

# **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 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

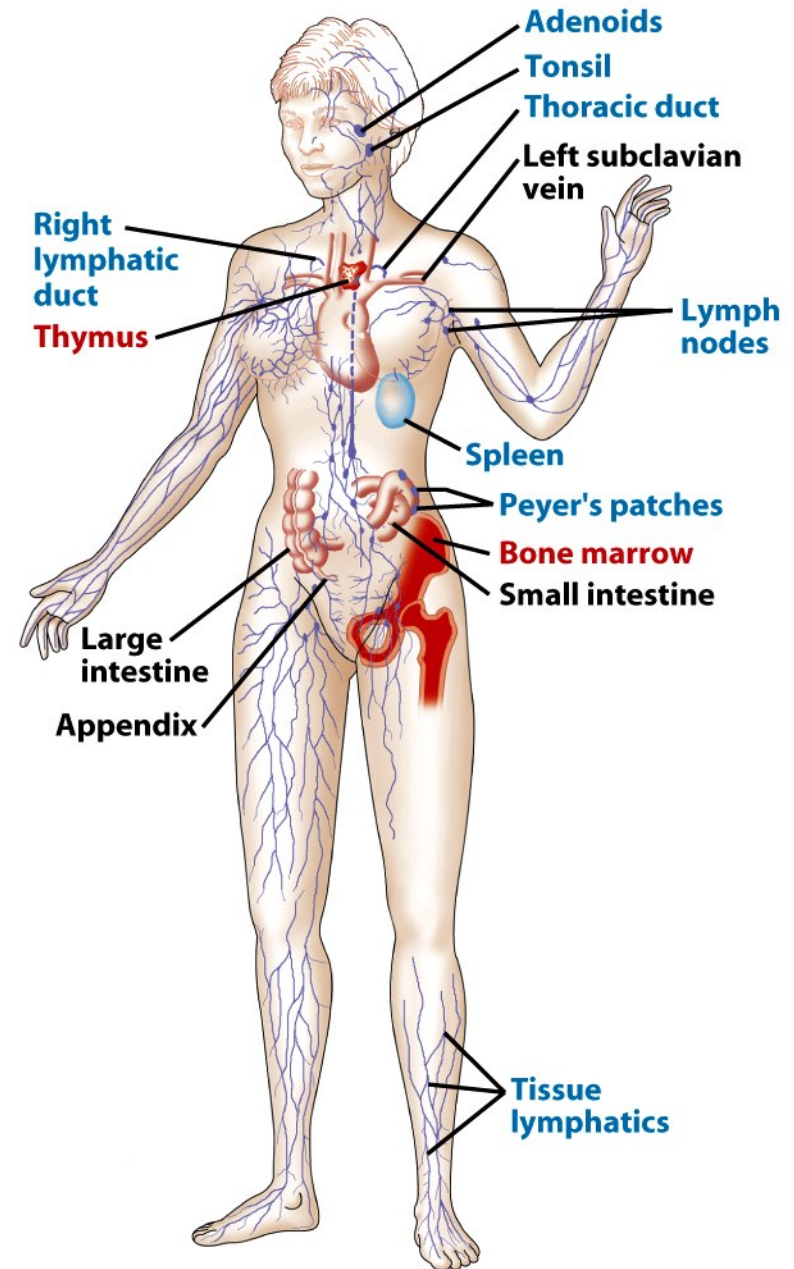


Figure 2-11  
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Not all who wander are lost.....



Lord of the Rings

.....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**

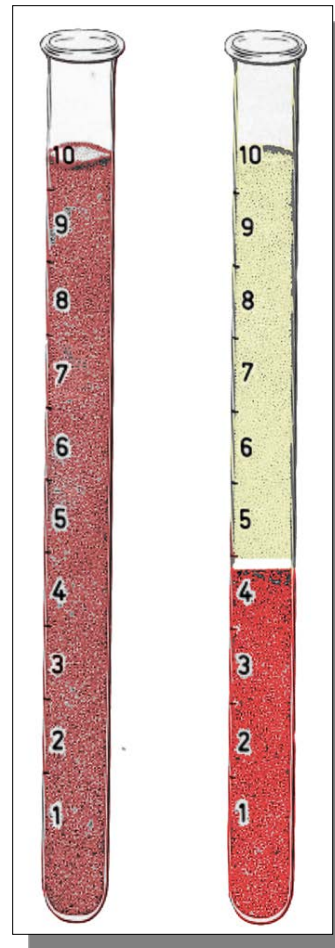
# Cells= Leukocytes= white blood cells

## 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?**

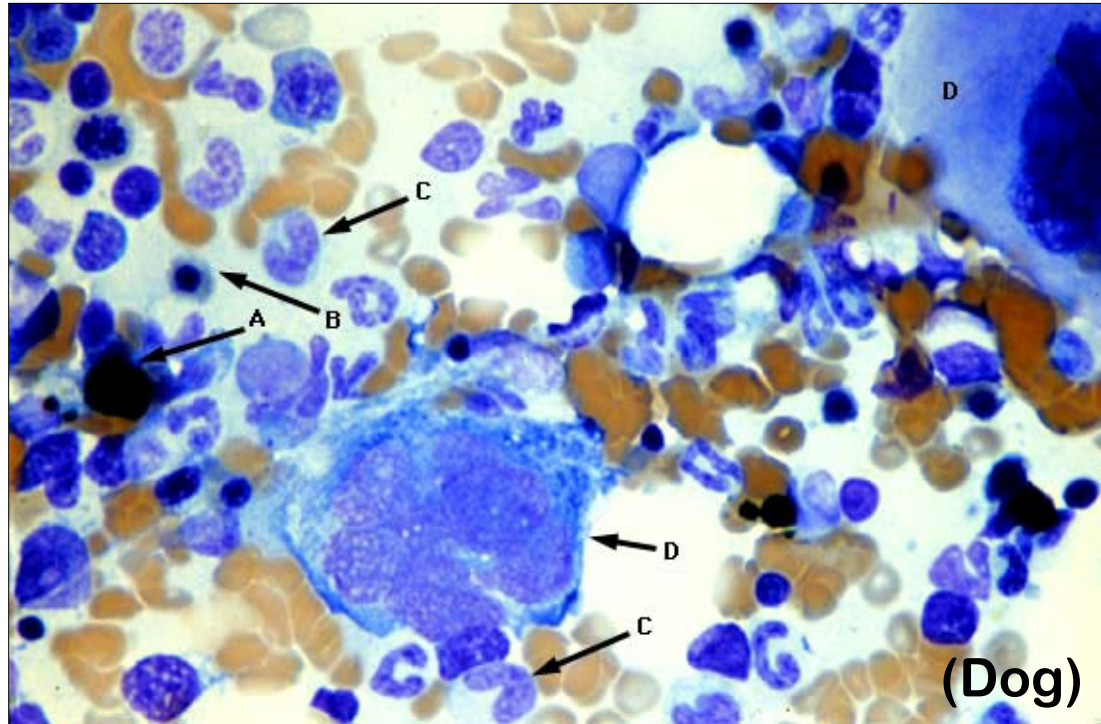
The cells of the immune system arise from pluripotent hematopoietic stem cells (HSC) through two main lines of differentiation

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

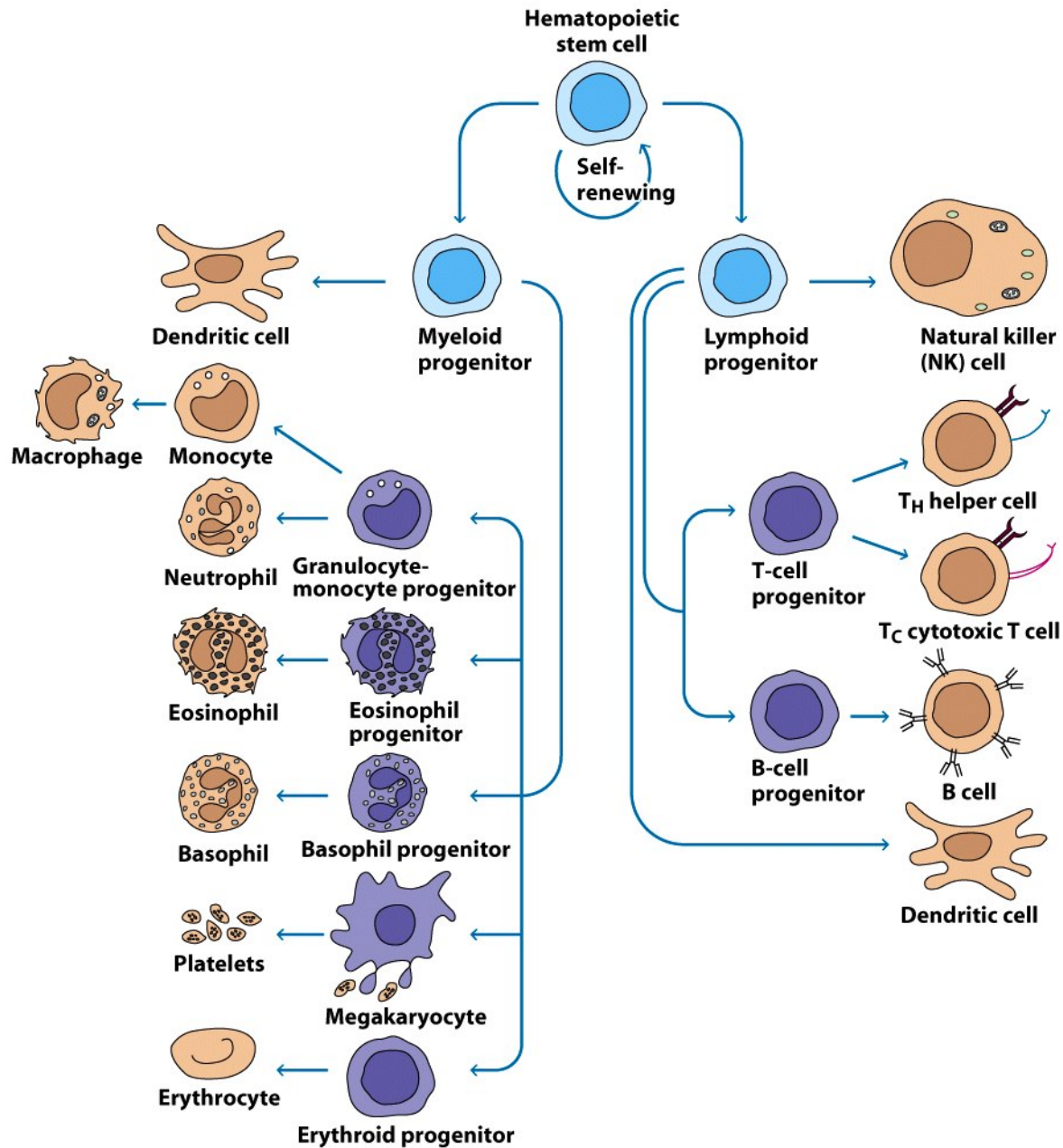


# Hematopoiesis

- Pluripotent Hematopoietic Stem Cells give rise to second generation stem cells with restricted lineage potential



