate of T-cell production peaks prior to puberty
- Greatly reduced but continuous through adulthood
- Thymus undergoes Involution
  - Fatty infiltration
  - Lymphocyte depletion

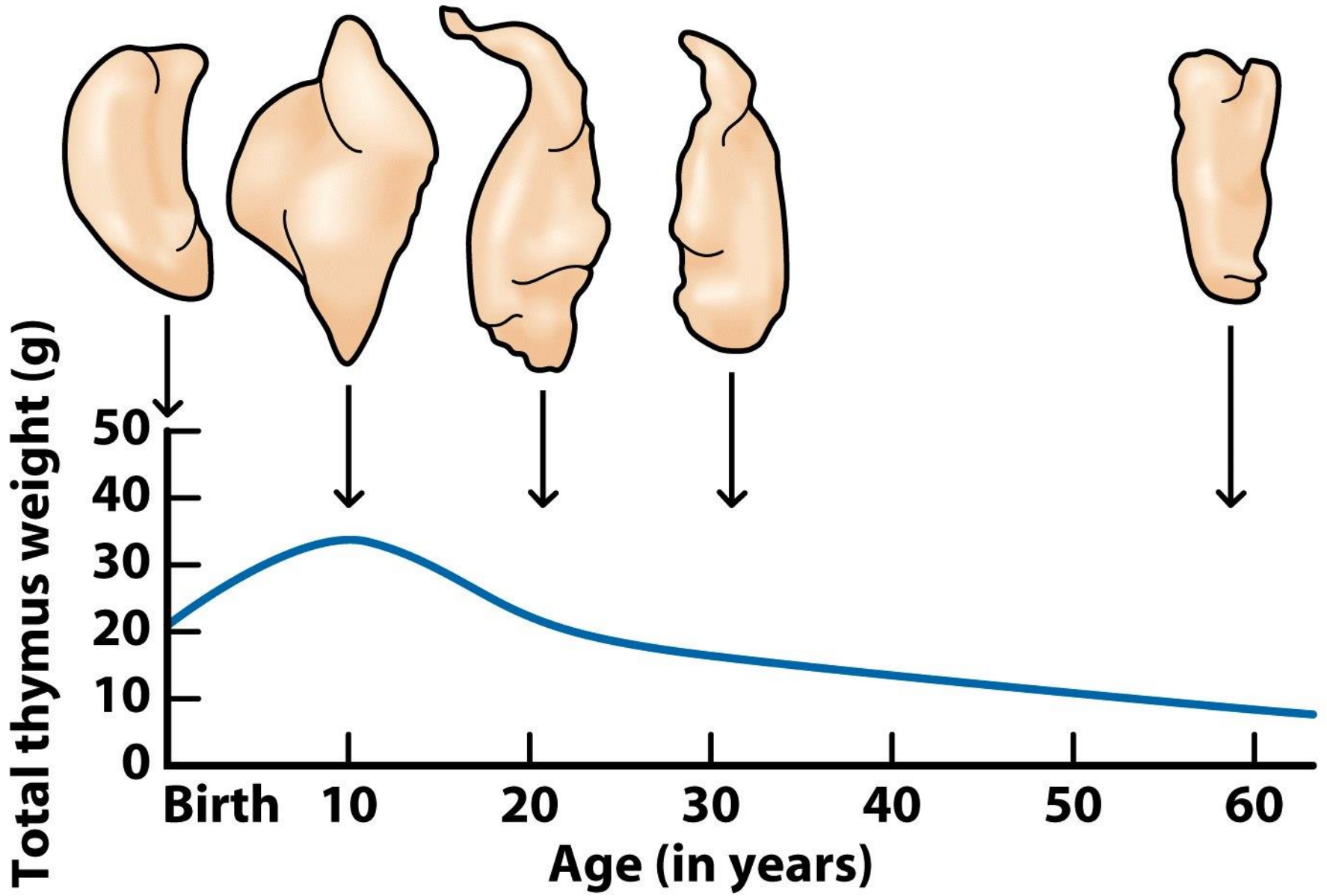


Figure 2-13
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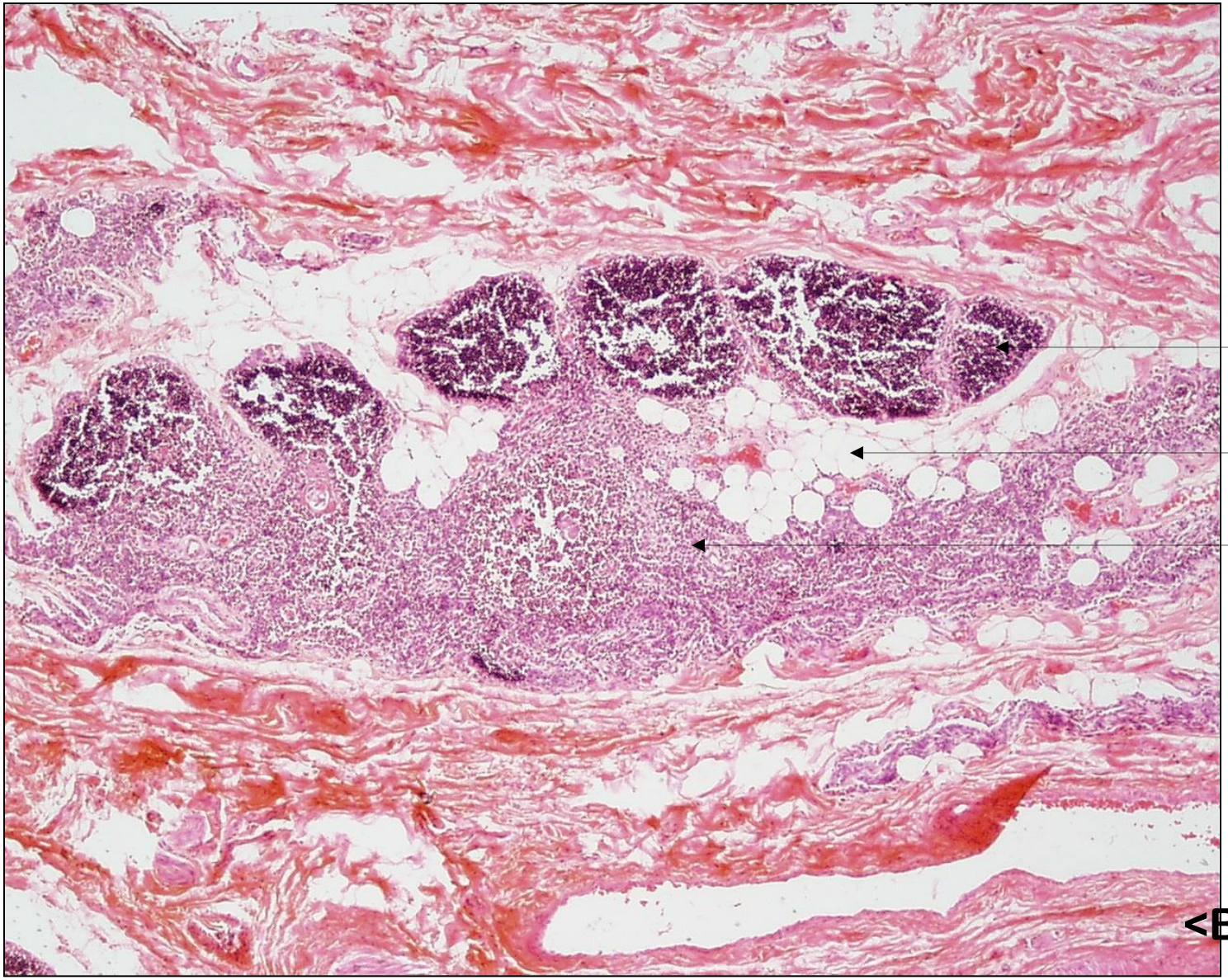
Adult thymus undergoing involution



<Blue Histol>

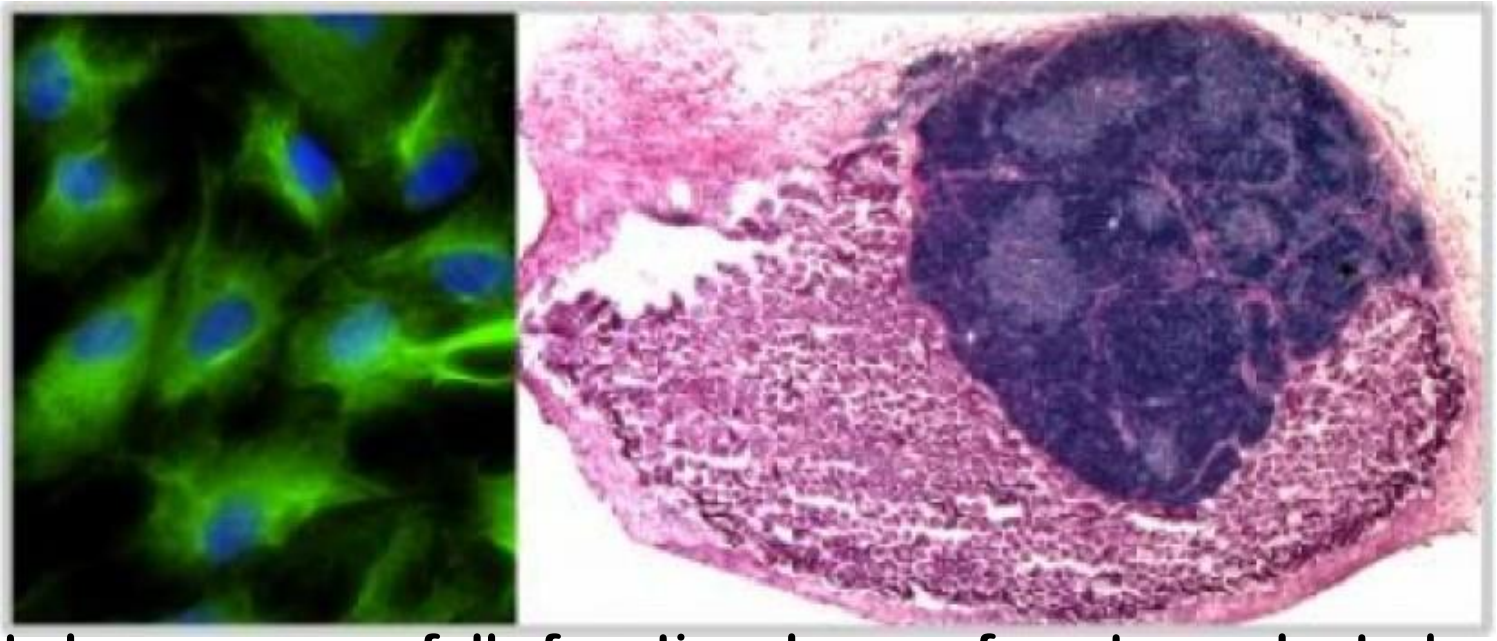
Nude mice

- Lack T-lymphocytes
- Recessive nude gene, chromosome 11
- Failure of thymic anlage to form
  - no “home” for presumptive T-lymphocytes
- Hairlessness
- SCID mice are also immunodeficient but for a different reason (failure of TCR, BCR gene rearrangements and T&B cells do not mature)

DiGeorge syndrome

- deletion on chromosome 22
- defect of cranial neural crest cell migration into arches
- congenital thymic hypoplasia= *anlage of the thymus does not form*
- variety of other defects involving facial, thyroid, parathyroid and cardiovascular system

"Anlage"- an organ in its earliest stage of development; the foundation for subsequent development, primordium



Scientists have grown a fully functional organ from transplanted laboratory-created cells in a living animal for the first time.