- 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



**Figure 2-2**  
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# “First Responders”

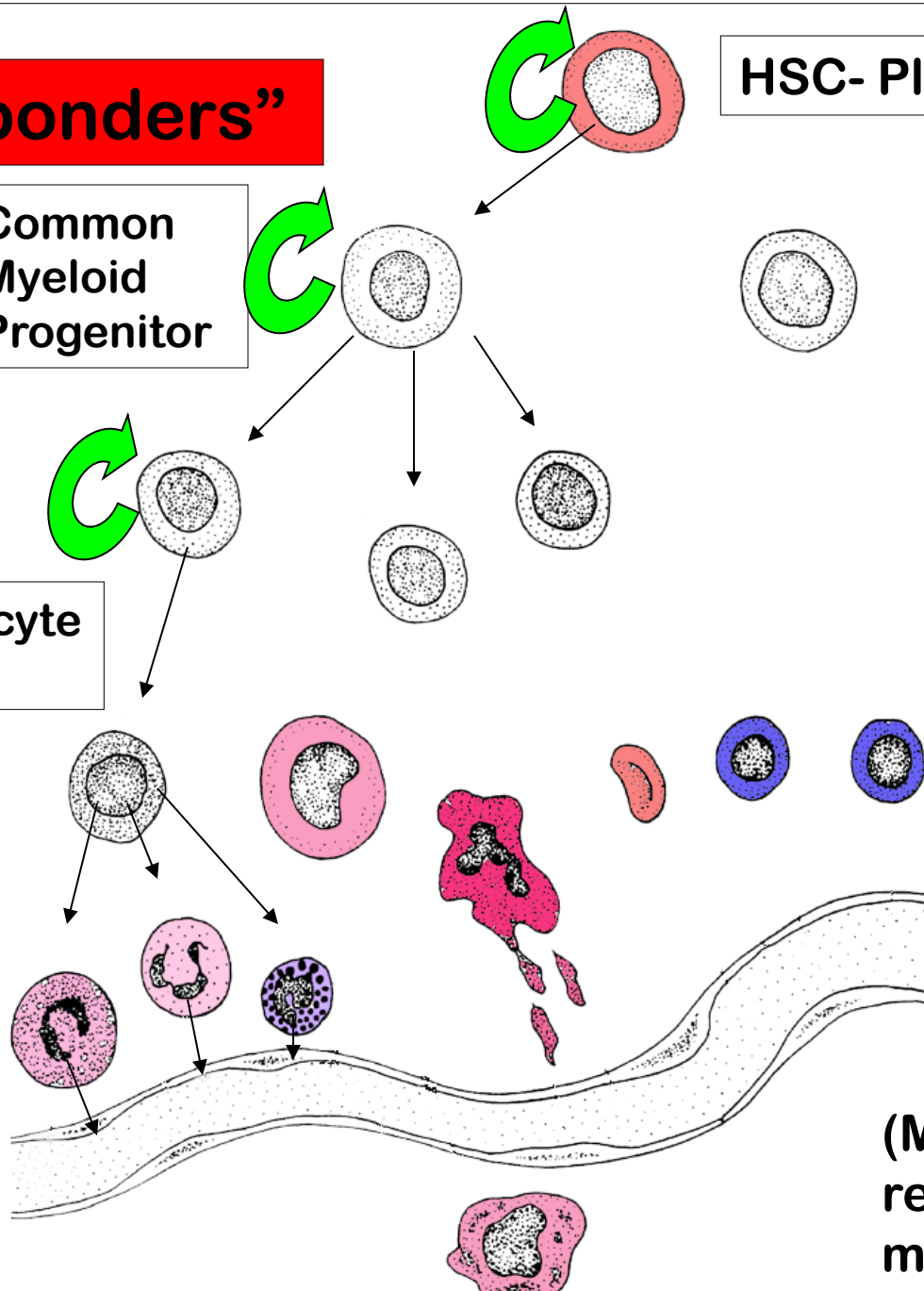
HSC- Pleuripotent

Common Myeloid Progenitor

Granulocyte lineage

Eosinophil  
Neutrophil  
Basophil

(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**

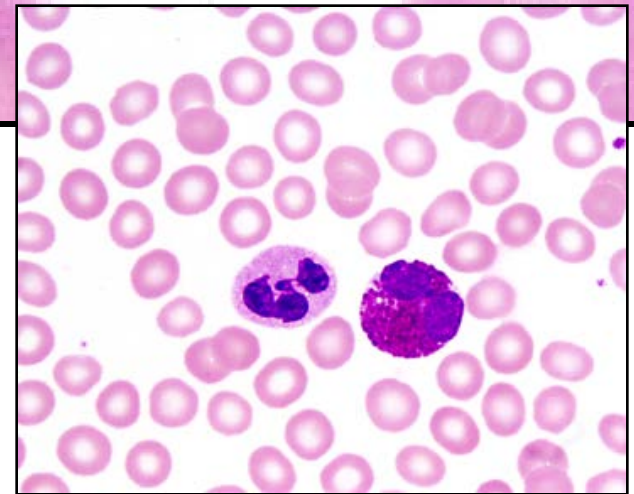
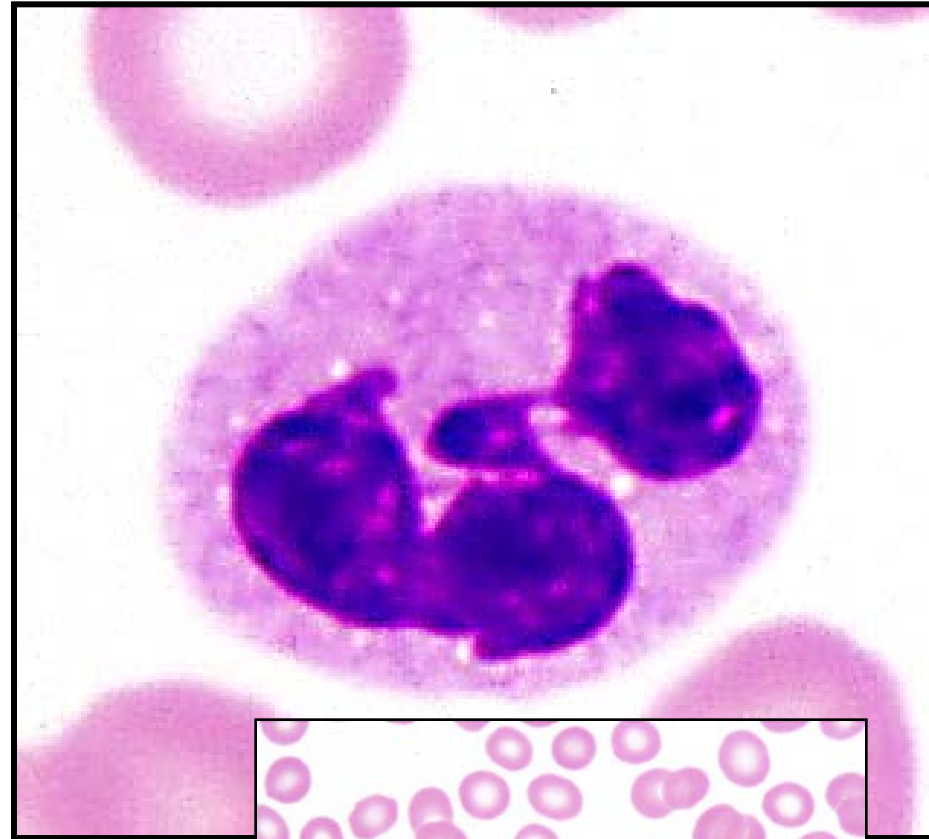
# Neutrophils

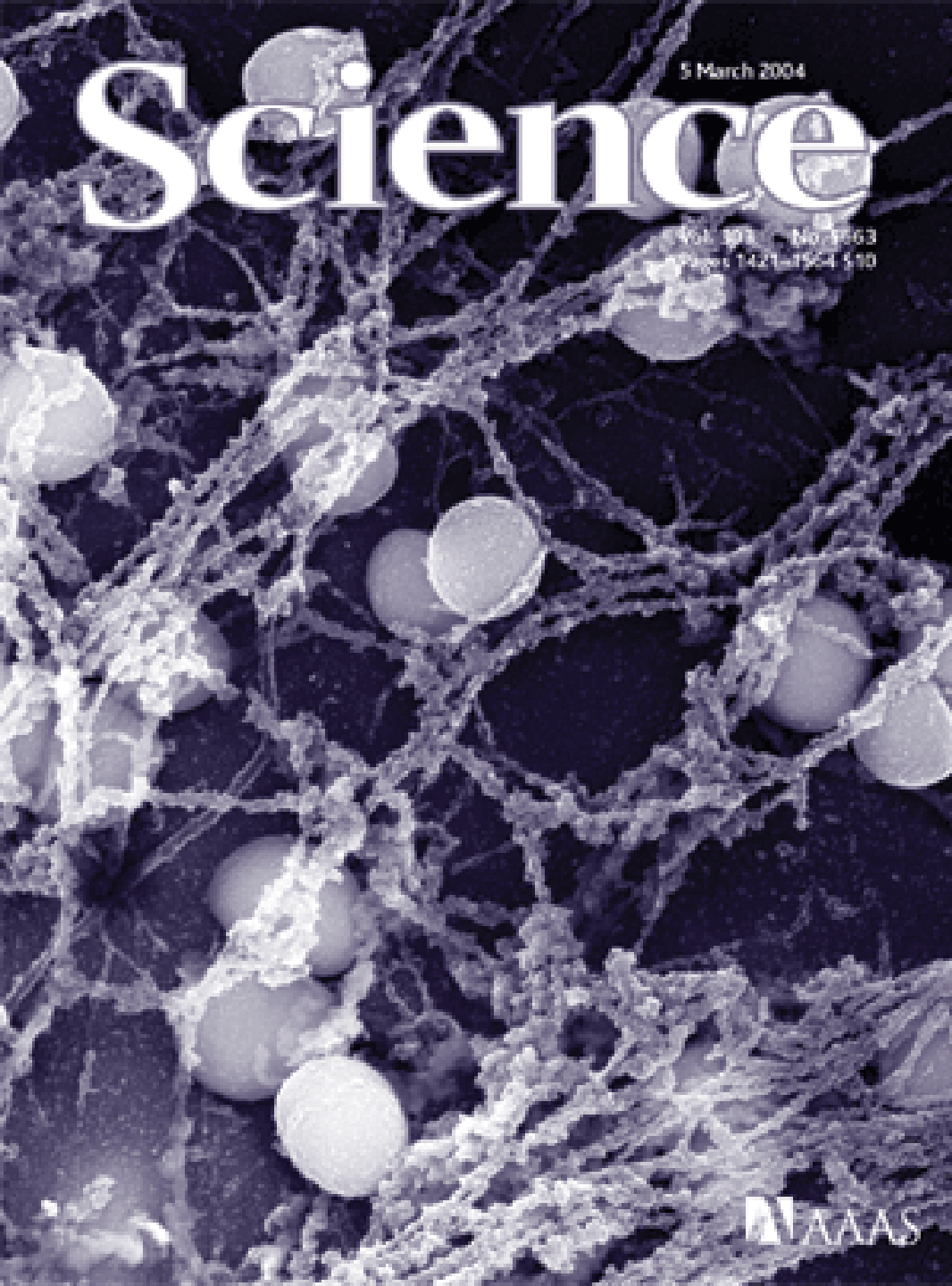
- One of the main effector cells in the innate immune system
- 50-70% of white blood cells
- Released from bone marrow, circulate 7-10 hrs, enter tissues, live only a few days
- Numbers & recruitment increases during infections~ “leukocytosis”~ diagnostic
- shown to kill microorganisms by phagocytosis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