- **They grew a working thymus -- an important organ that supplies the body with immune cells.**
- **Left: thymus epithelial cells were developed from MEF cells by reprogramming.**
- **Right: transplanted to mouse kidney to form an organized and functional mini-thymus in a living animal- sustained T-cell develop**

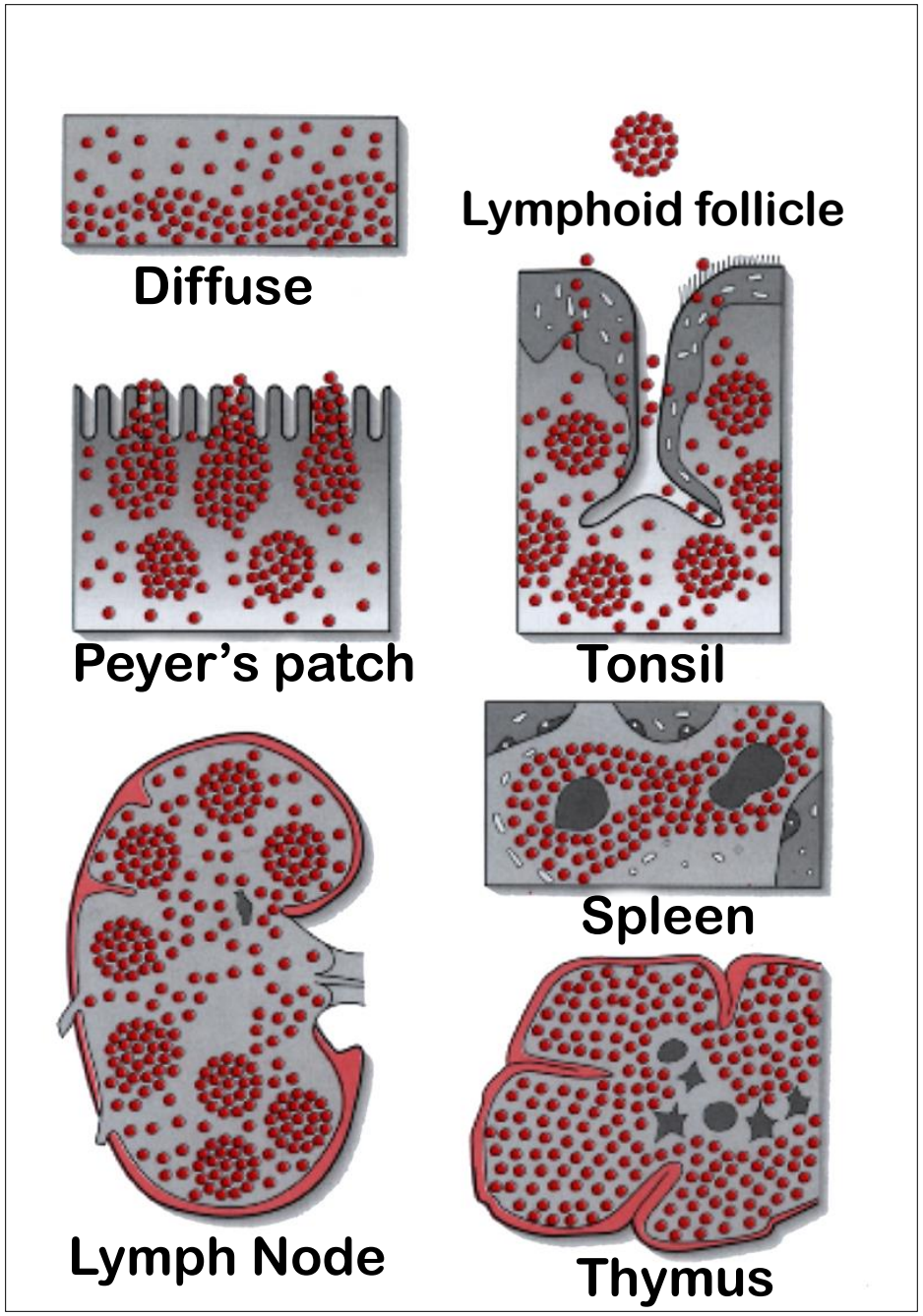
Nicholas Bredenkamp, Svetlana Ulyanchenko, Kathy Emma O'Neill, Nancy Ruth Manley, Harsh Jayesh Vaidya, Catherine Clare Blackburn. **An organized and functional thymus generated from FOXN1-reprogrammed fibroblasts**. *Nature Cell Biology*, 2014; DOI: 10.1038/ncb3023

Secondary lymphoid organs

- Specialized for trapping antigen facilitating presentation to lymphocytes
- Characterized by:
  - Localized areas for T-cells and B-cells
  - Follicles where B cells mature

Schematic diagrams of various types of lymphoid tissue

- Diffuse
- Solitary follicle
- Aggregated follicle
- Lymph Node
- Spleen
- Thymus

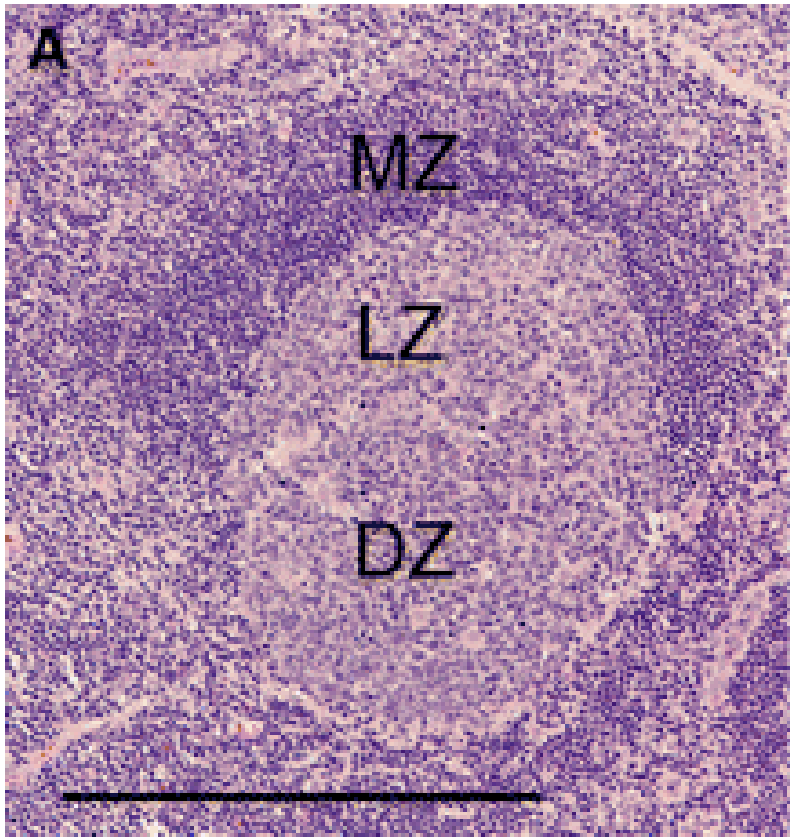


Lymphoid follicle

Germinal Centers

- Are formed when activated B cells enter lymphoid follicles and proliferate
  - Somatic hypermutation
  - Affinity maturation
  - Isotype switching of Ab class
- Selected B cells will mature to plasma cells or become memory cells

Follicle with germinal center



Germinal Center

Mantle Zone: resting cells

Light zone: more mature, smaller centrocytes contact follicular dendritic cells

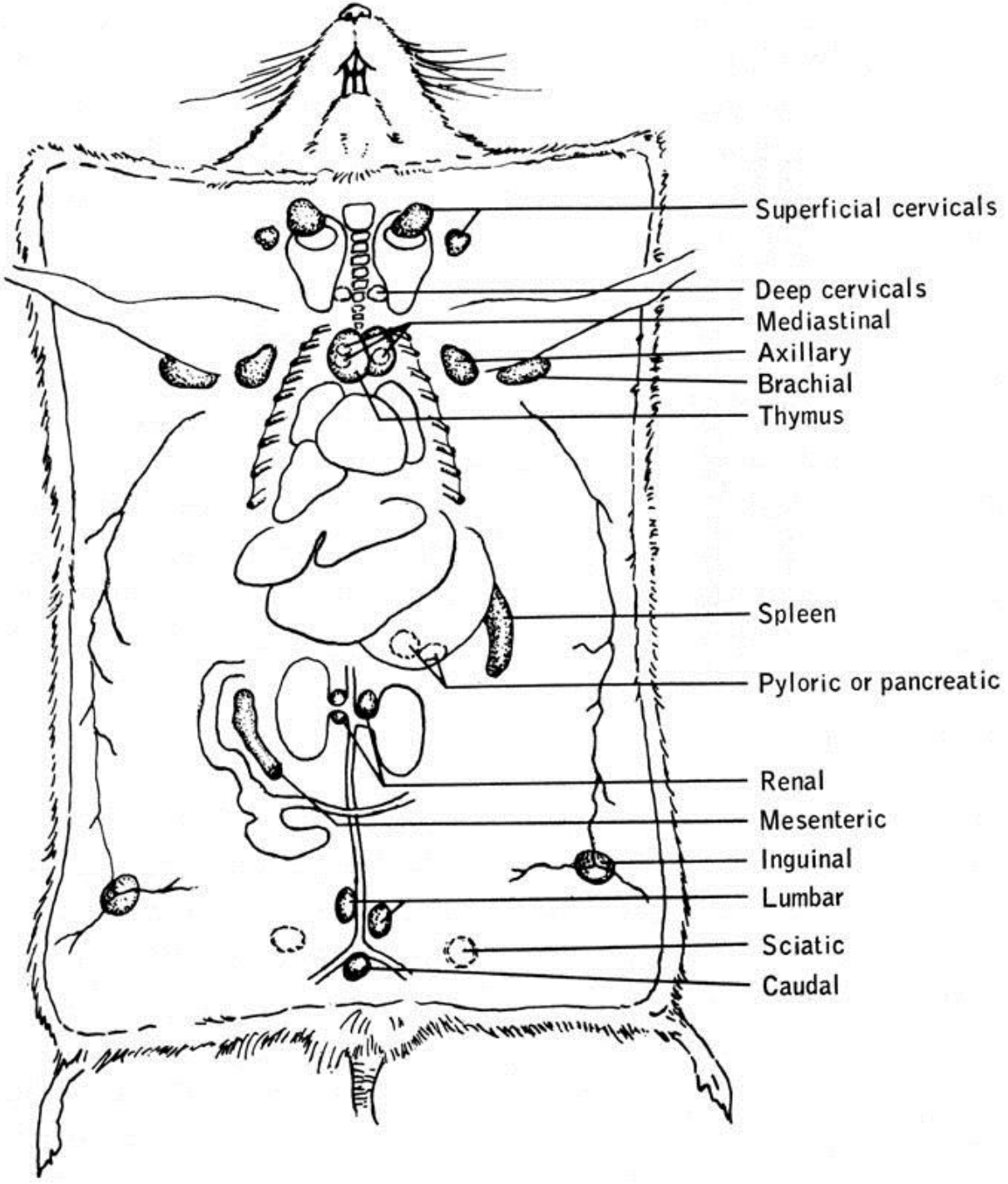
Dark zone: closely packed, rapidly dividing centroblasts

Encapsulated peripheral lymphoid organs

- Lymph nodes-
  - filter Ag from lymph
  - Receive Ags and APCs from local sites
- Spleen-
  - filters Ag from blood
  - Ags from systemic infections

The Lymph Node: filters lymph

- Filters lymph
- Filtering stations interposed in the lymphatic vessels
- Present everywhere, but large and numerous ones are found in certain sites: axillary, groin (inguinal LNs), near the abdominal aorta (coeliac LNs), in the neck (cervical LNs) and in the mesentery (mesenteric LNs)
- Regional nodes: draining particular regions or organs


Superficial cervicals
Deep cervicals
Mediastinal
Axillary
Brachial
Thymus
Spleen
Pyloric or pancreatic
Renal
Mesenteric
Inguinal
Lumbar
Sciatic
Caudal

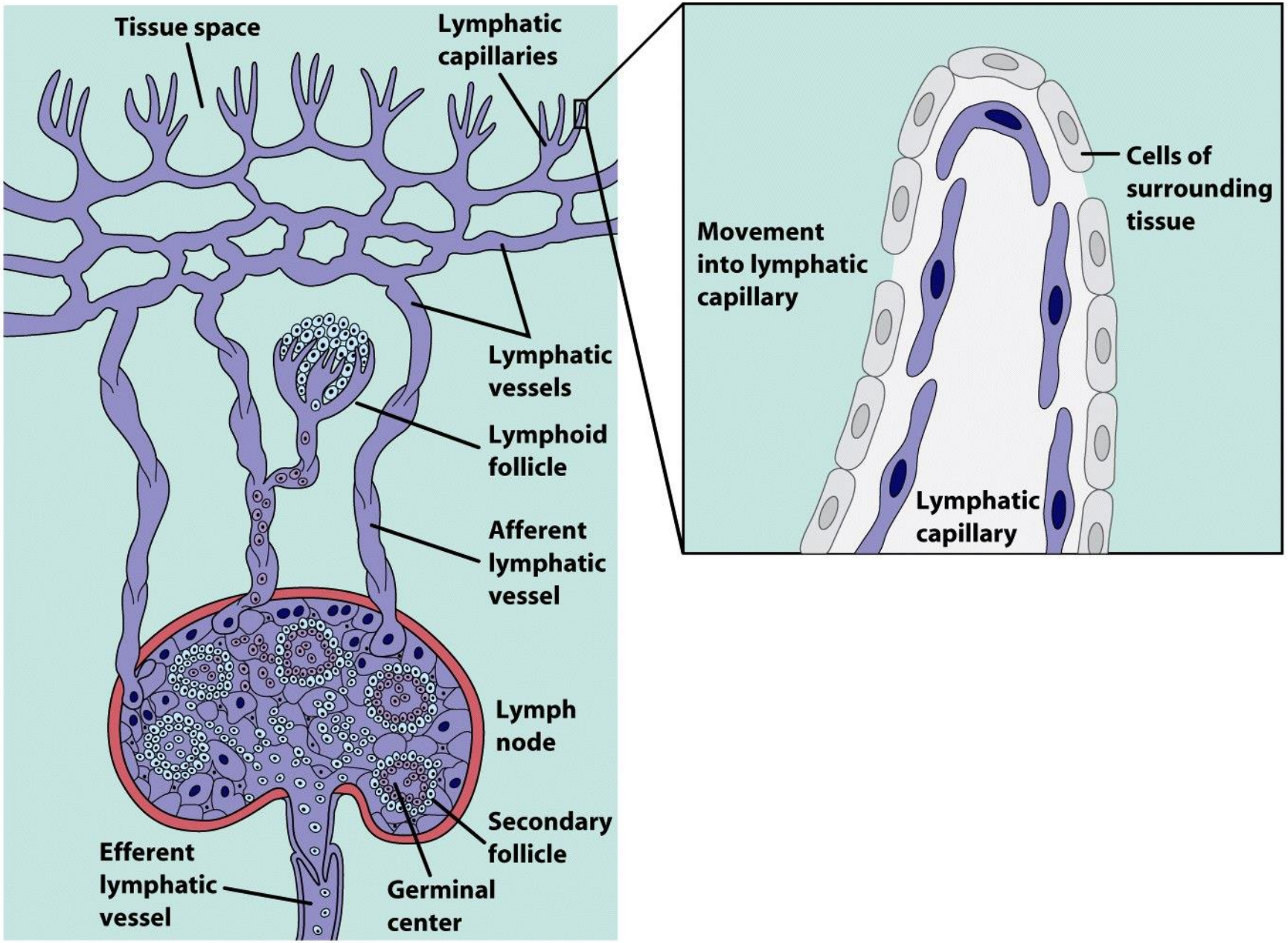


Figure 2-14
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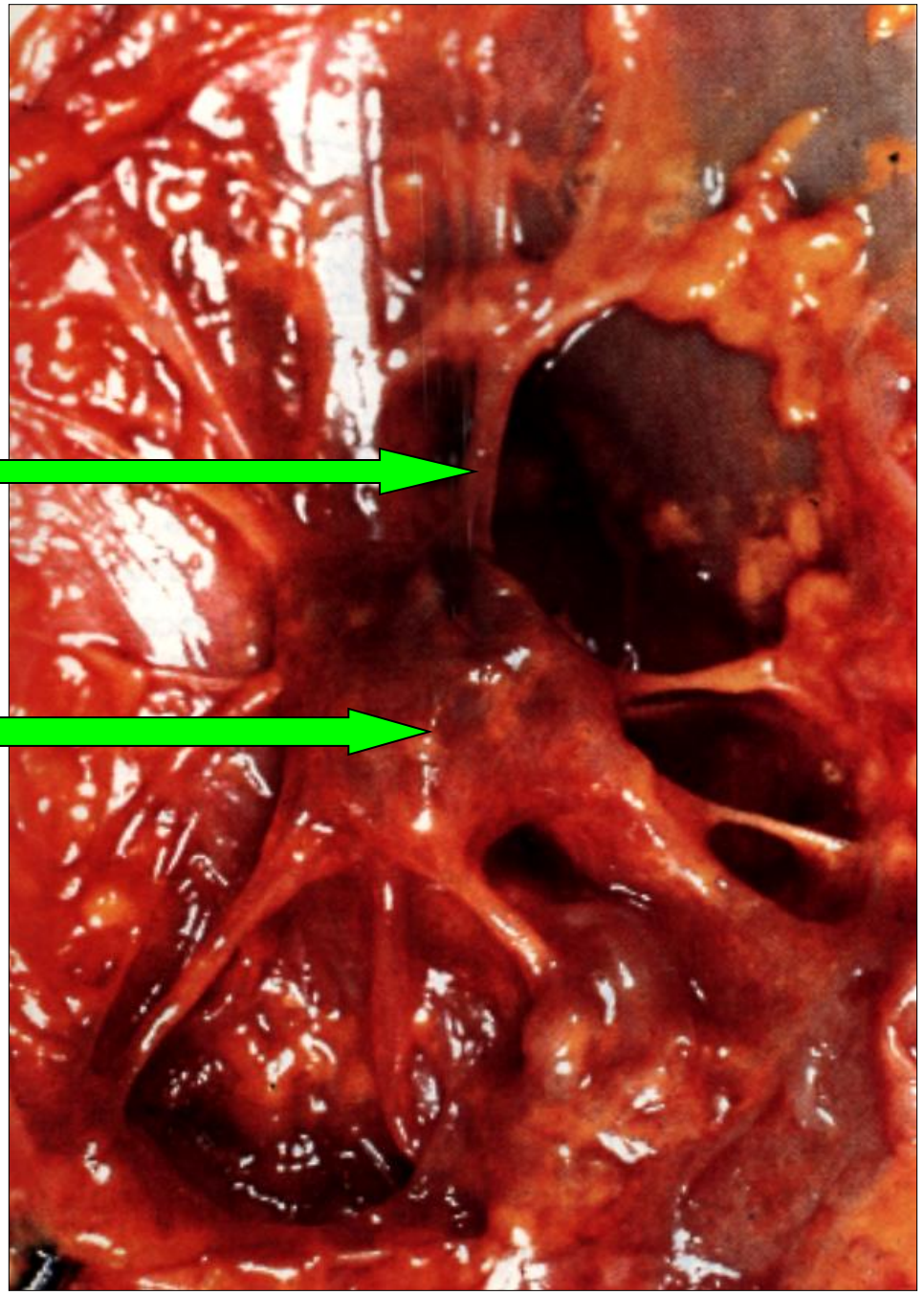
Lymph nodes filter lymph

Lymphatic vessels

Lymph node



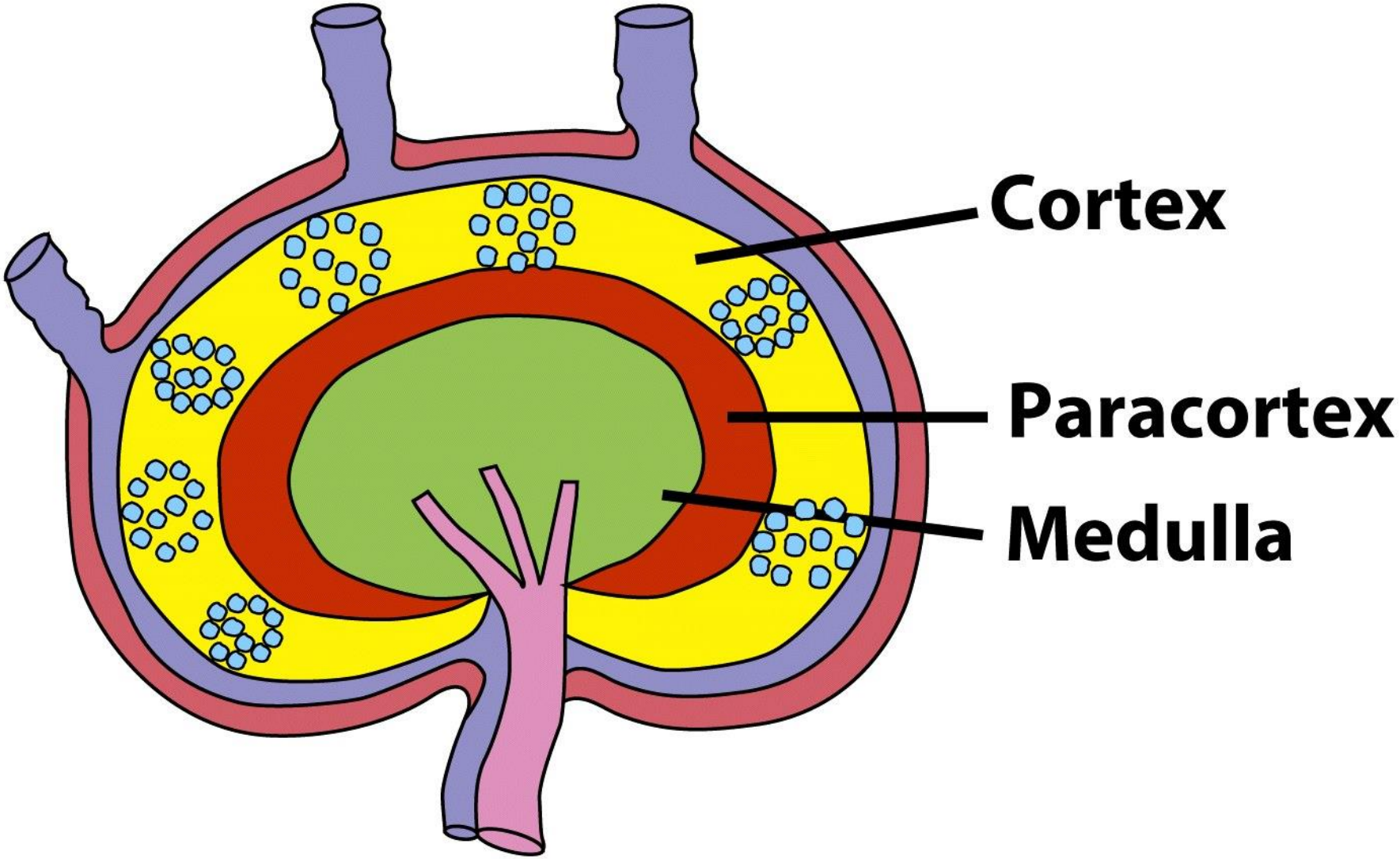


Figure 2-16a
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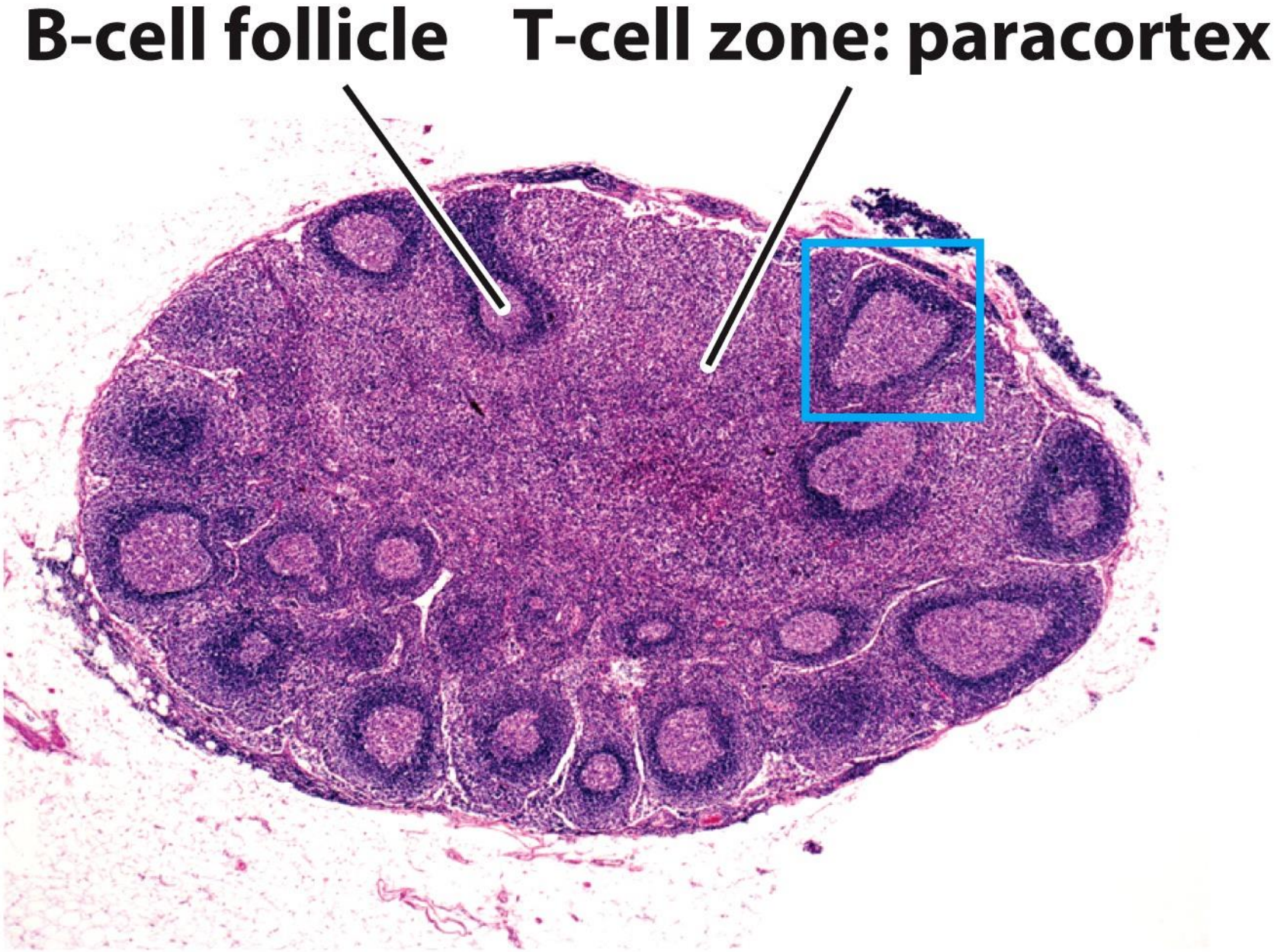