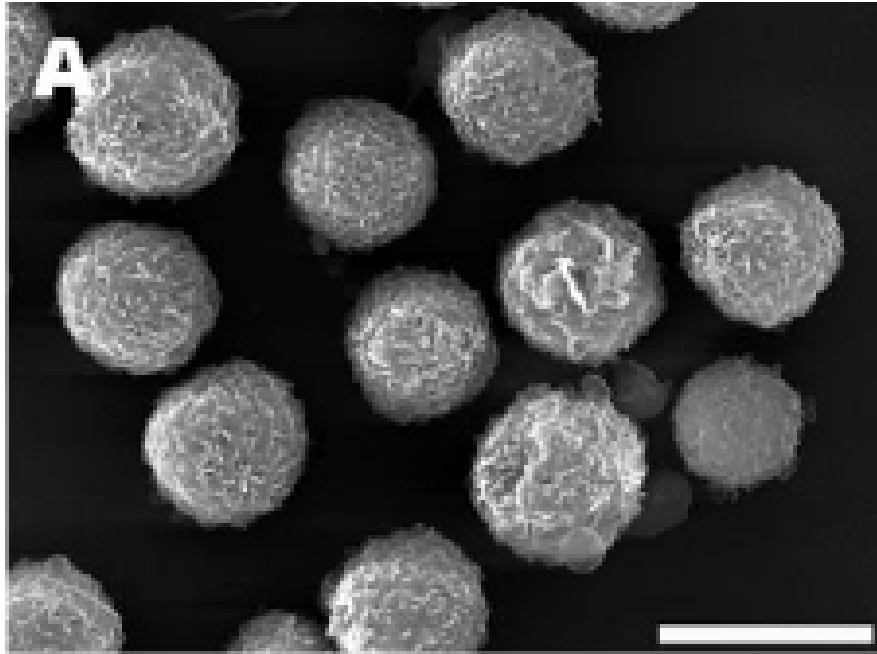




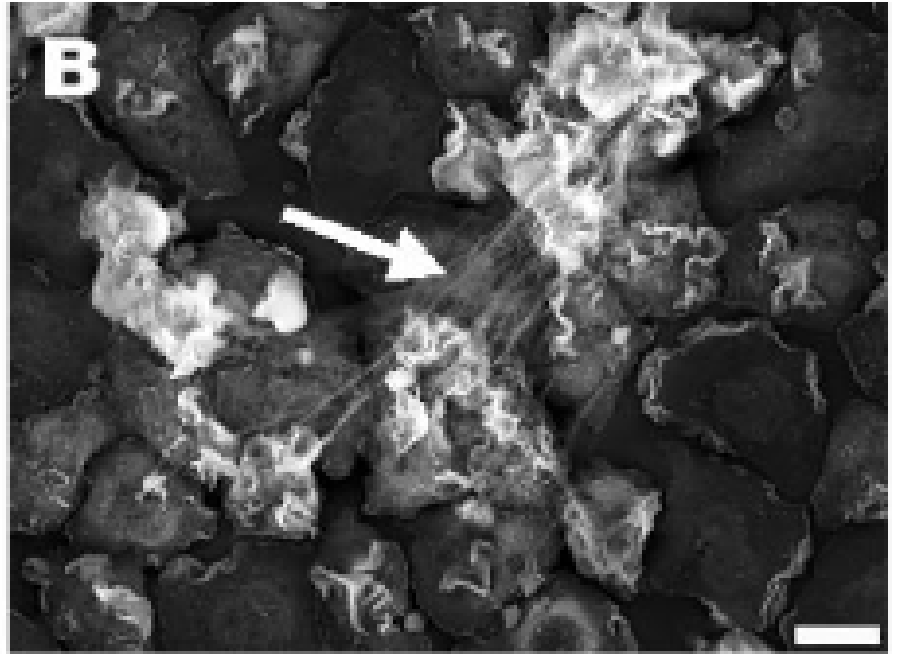
## COVER

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

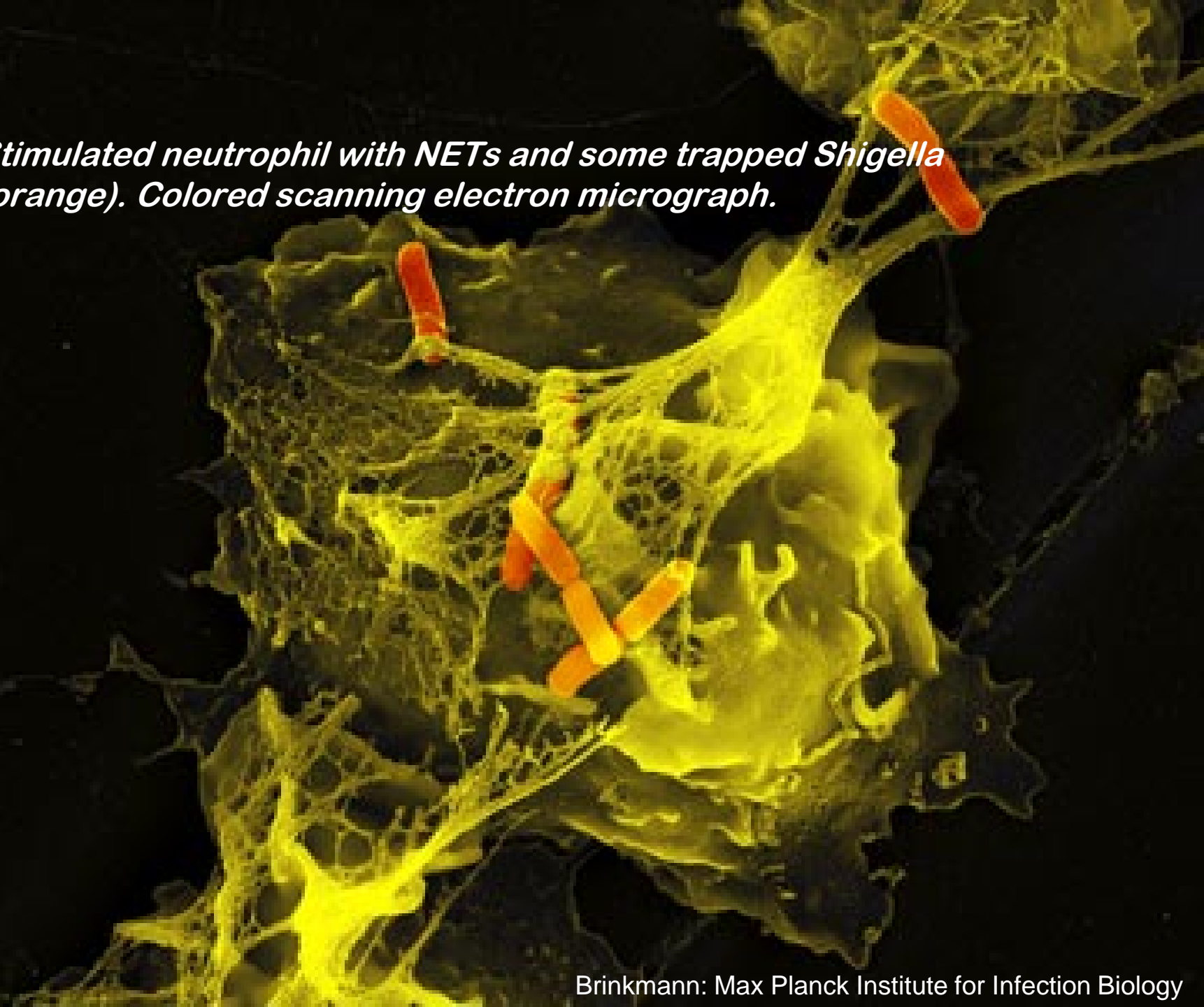


neutrophils activated

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

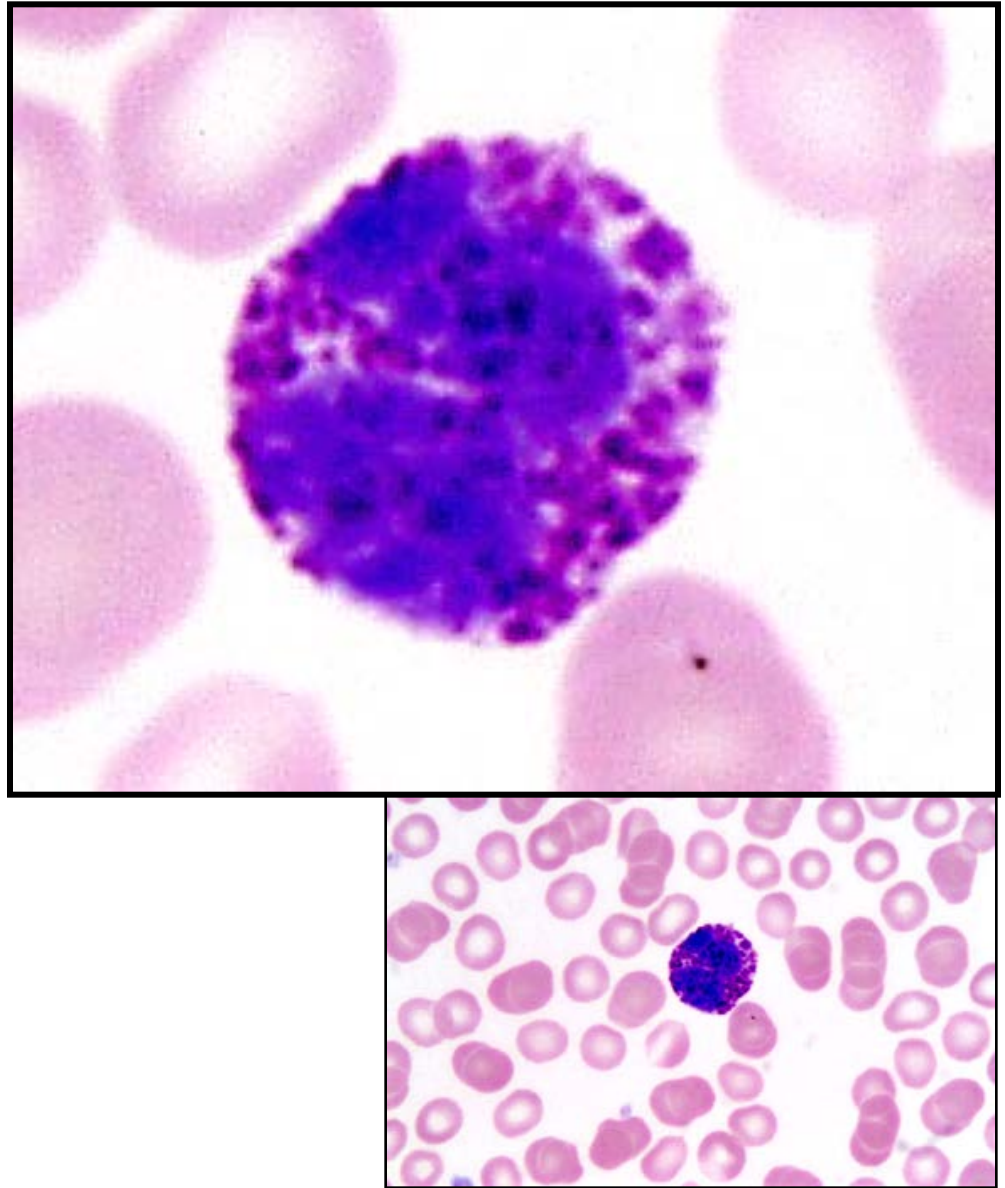


*Stimulated neutrophil with NETs and some trapped Shigella (orange). Colored scanning electron micrograph.*