Figure 2-8c
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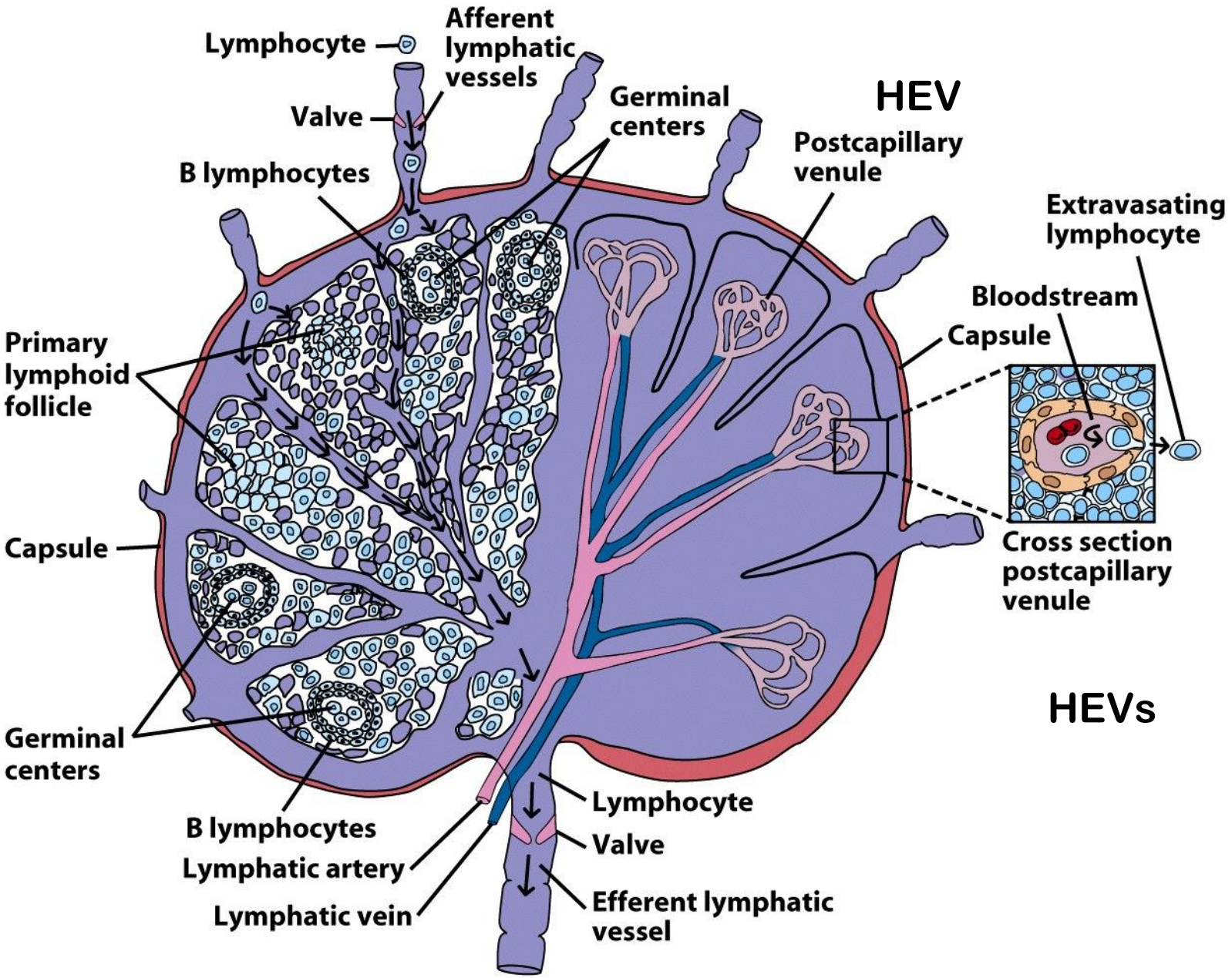

Figure 2-16b
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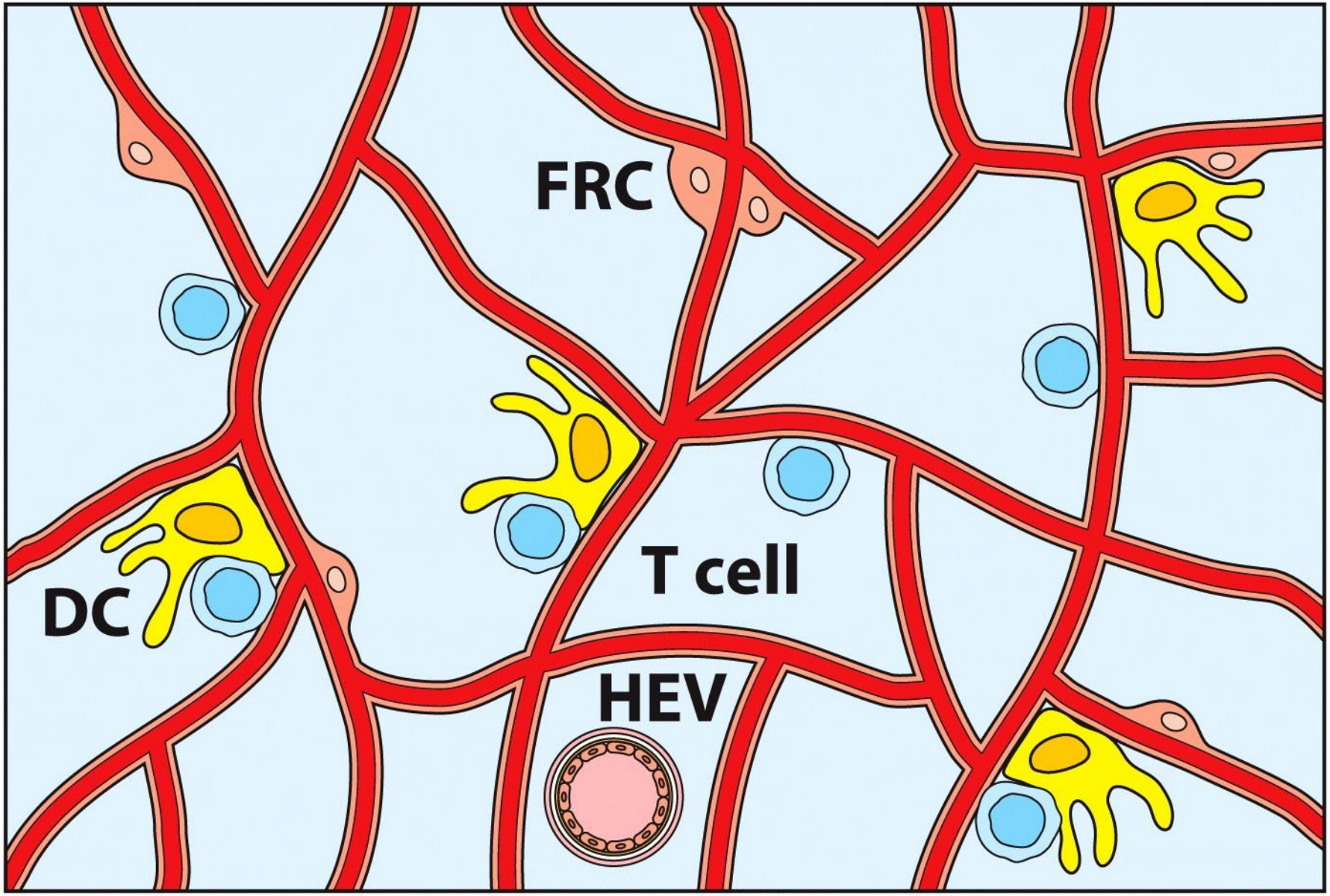

Figure 2-9b part 2
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The Spleen: filters blood

- In contrast to lymph nodes, which are inserted in the lymph circulation, the spleen is inserted in the **blood** circulation.
- Oblong, purplish body the size of a fist, on the left side
- Smooth surfaced except for hilus, where blood vessels enter and leave

* <u>There are no lymphatics leading to the spleen.</u>

The Spleen has 2 major regions

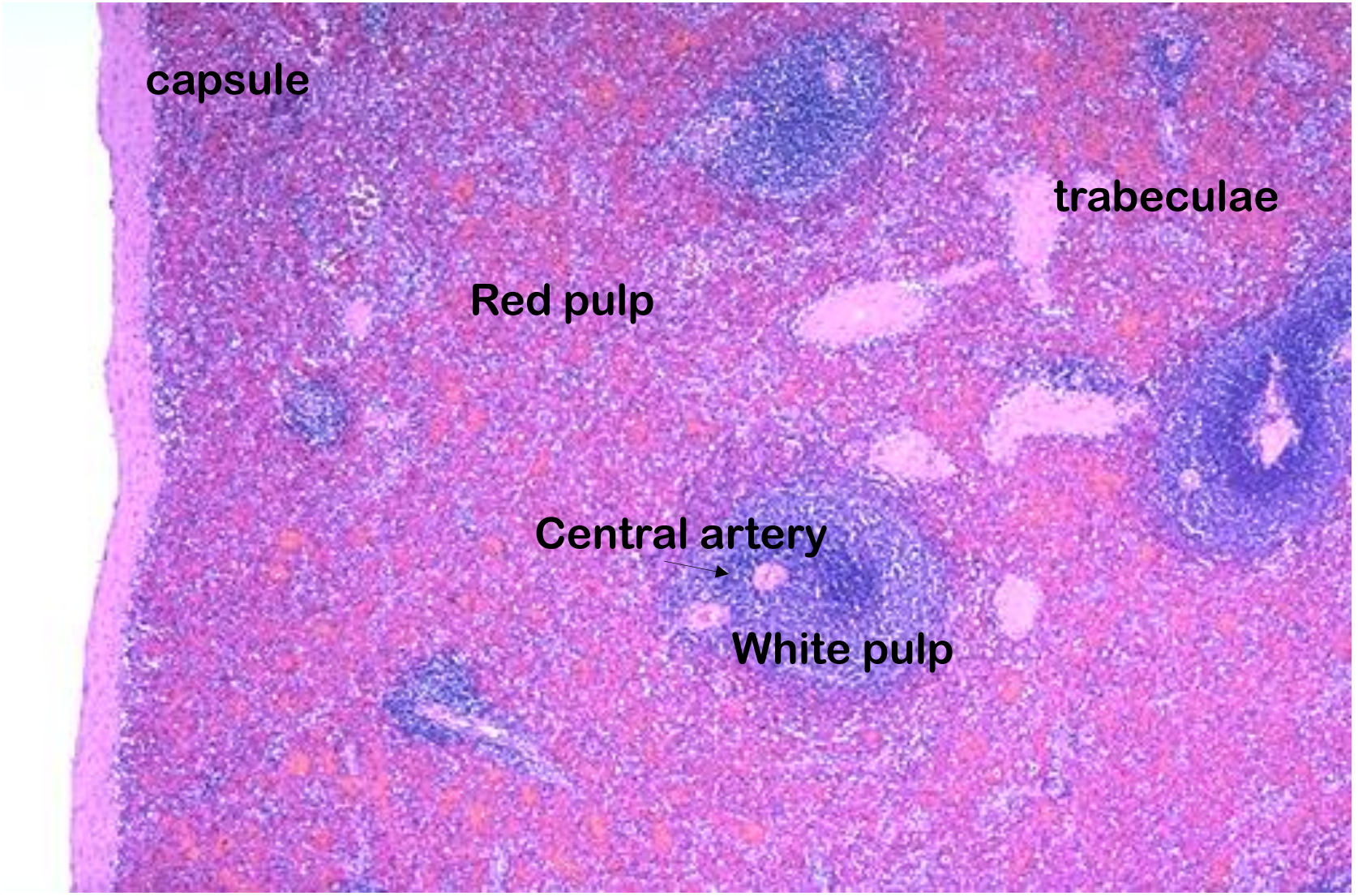
- **White Pulp: lymphatic**
  - Small arterioles surrounded by sheaths of lymphocytes= Peri-Arteriole Lymphoid Sheaths (PALS- human arrangement slightly different)
  - Surrounded by marginal zone
- **Red Pulp: clears RBCs**
  - "Cords" of cells: Erythrocytes, macrophages, dendritic cells, few lymphocytes and plasma cells
  - Also contains venous Sinusoids

Spleen- surface of a fresh cut appears stippled due to red and white pulp

White pulp: two components

1. **PALS- T cells**
   - periarteriole lymphoid sheath
2. **Lymphoid follicles- B cells**
   - spherical structures Scattered throughout PALS
   - Visible to the naked eye on the surface of a freshly cut spleen as white spots.