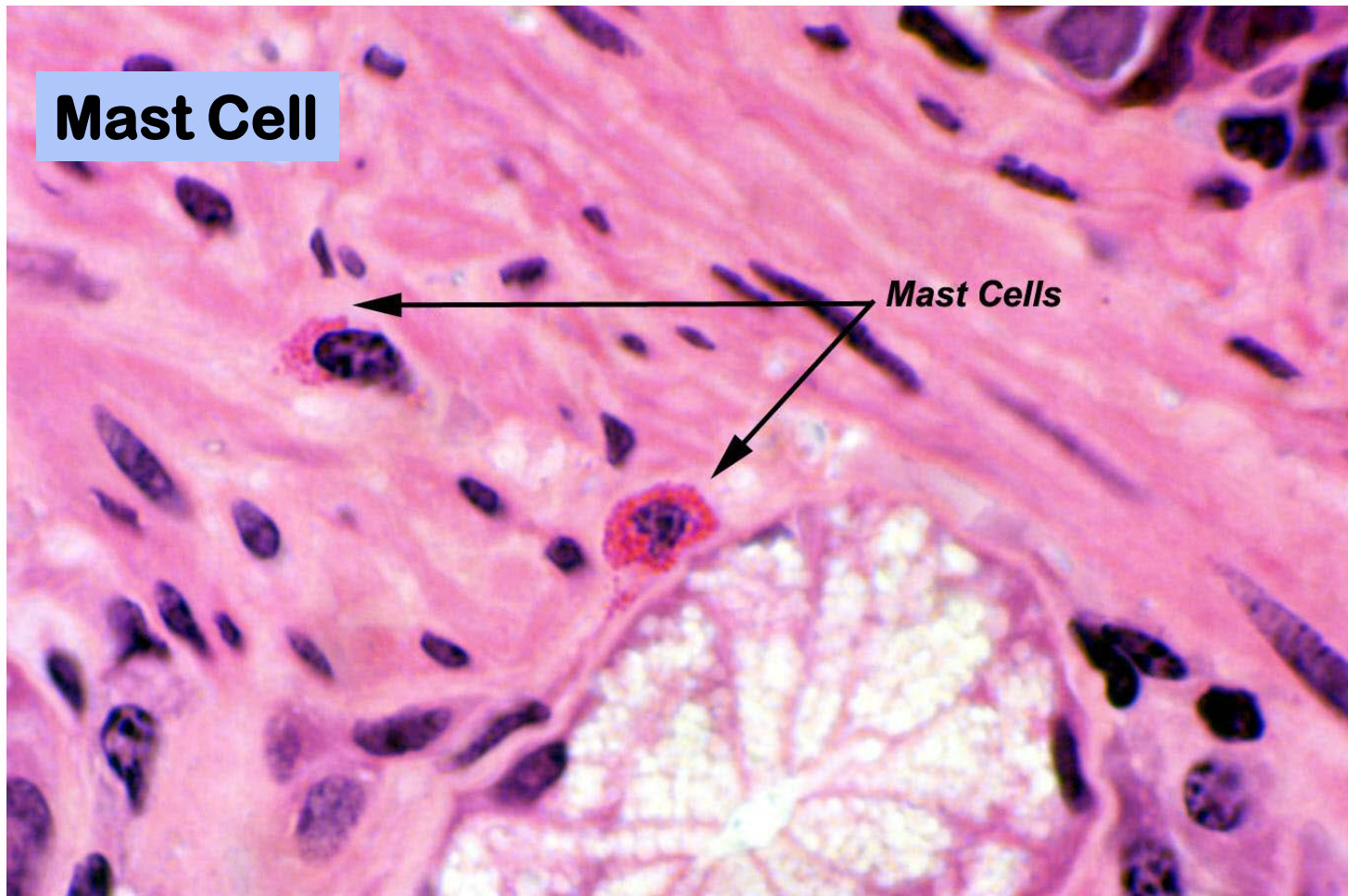


# Basophil

- <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



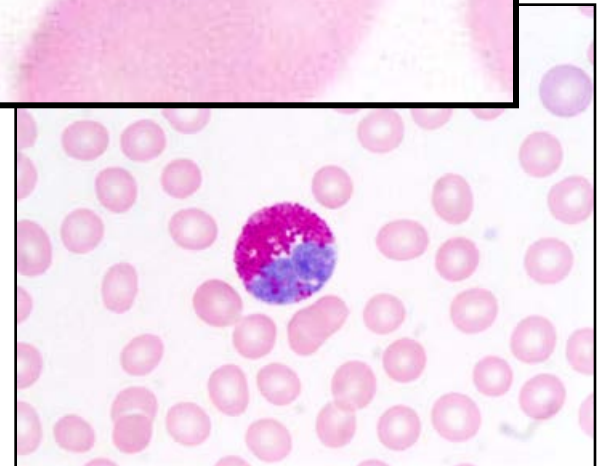
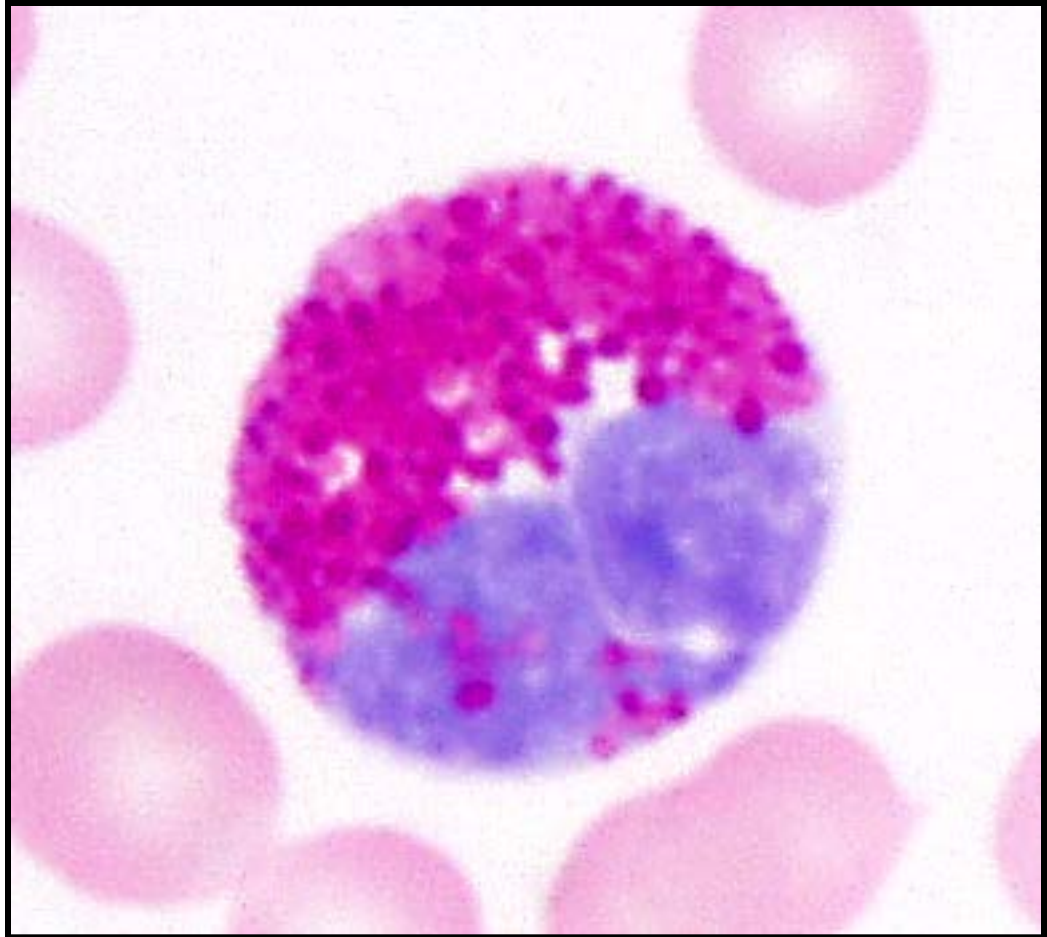
## Mast Cell



- 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



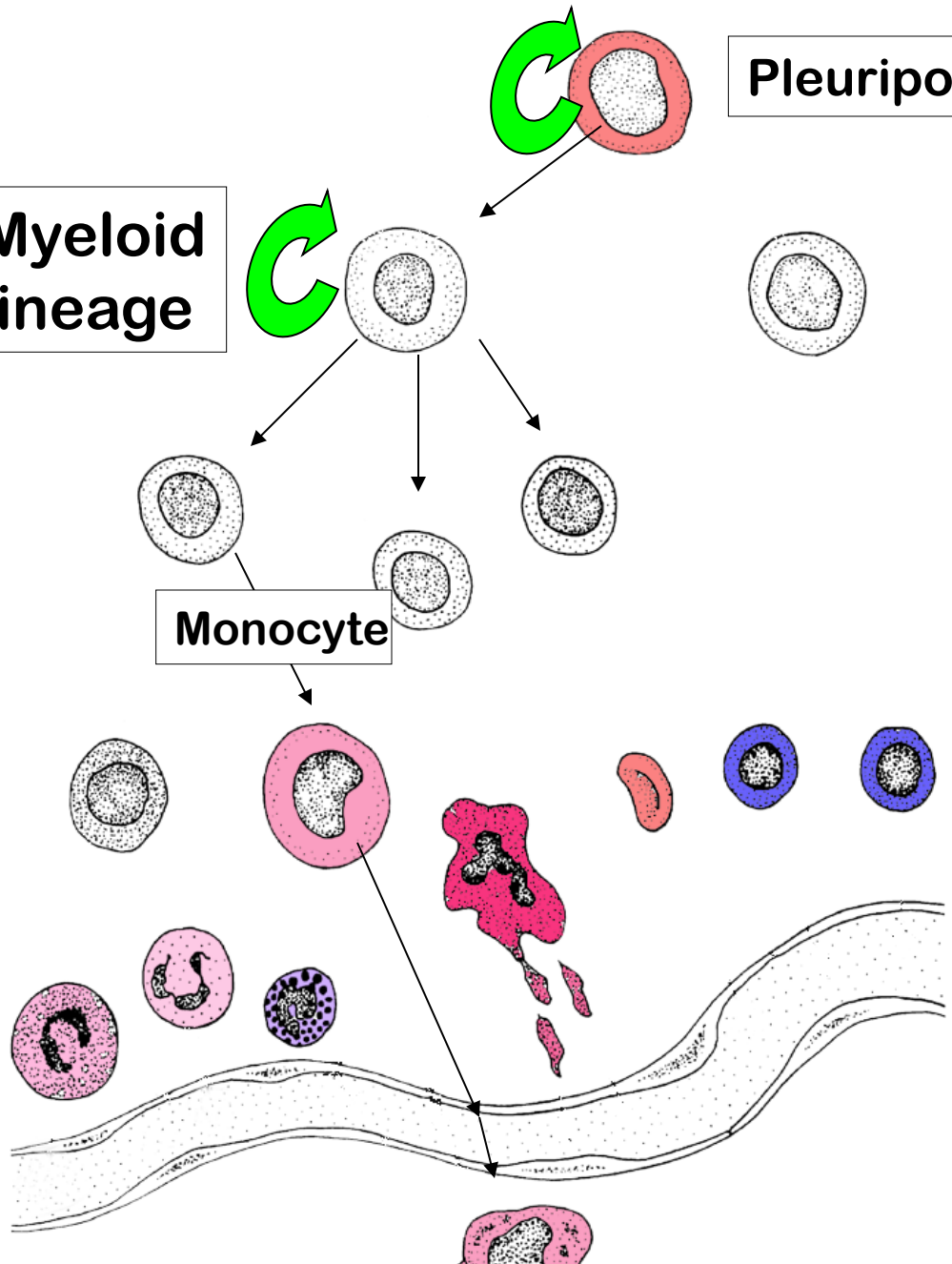
# Myeloid antigen presenting cells:

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

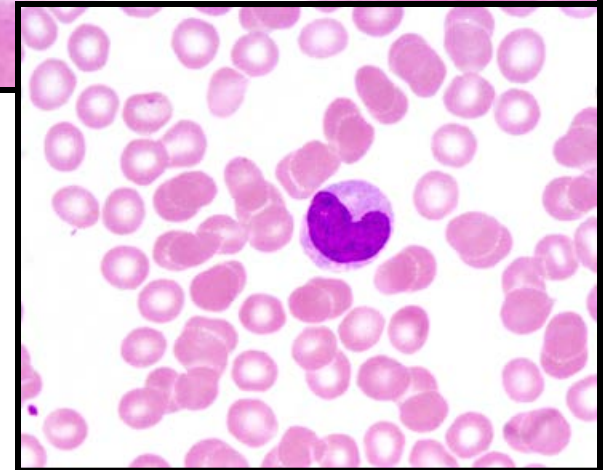
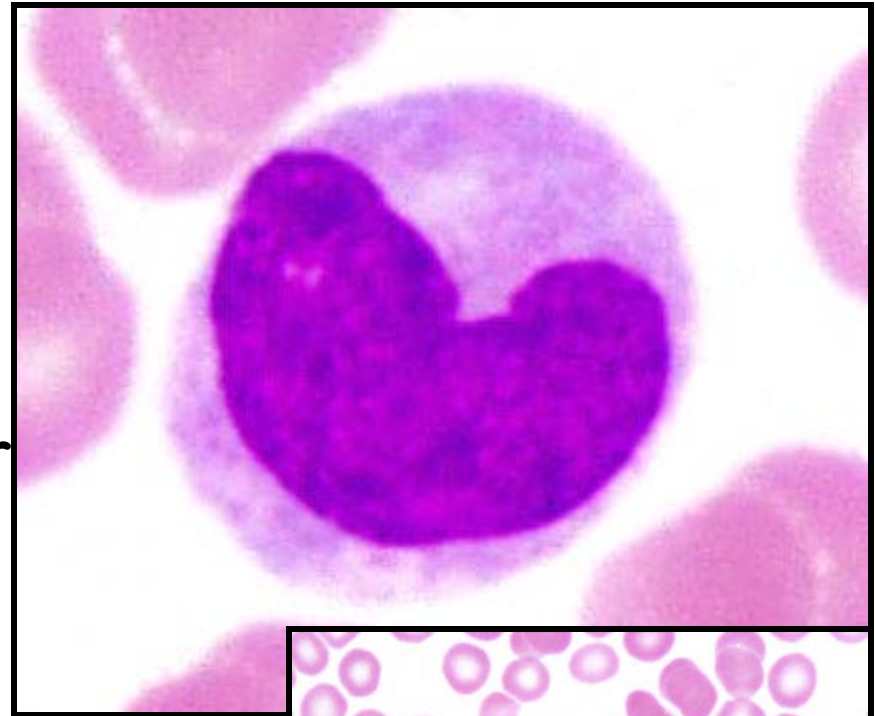


Monocyte

Monocytes- macrophages & DCs

# Monocyte

- Mononuclear
- Circulate in blood ~ 8 hrs
- Bean-shaped nucleus
- Enter tissues and become fully mature macrophages or dendritic cells
  - Enlarges
  - Becomes phagocytic
- Free vs fixed tissue m $\Phi$ 
  - Special names in different organs- Kupffer cells-liver
- Digest and/or *present* Ag
- Surface receptors for Abs (opsinized Ags)



# 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)

## Macrophage

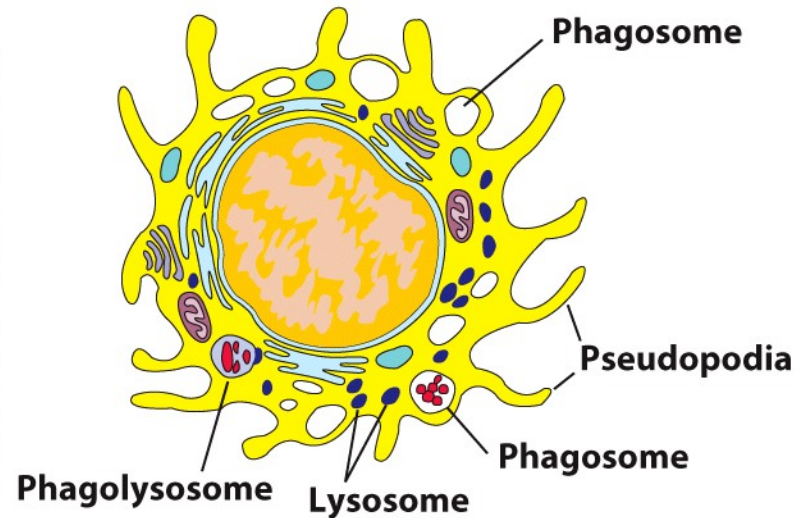
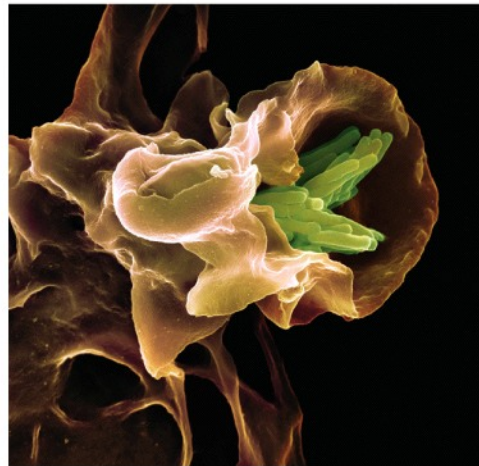
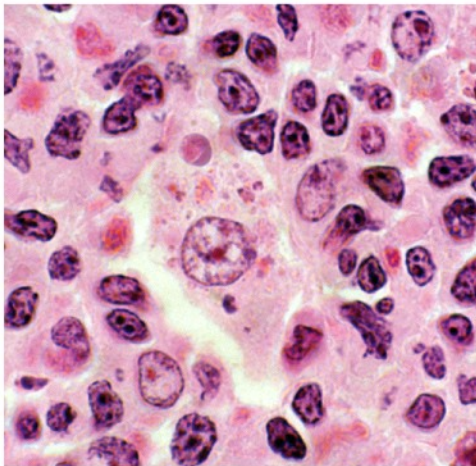


Figure 2-3b

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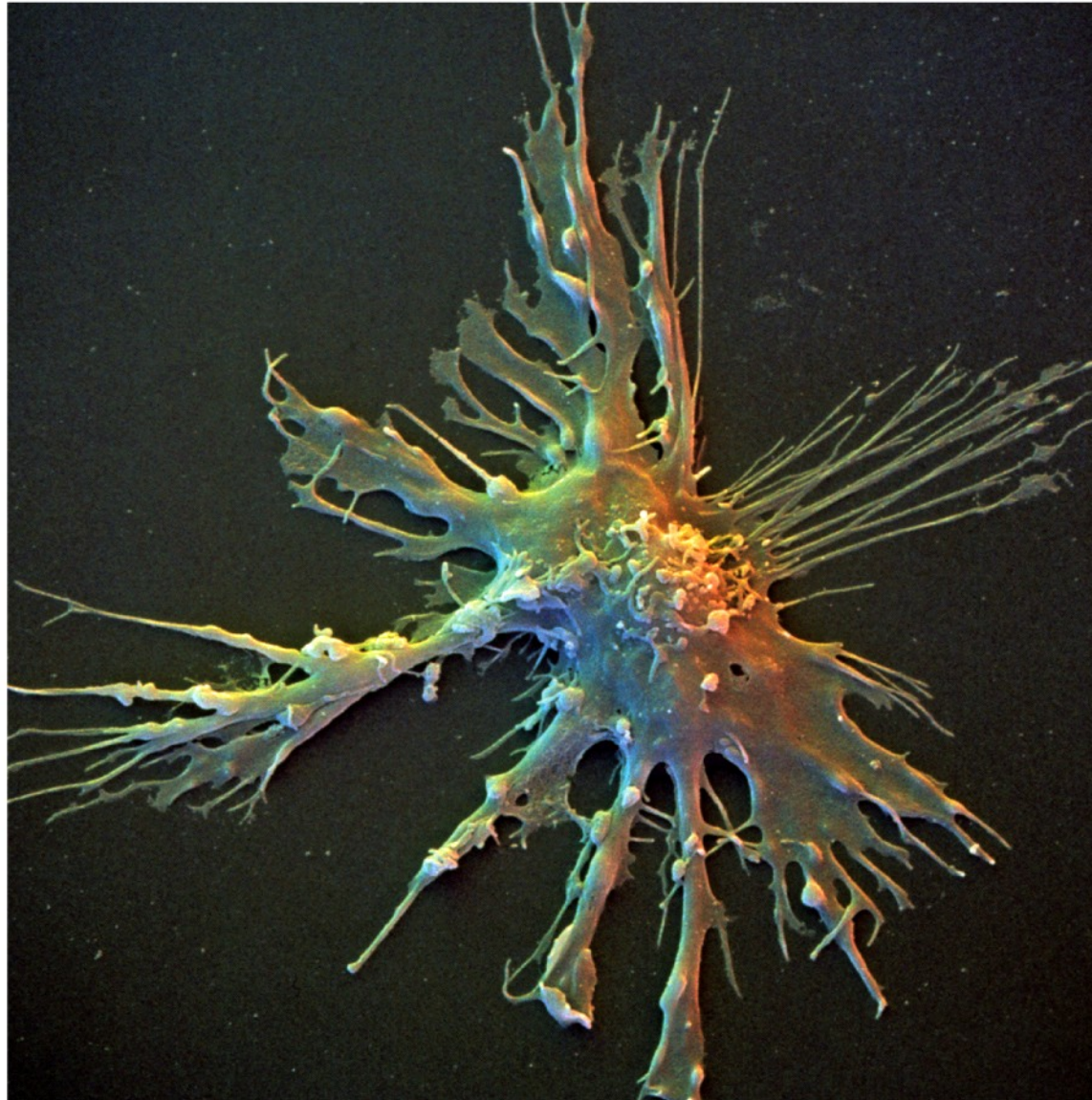