Spleen- human



What does the spleen do?

https://www.youtube.com/watch?v=aEi_4Cyx4Uw

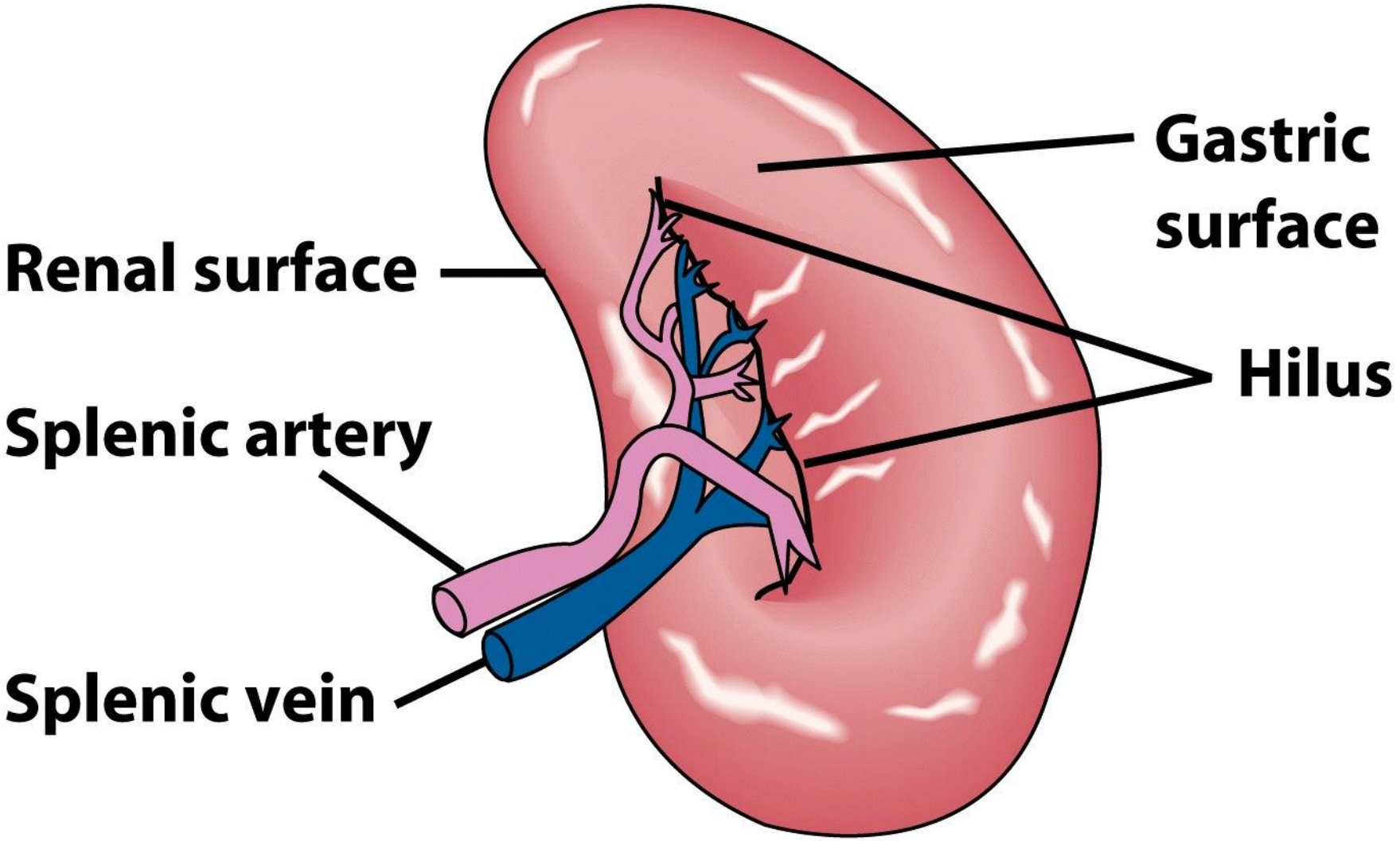


Figure 2-17a
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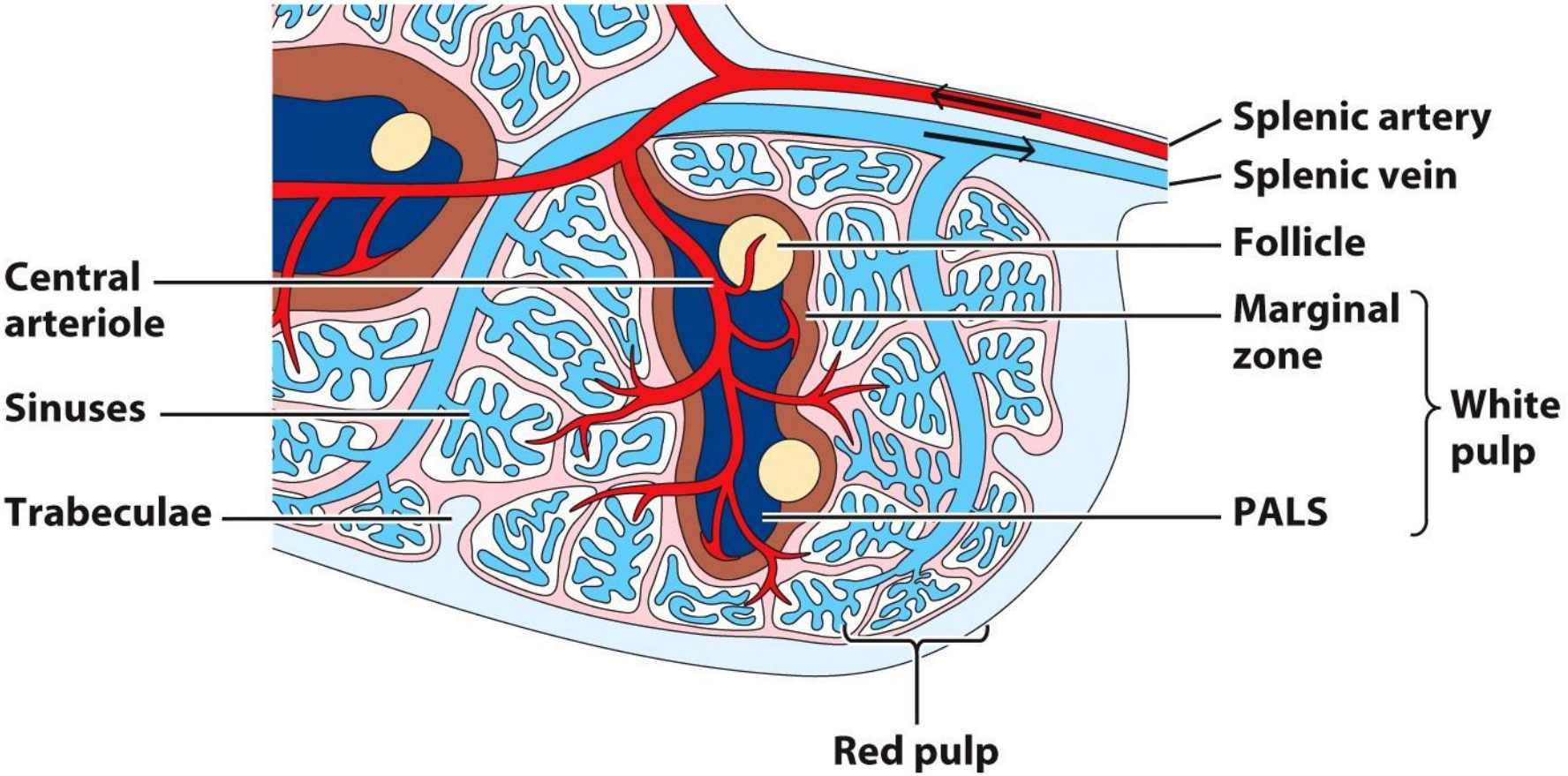

Figure 2-10d
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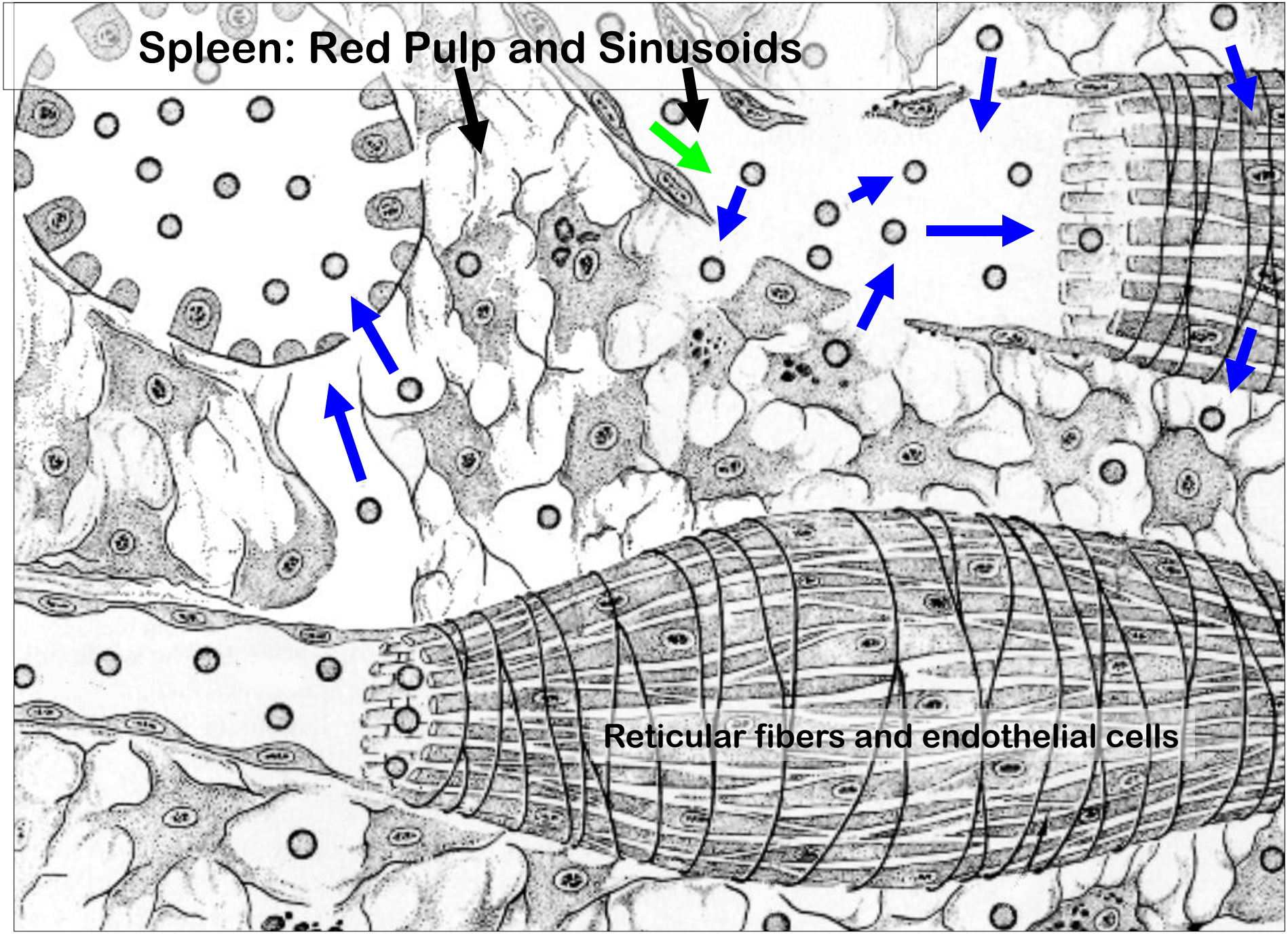
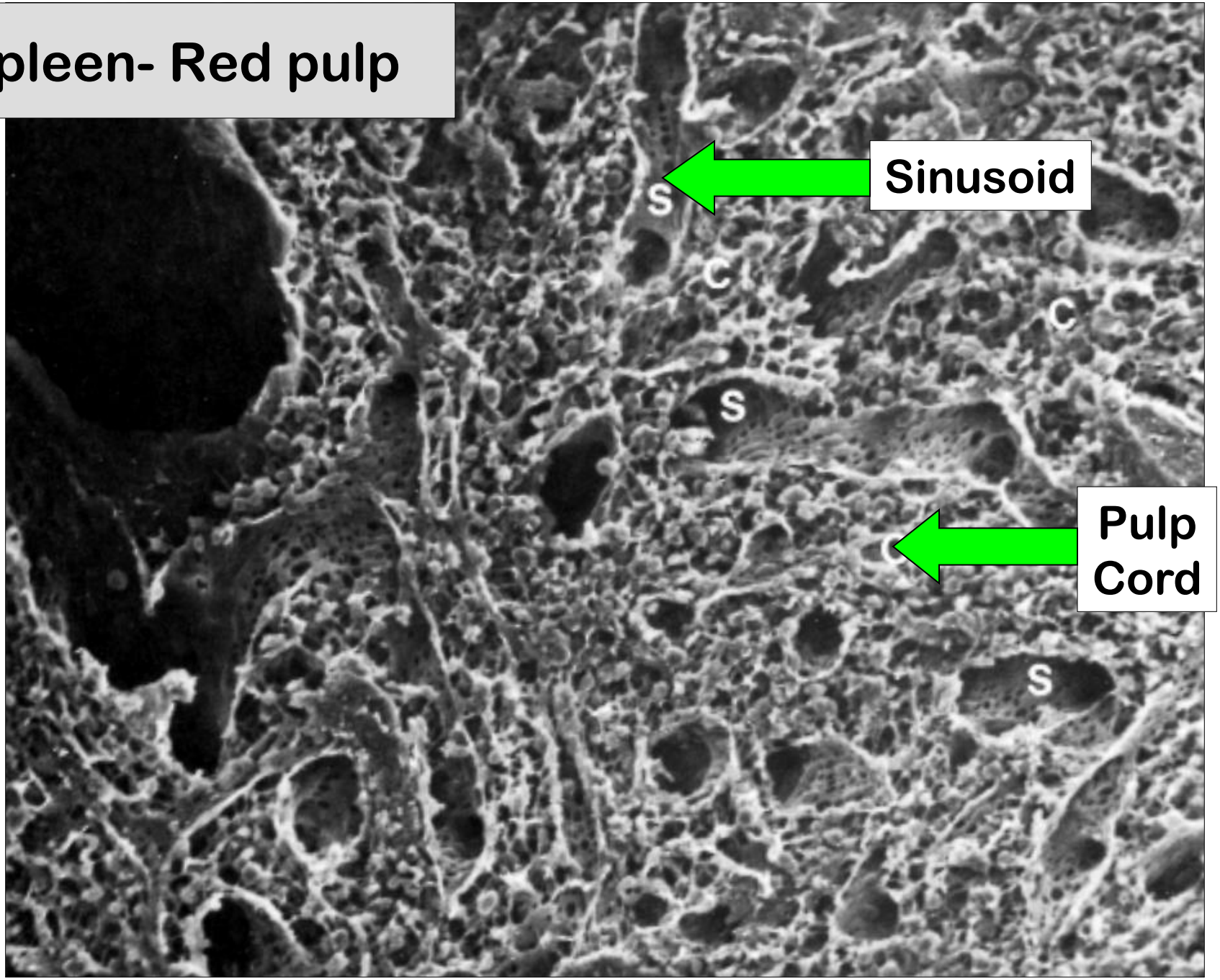