# **Dendritic cells:**

**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**

# Dendritic cell



**Figure 2-3c part 1**

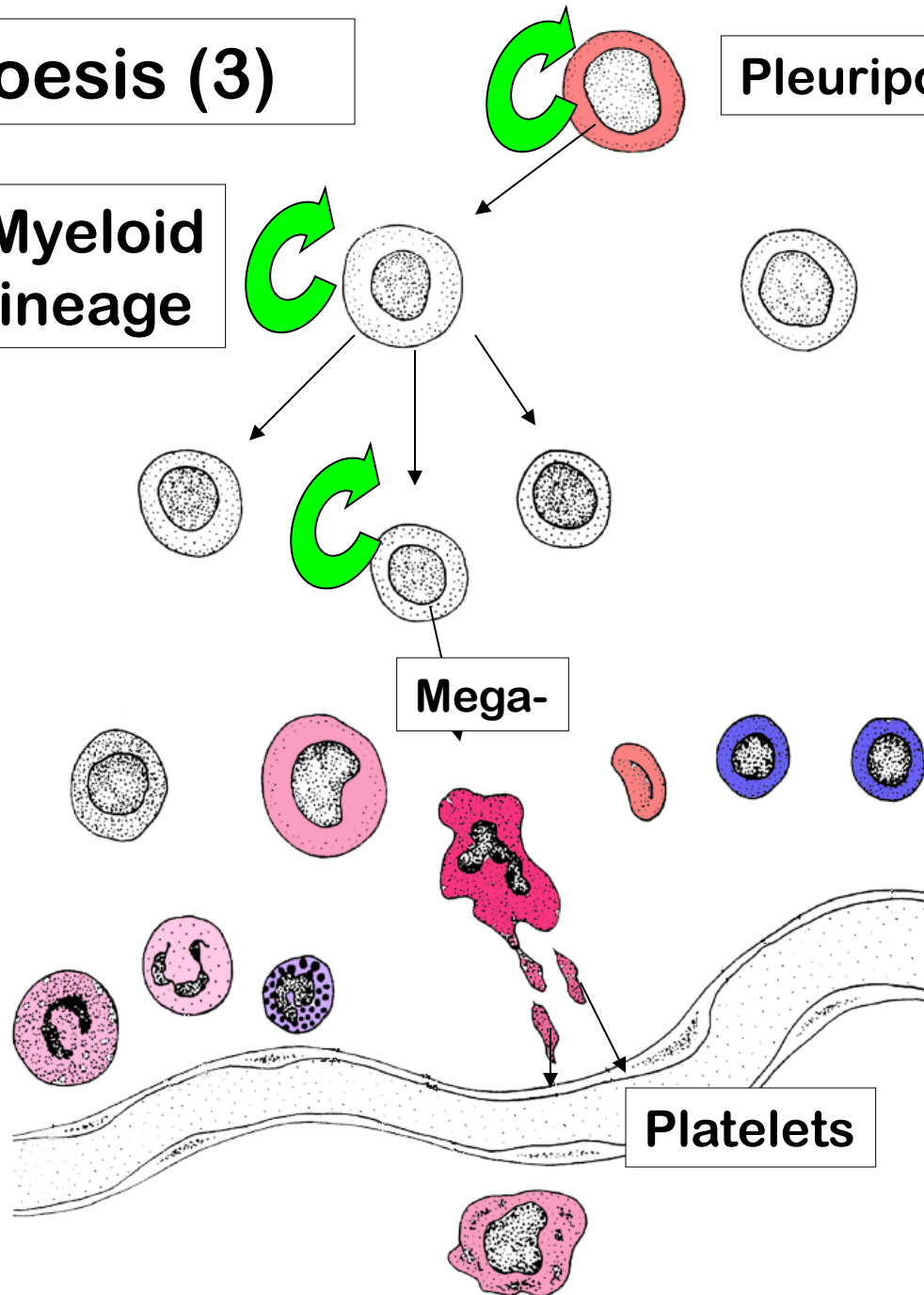
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# Hematopoiesis (3)

Pleuropotent Stem Cell

Myeloid lineage



# Megakaryocyte

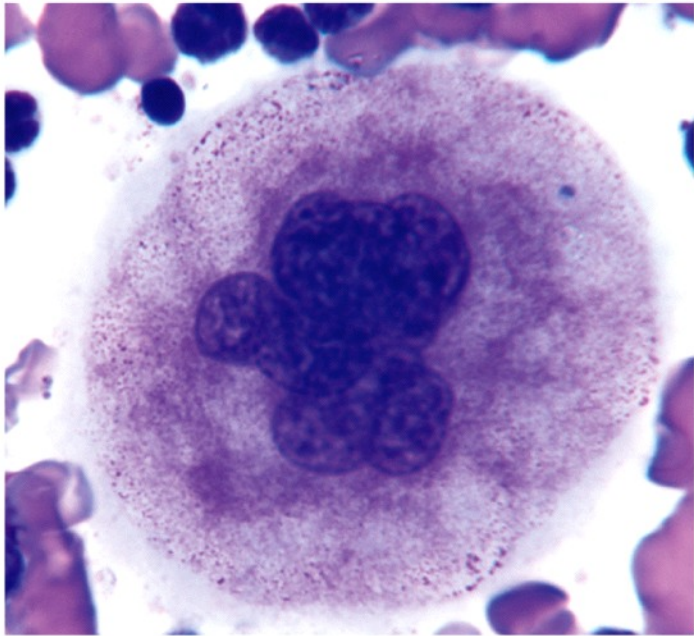
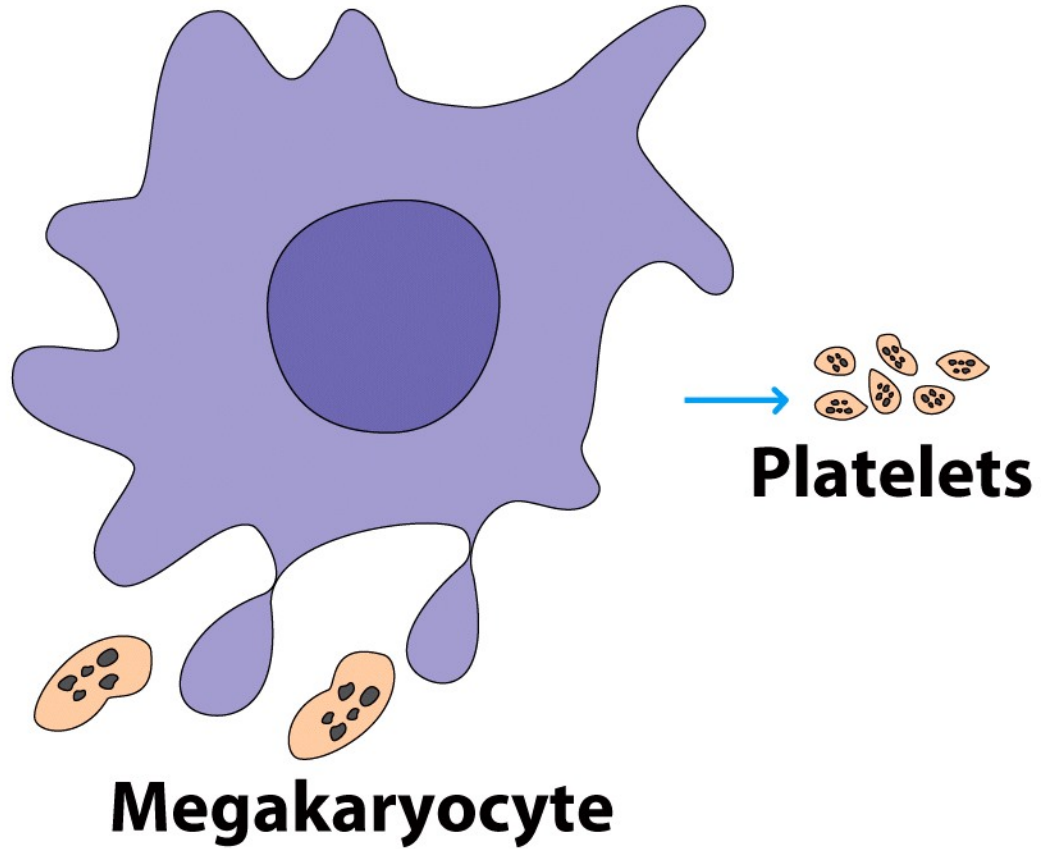
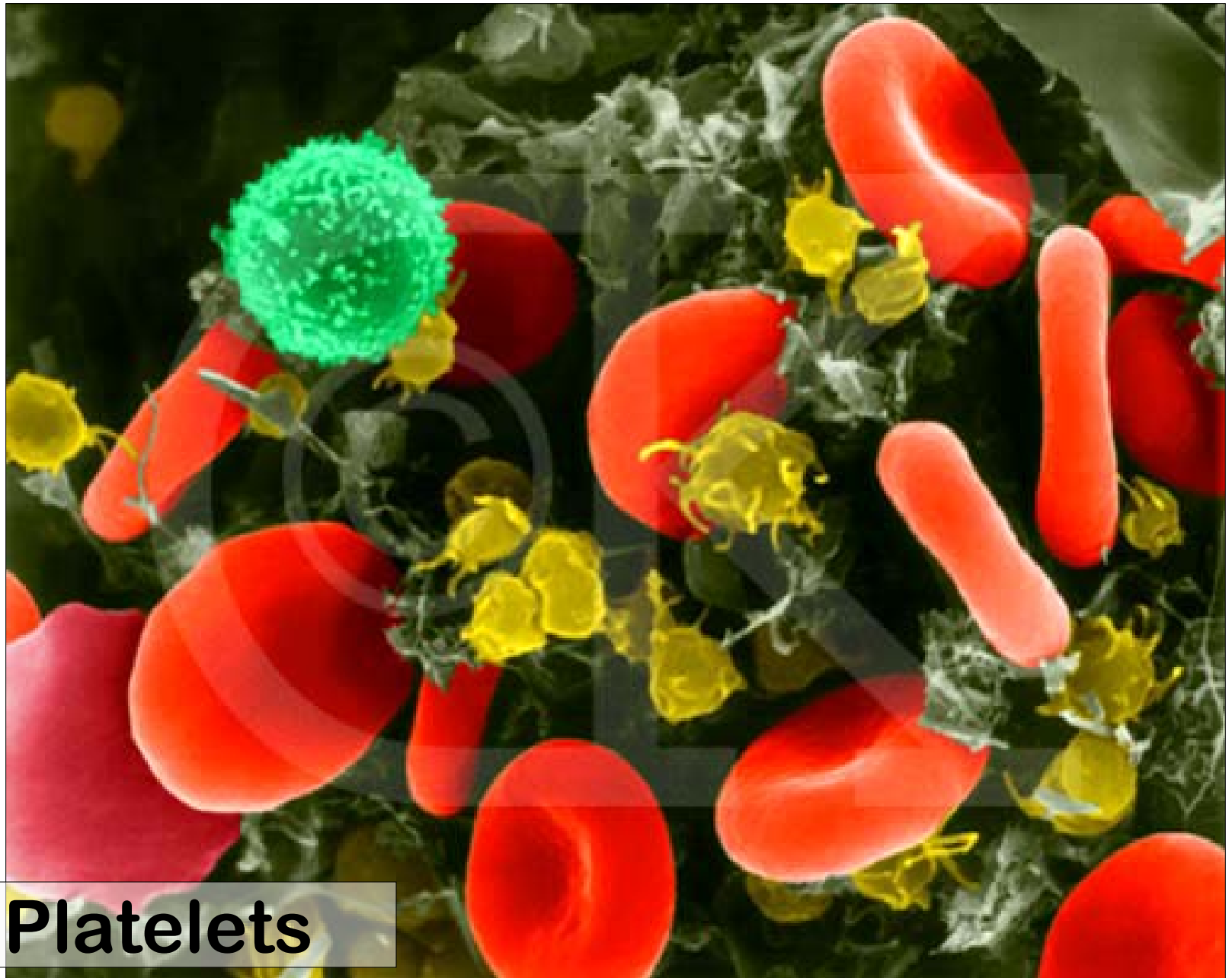


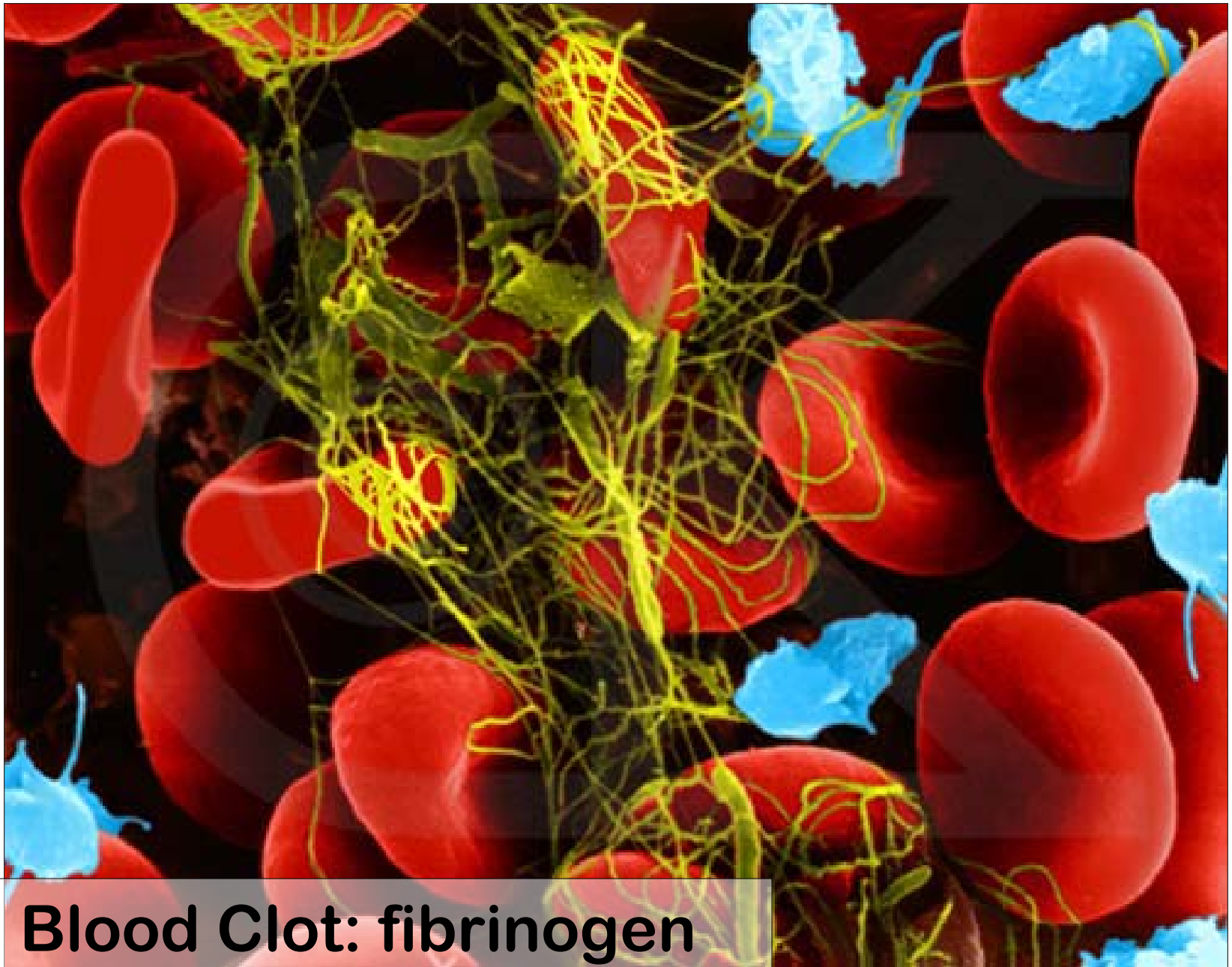
Figure 2-3d

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**Platelets**



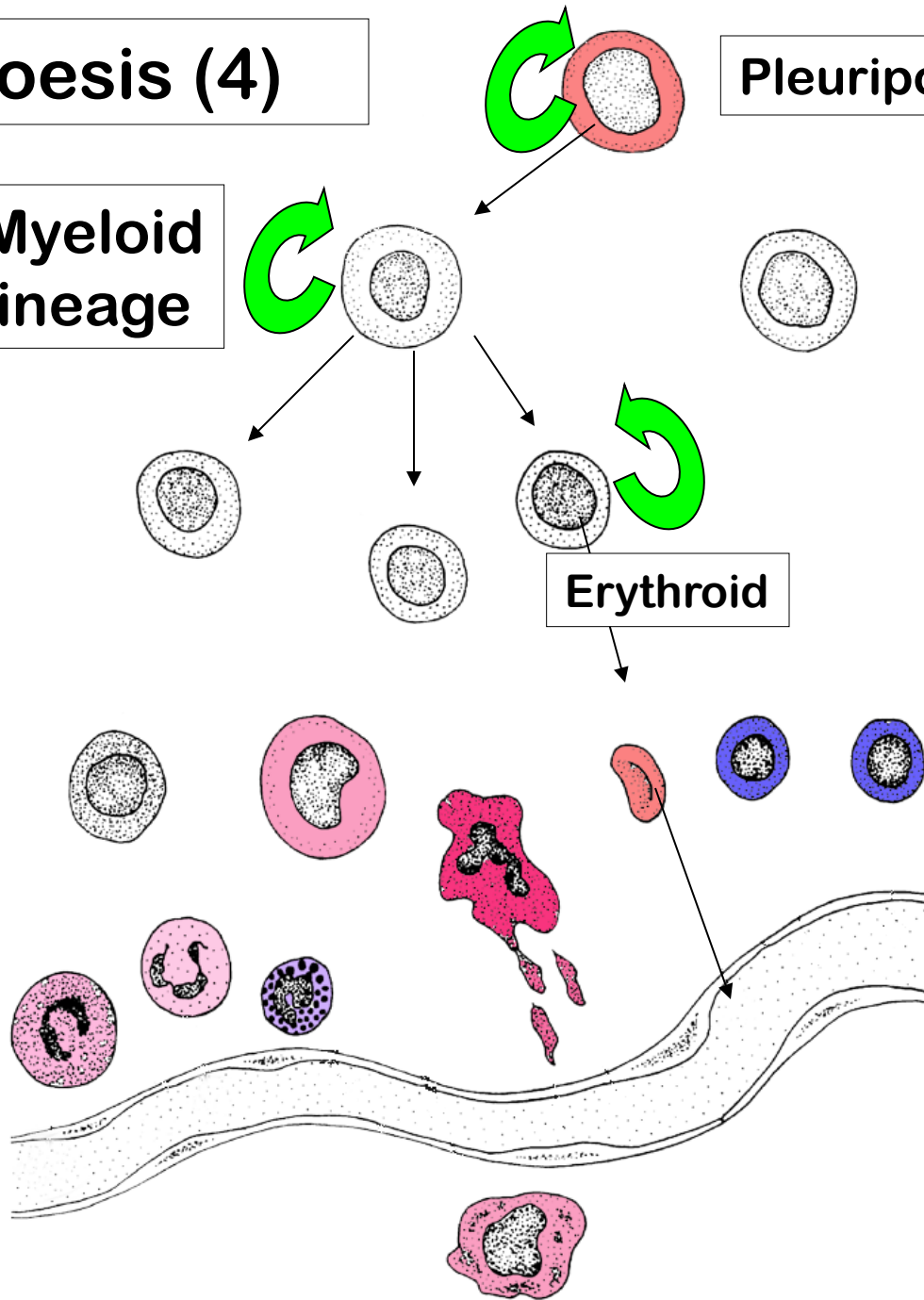
**Blood Clot: fibrinogen**

# Hematopoiesis (4)

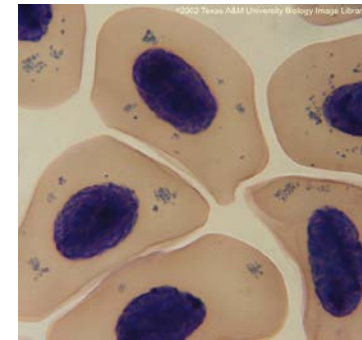
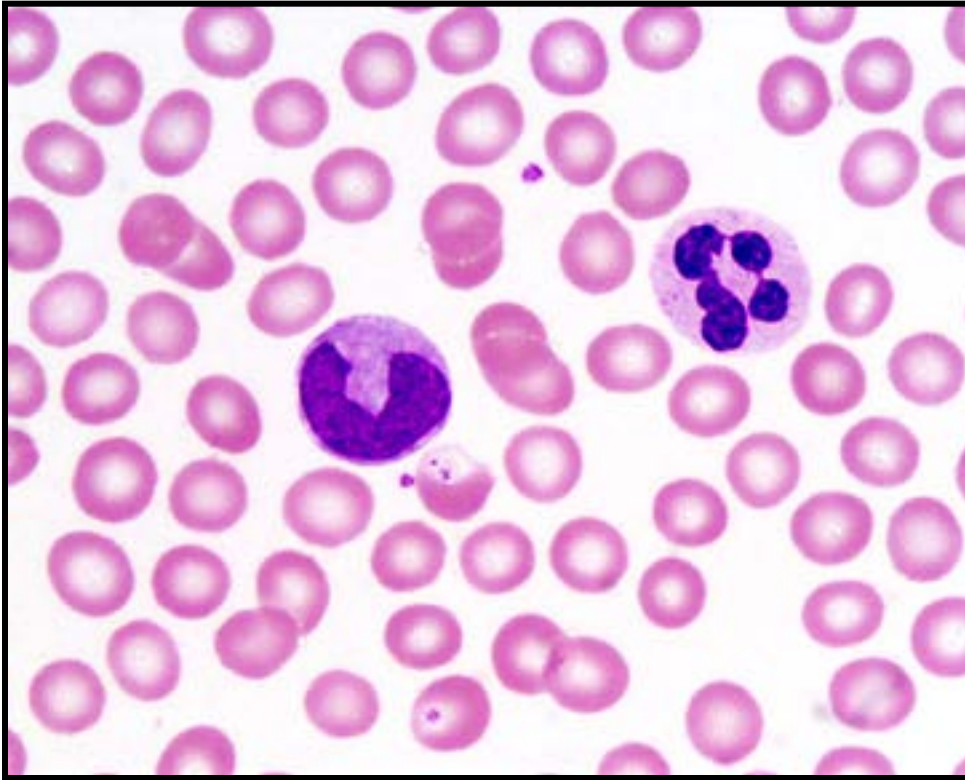
Pleuropotent Stem Cell