Spleen: Red Pulp and Sinusoids
Reticular fibers and endothelial cells

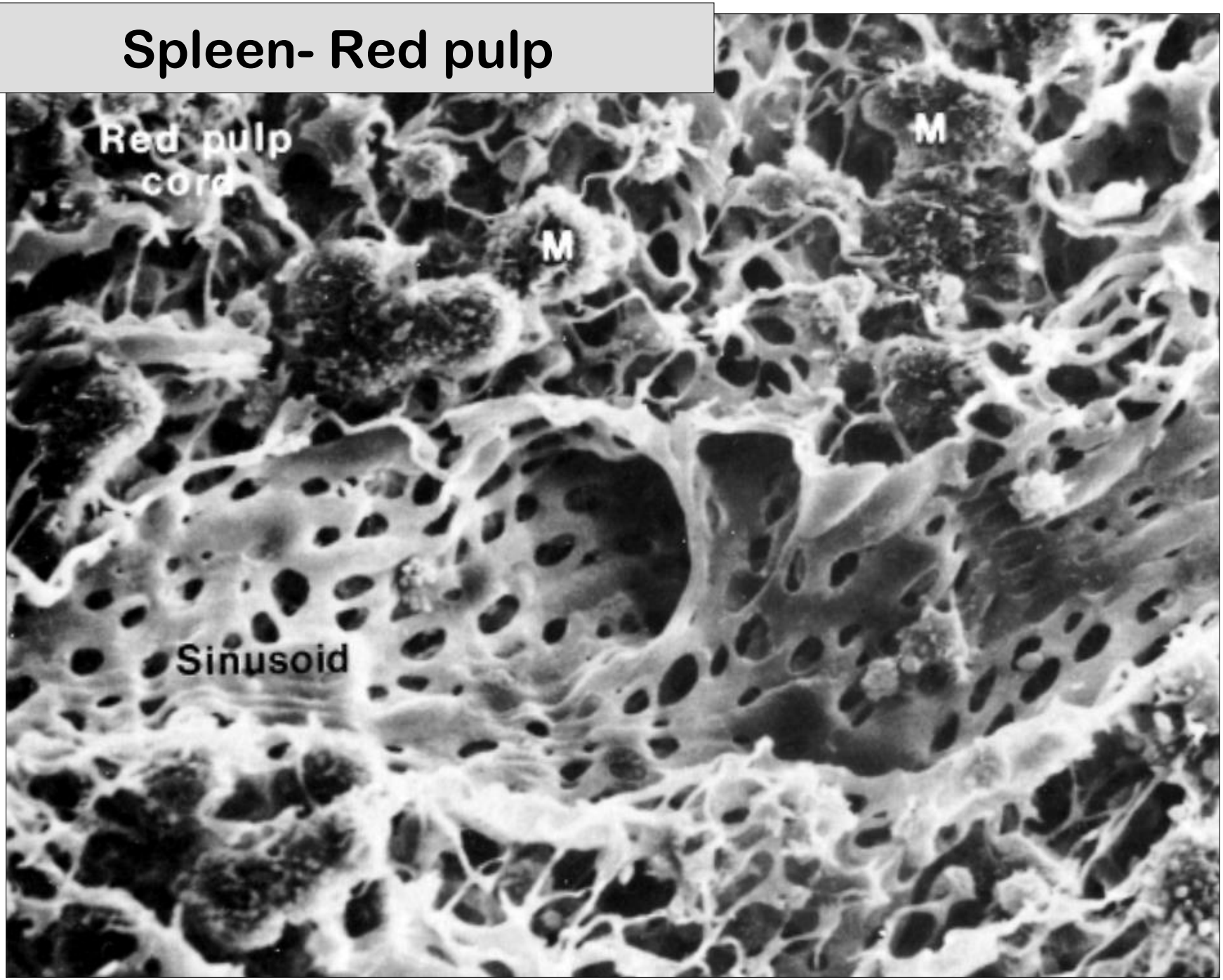
Function of the spleen cont.

- Erythrocytes enter the red pulp, push through the masses of macrophages filling the splenic cords and enter the sinuses.
  - Macrophages engulf old rbcs and antigens in blood
- Lymphocytes are brought into the spleen by the arteries and arterioles; they enter the marginal sinus and then migrate to their respective domains
  - B cells to the follicles, T cells to the PALS

Spleen- Red pulp



Spleen- Red pulp



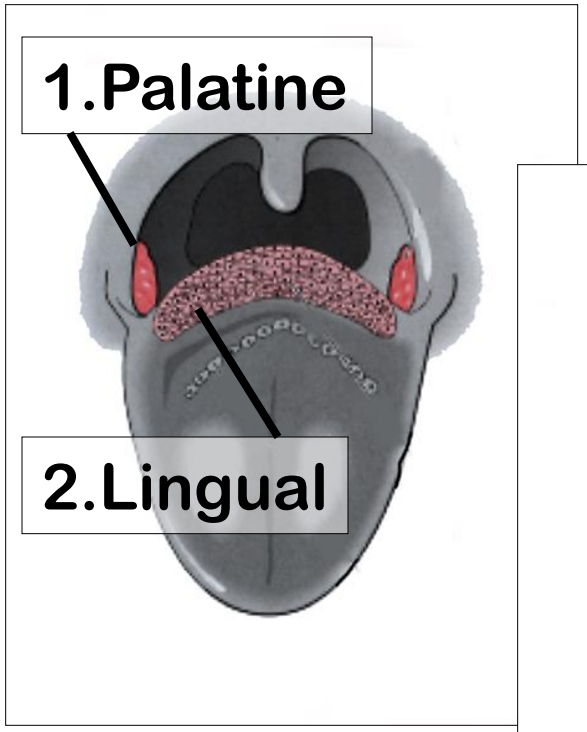
Mucosal Immune System
MALT- Mucosal Associated Lymphoid Tissue

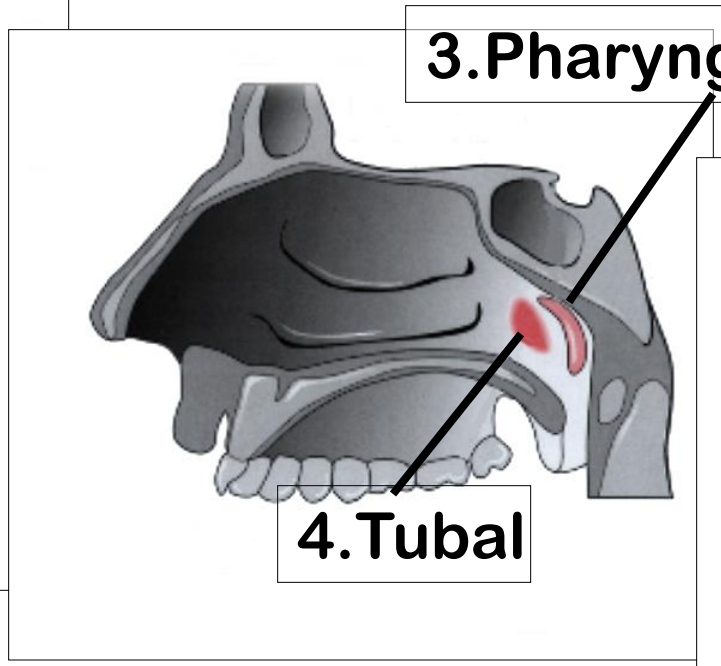
- Mucosal surfaces of mouth, respiratory and reproductive tracts are colonized by lymphocytes and accessory cells
- Respond to ingested, inhaled antigens
- BALT (bronchial) :
- GALT (gut) :
  - Tonsils
  - Peyer's Patches
  - Appendix

Tonsils

- Latin *tonsa* (stake set up on the shore)
- At entrance to GI tract:
  - 1 pharangeal= “adenoids”
  - 2 tubal
  - 2 palatine= “tonsils” (from pouch 2)
  - 1 lingual

Human Tonsils





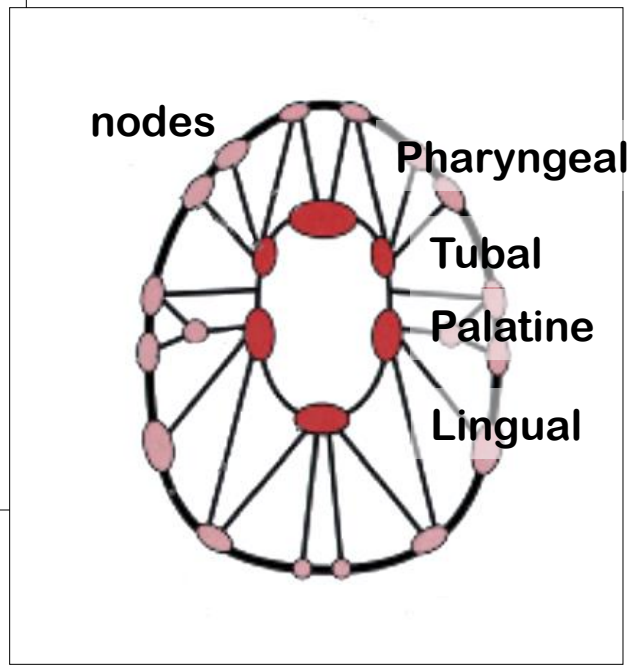
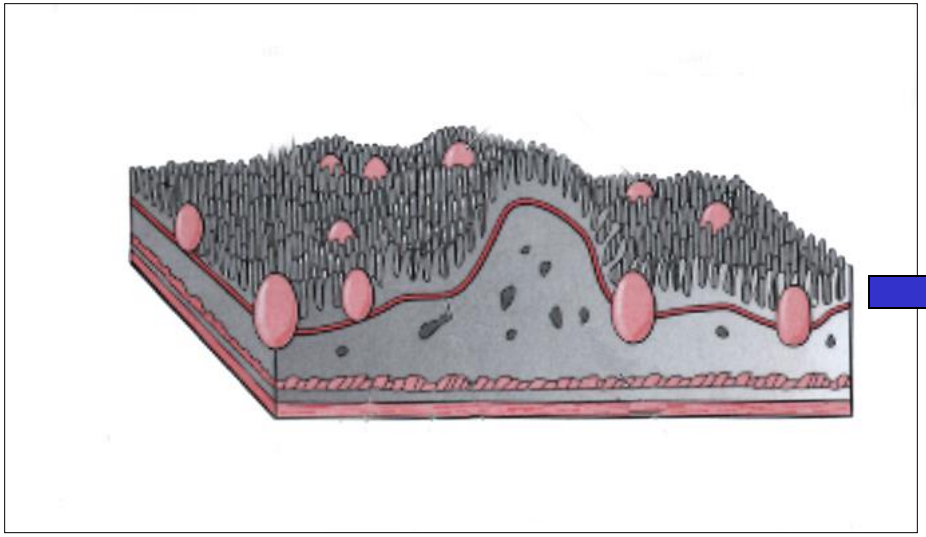


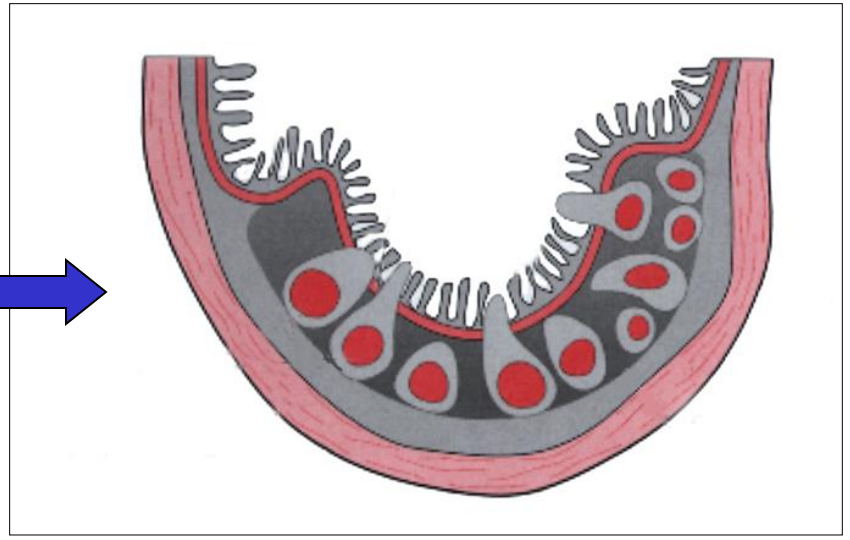
Diagram of the

Tonsil

- <u>Aggregated lymphoid follicles</u>
- Corrugated surface with cracks and pits CRYPTS lined with *stratified squamous epithelium*
- become filled with sloughed off cells, dead lymphocytes and fluid
- good culture medium for bacteria

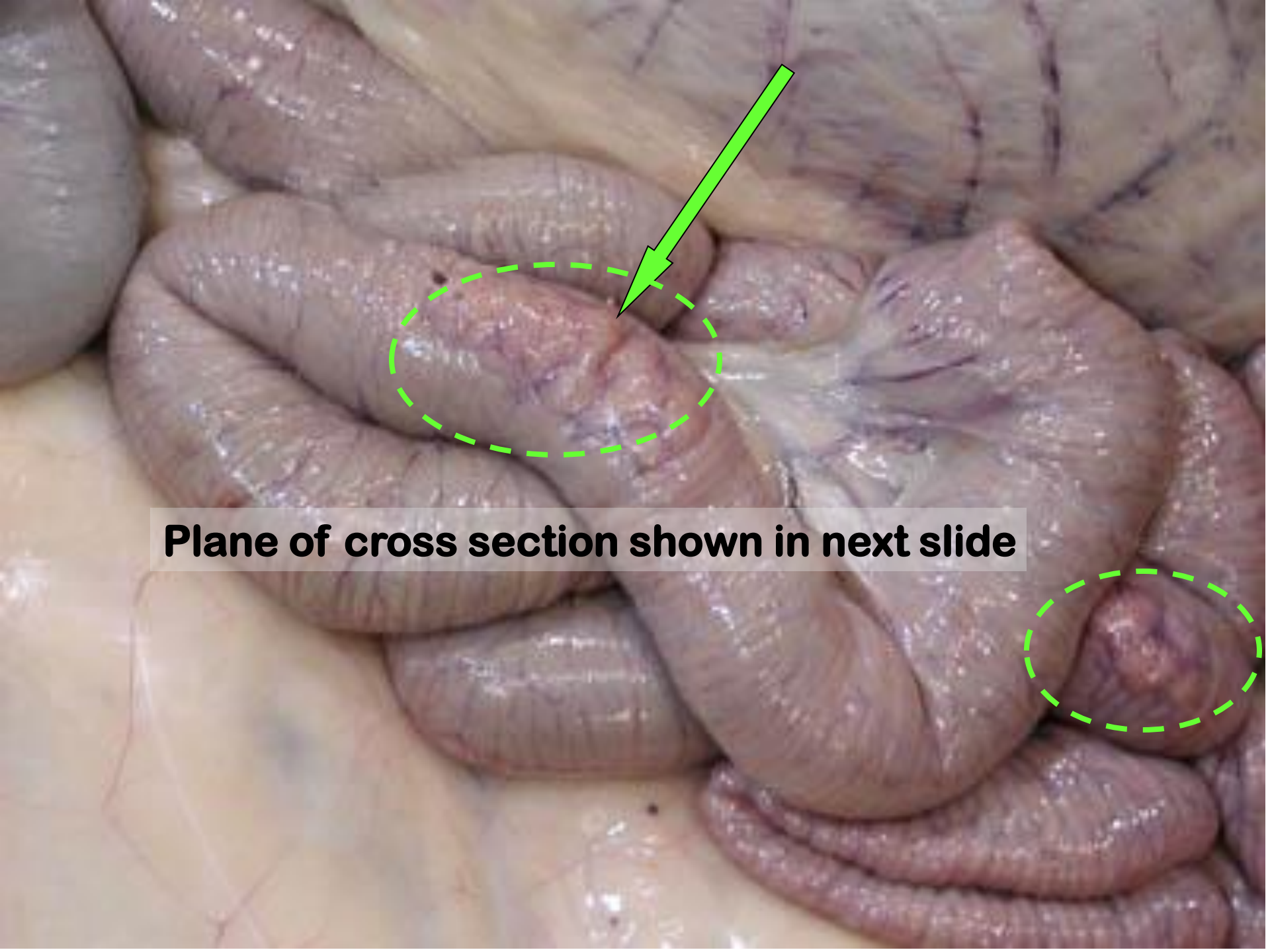
Peyer's Patches (~30) are found in the ileum (small intestine) in the wall opposite the mesentary



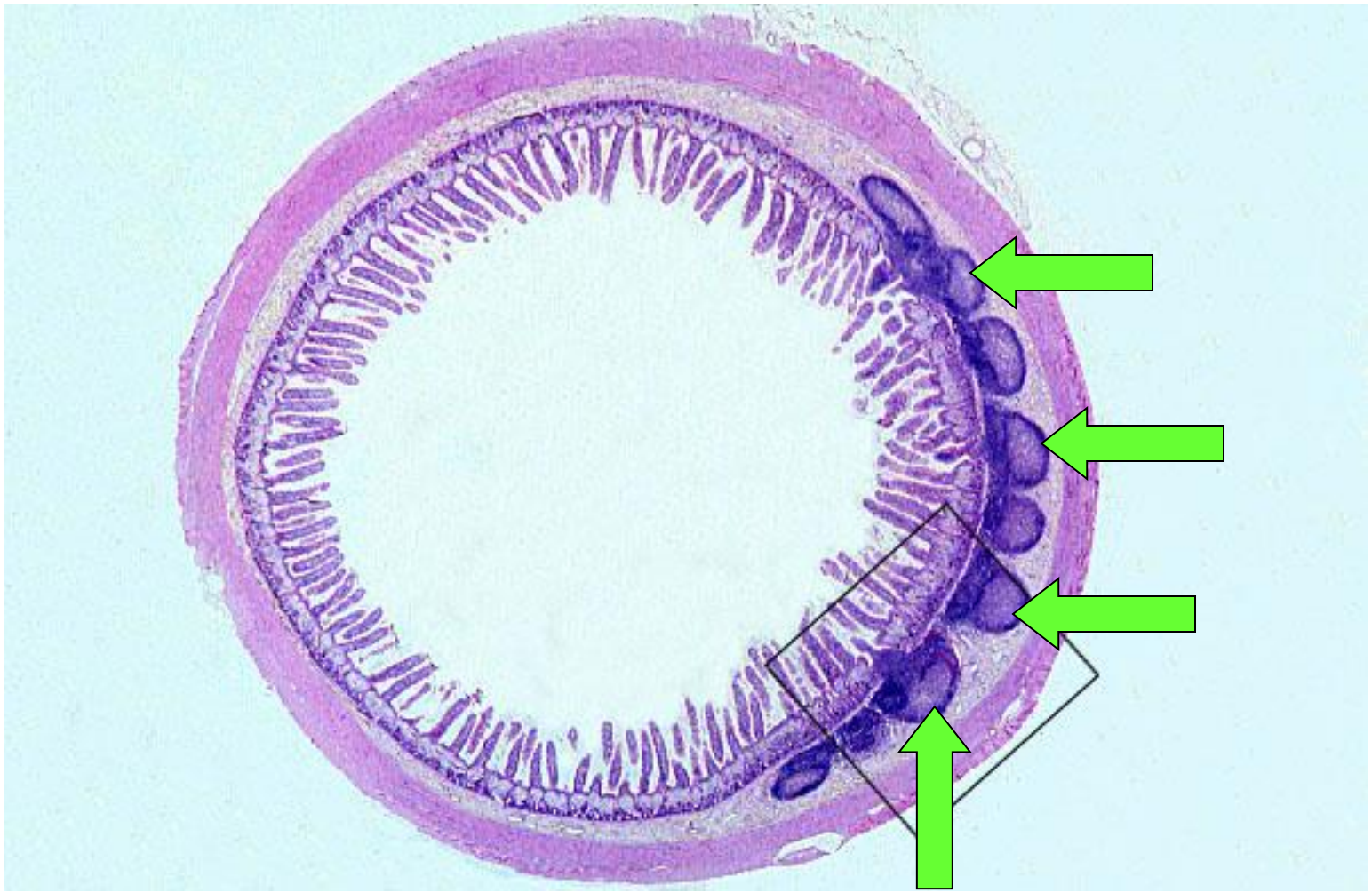


Each is a collection of many individual lymphoid follicles (pink) scattered between the microvilli "like puffballs on a lawn"

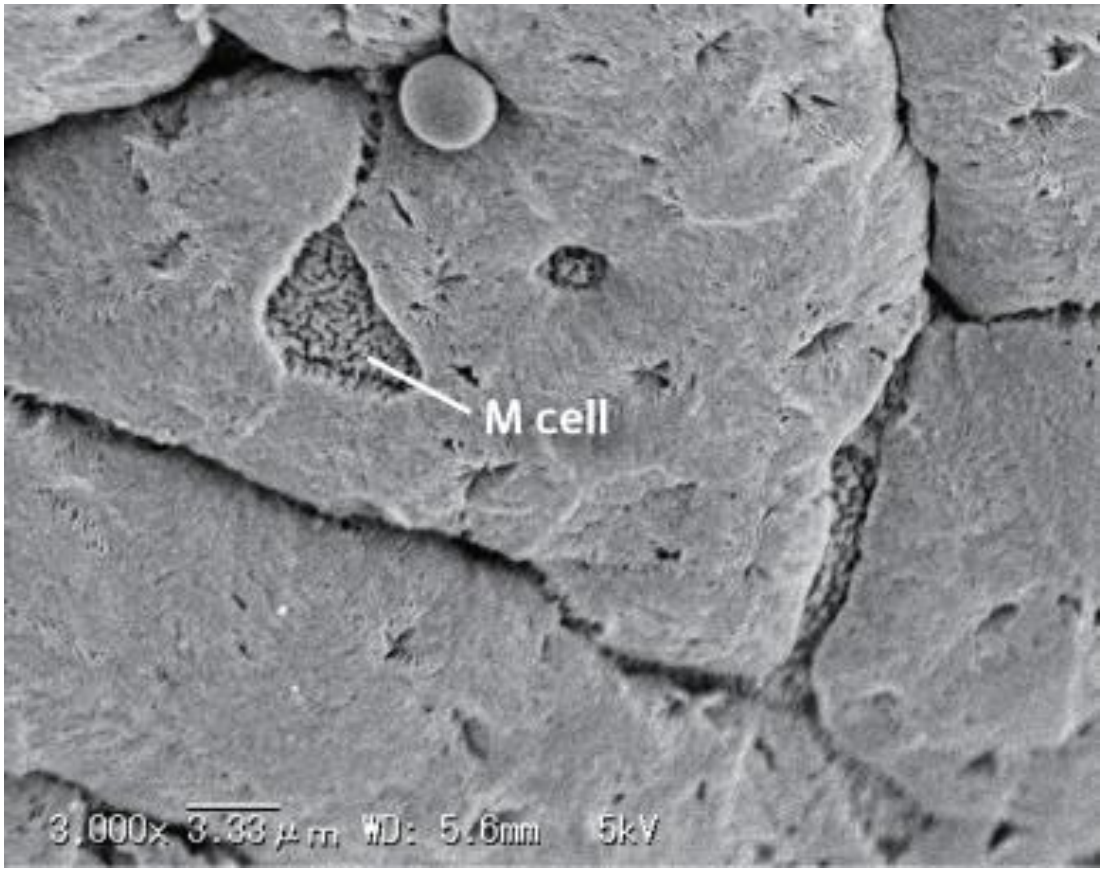
X-section showing the follicles in the submucosa


Plane of cross section shown in next slide

Identify the lymphoid organ indicated by the green arrows.



M cell (microfold cell) in the surface of the Peyer's patch is the cell specialized to uptake Ag from the gut



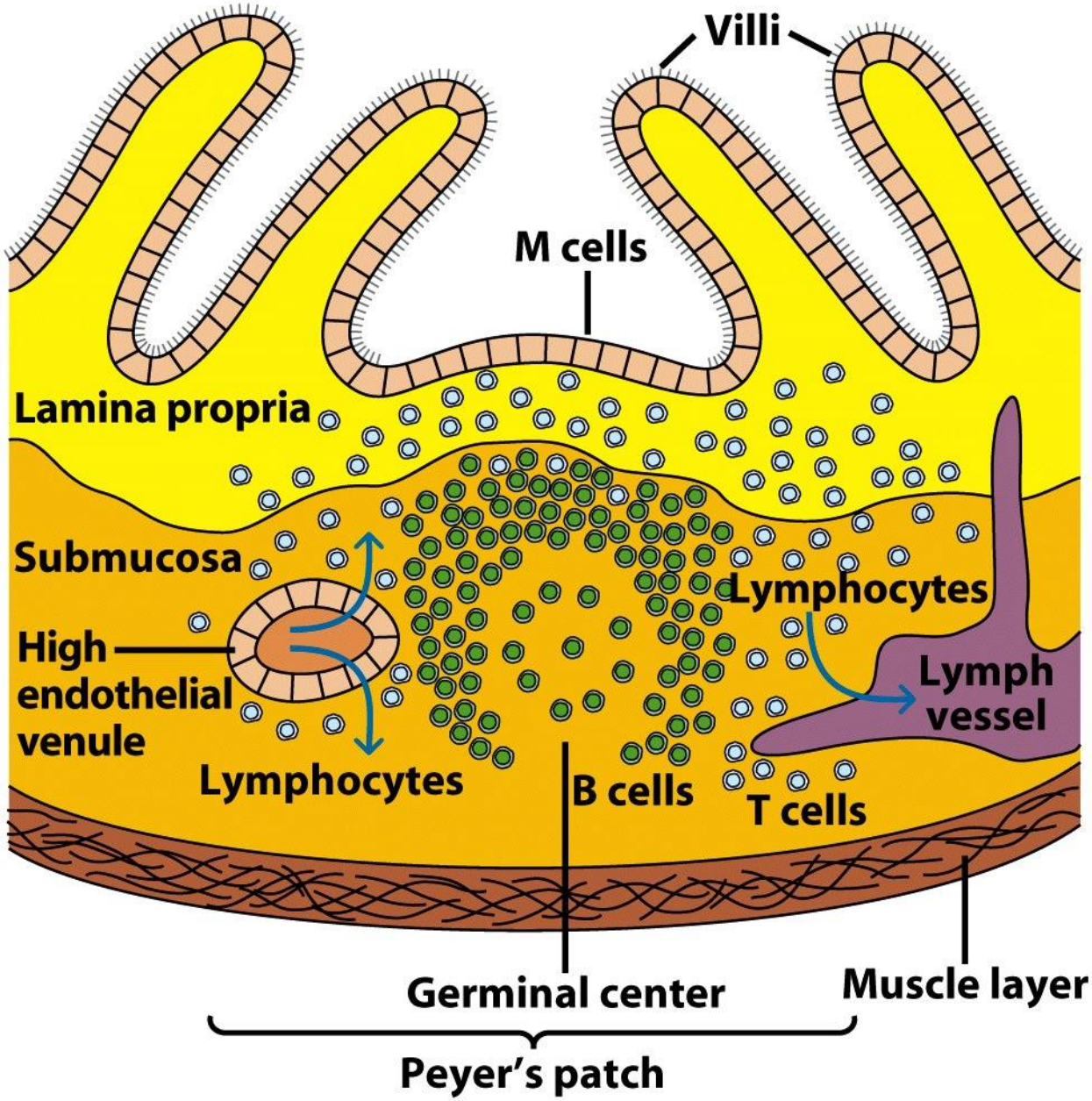


Figure 2-18
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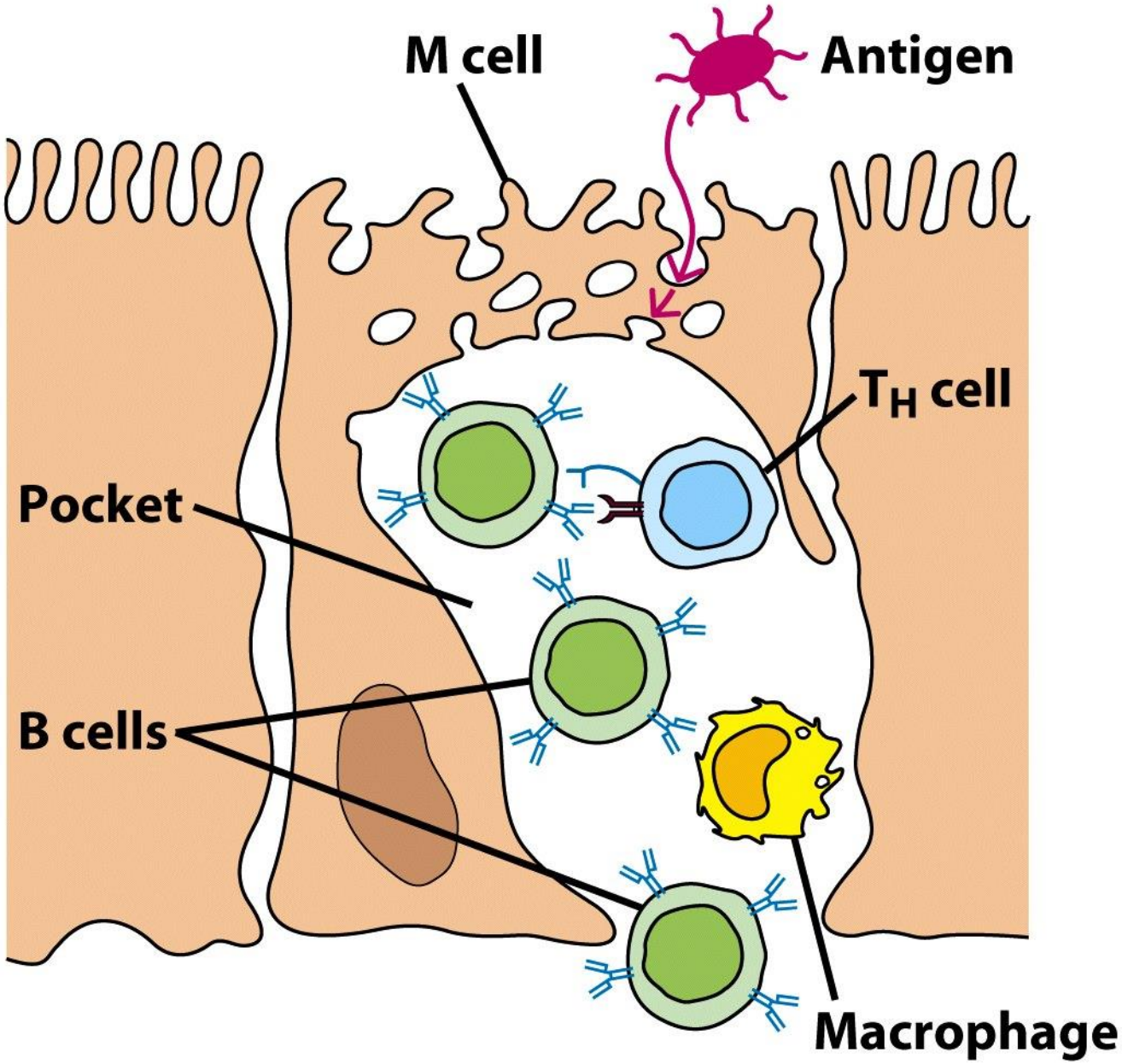


Figure 2-19a
Kuby IMMUNOLOGY, Sixth Edition

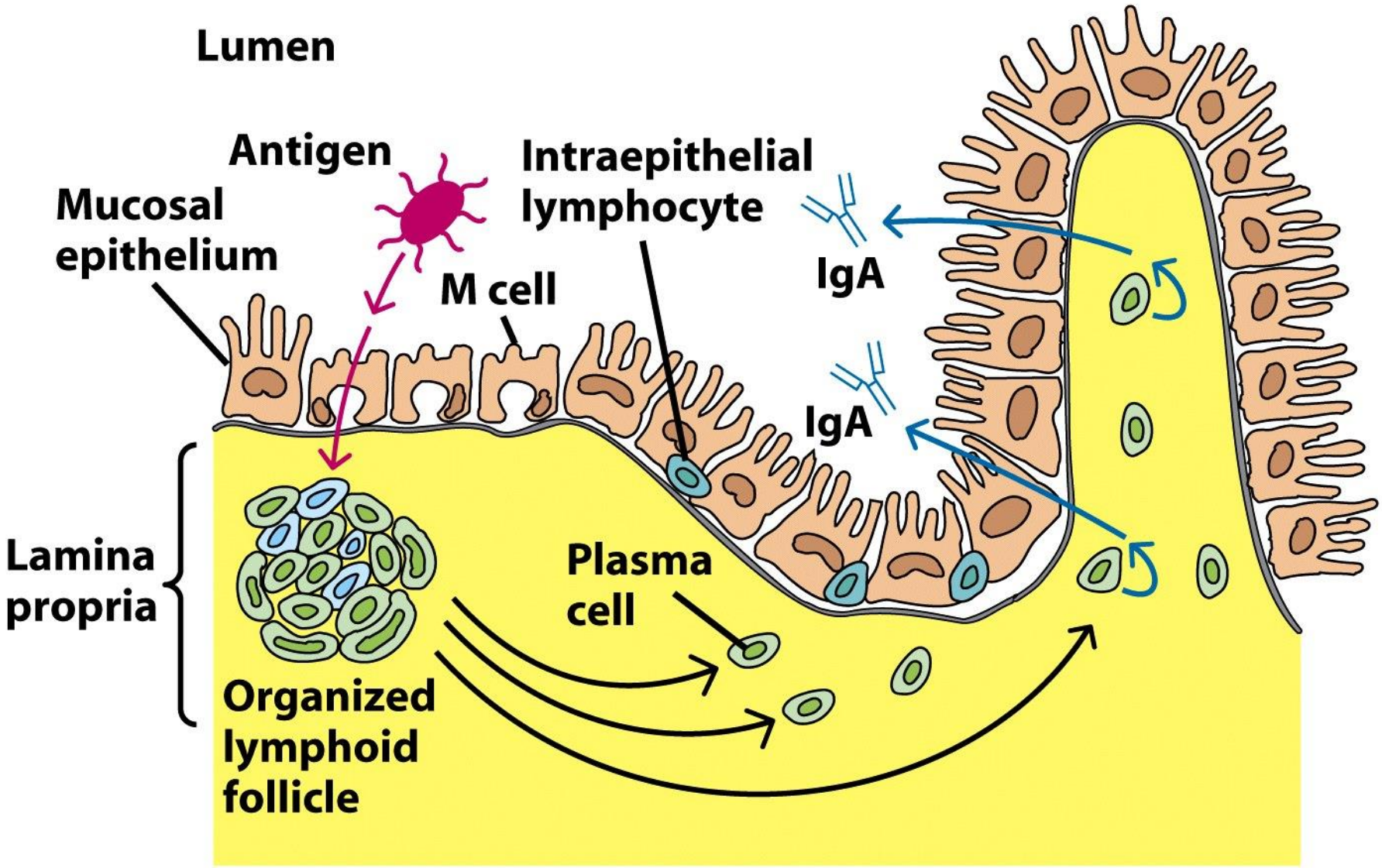
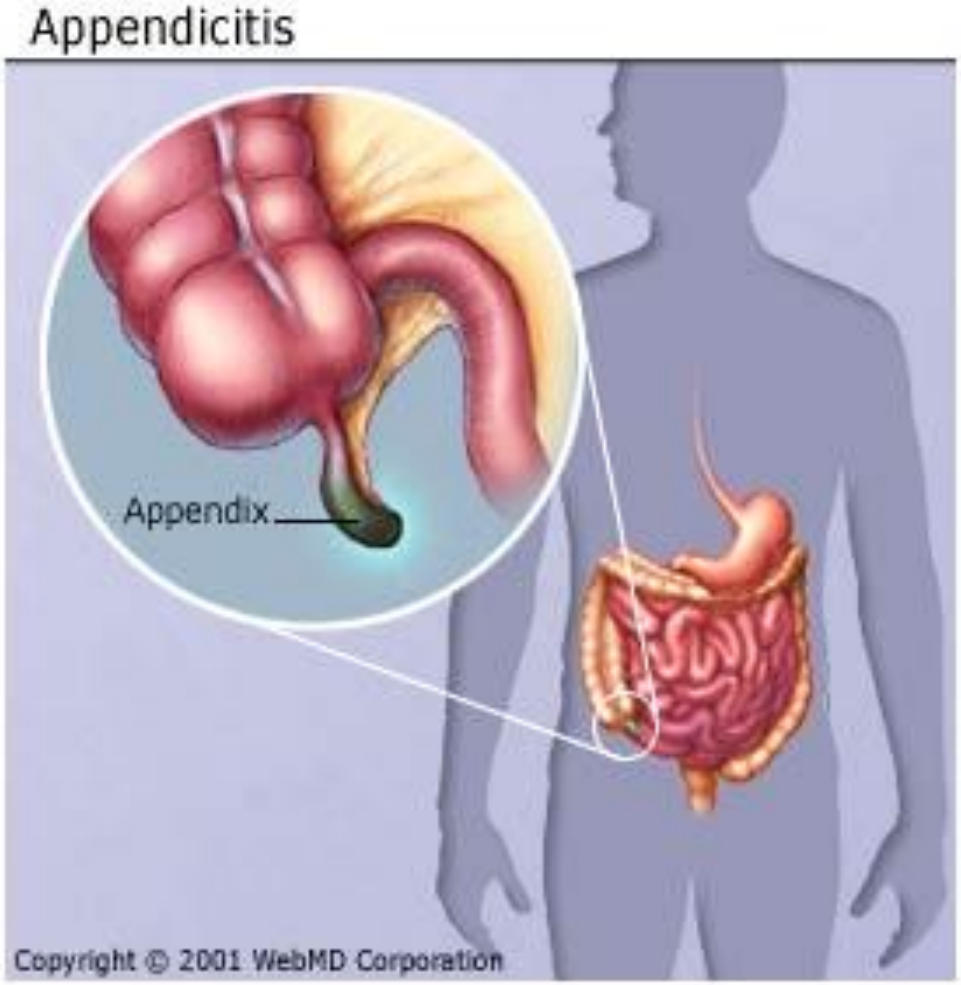


Figure 2-19b
Kuby IMMUNOLOGY, Sixth Edition

Appendix

- **Worm-like projection of the human large intestine, 10-15 cm long and up to 8mm in diameter.**
- **The lamina propria contains dense, diffuse lymphoid tissue packed with some 200 lymphoid follicles.**

Appendix



There is a network of lymphatics surrounding each follicle

Summary

- The immune system is composed of many cells, tissues and organs
- The anatomical arrangement of the immune system facilitates interactions between antigens and cells at appropriate times
- If you understand the anatomy, you will be able to better understand the context of these interactions… (see gut animation)

http://www.nature.com/ni/multimedia/mucosal/animation/index.html

- The gut mucosa is the largest and most dynamic immunological environment of the body. It's often the first point of pathogen exposure and many microbes use it as a beachhead into the rest of the body. The gut immune system therefore needs to be ready to respond to pathogens but at the same time it is constantly exposed to innocuous environmental antigens, food particles and commensal microflora which need to be tolerated. Misdirected immune responses to harmless antigens are the underlying cause of food allergies and debilitating conditions such as inflammatory bowel disease.
- This animation introduces the key cells and molecular players involved in gut immunohomeostasis and disease.

- **Nature Immunology September 2013 - Vol 14 No 9**