Myeloid lineage

Erythroid



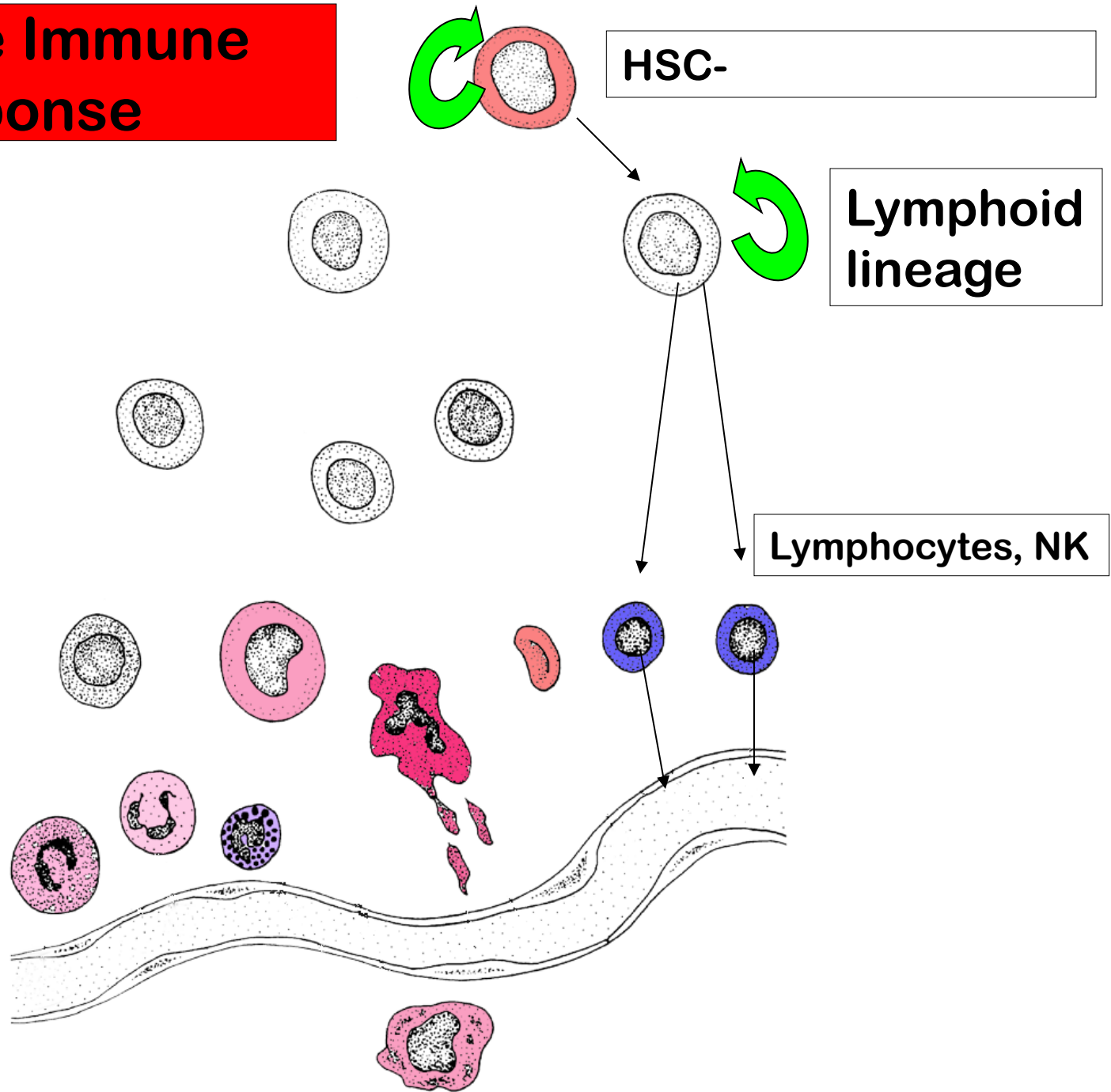
**Mature human and mouse RBCs have no nuclei**



**Salamander RBCs**



# Adaptive Immune Response

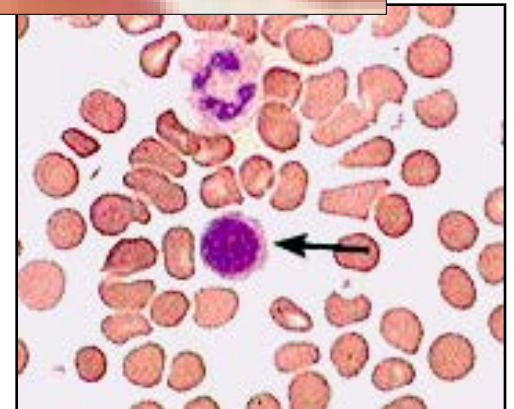
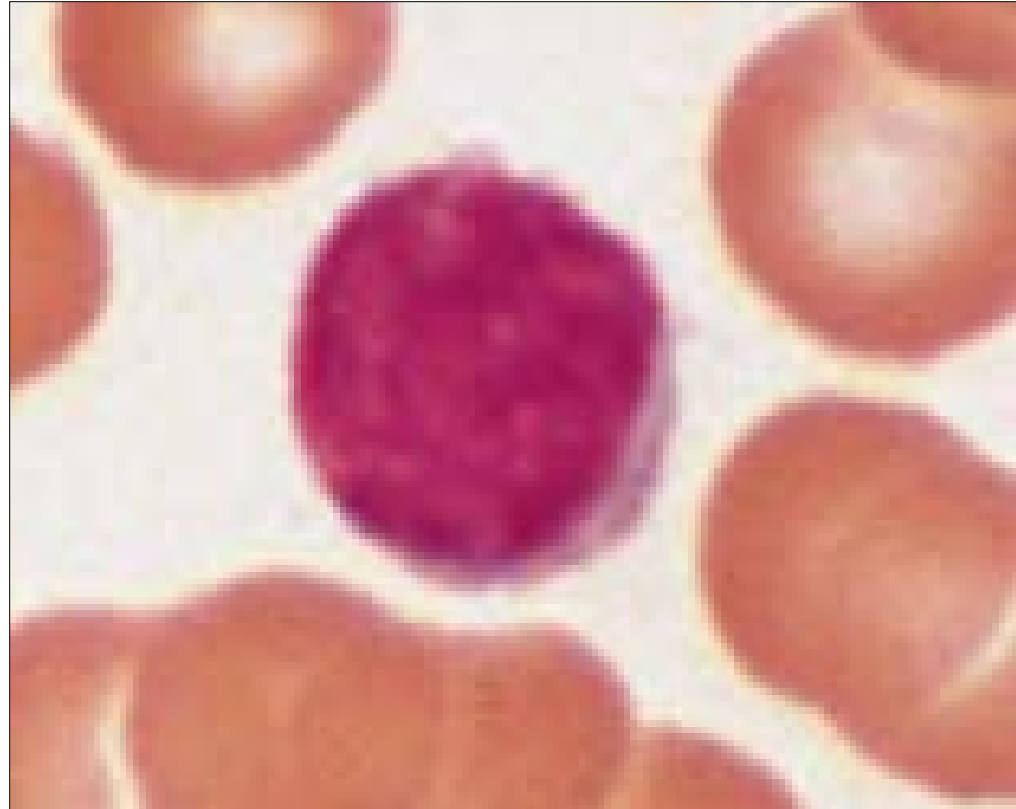


# Lymphocytes: 3 types

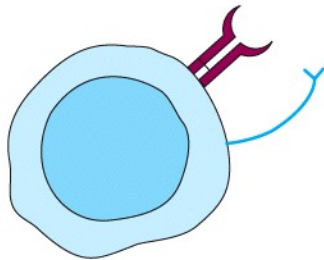
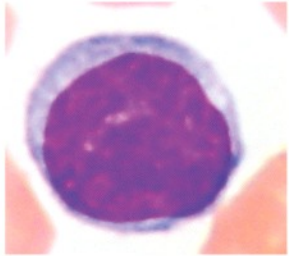
- **20-40% of WBC**
- **Cannot be distinguished morphologically**
- **T-cells**
  - helper CD4+ recognize Ag in context of MHCII
  - cytotoxic CD8+ recognize Ab in MHCI
- **B-cells**
  - become antibody producing plasma cells
- **NK cells**
  - part of the innate immune response

# T and B Lymphocytes

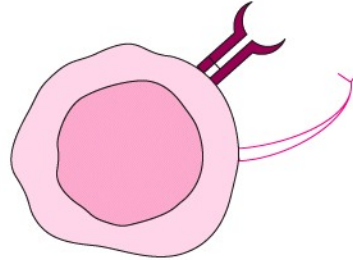
- Large nucleus with dense heterochromatin
- Thin rim of cytoplasm
- Recognizes specific antigenic determinants
- Therefore are responsible for specificity and memory of the adaptive immune response



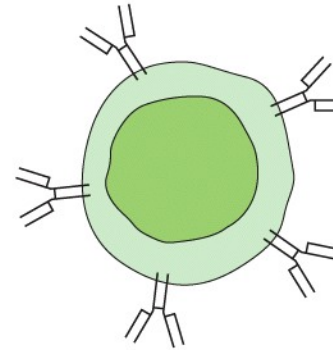
(a) Lymphocyte



TH helper cell

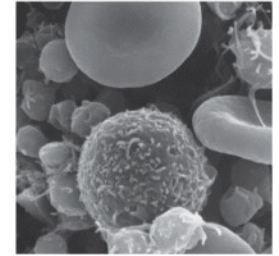


TC cytotoxic T cell

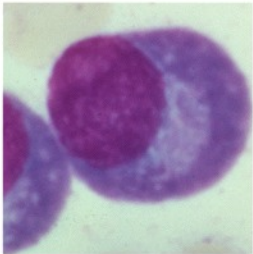


B cell

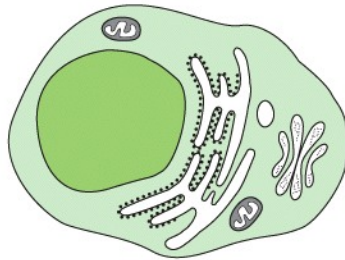
(b) Lymphocyte with red blood cells



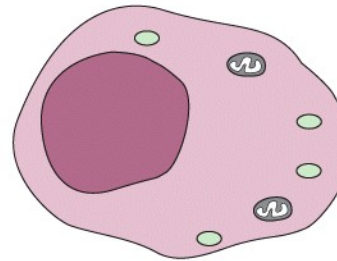
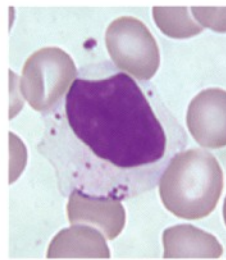
(c) Plasma cell



Plasma cell



(d) NK cell



Natural killer (NK) cell

(e)

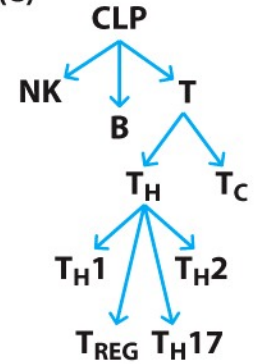


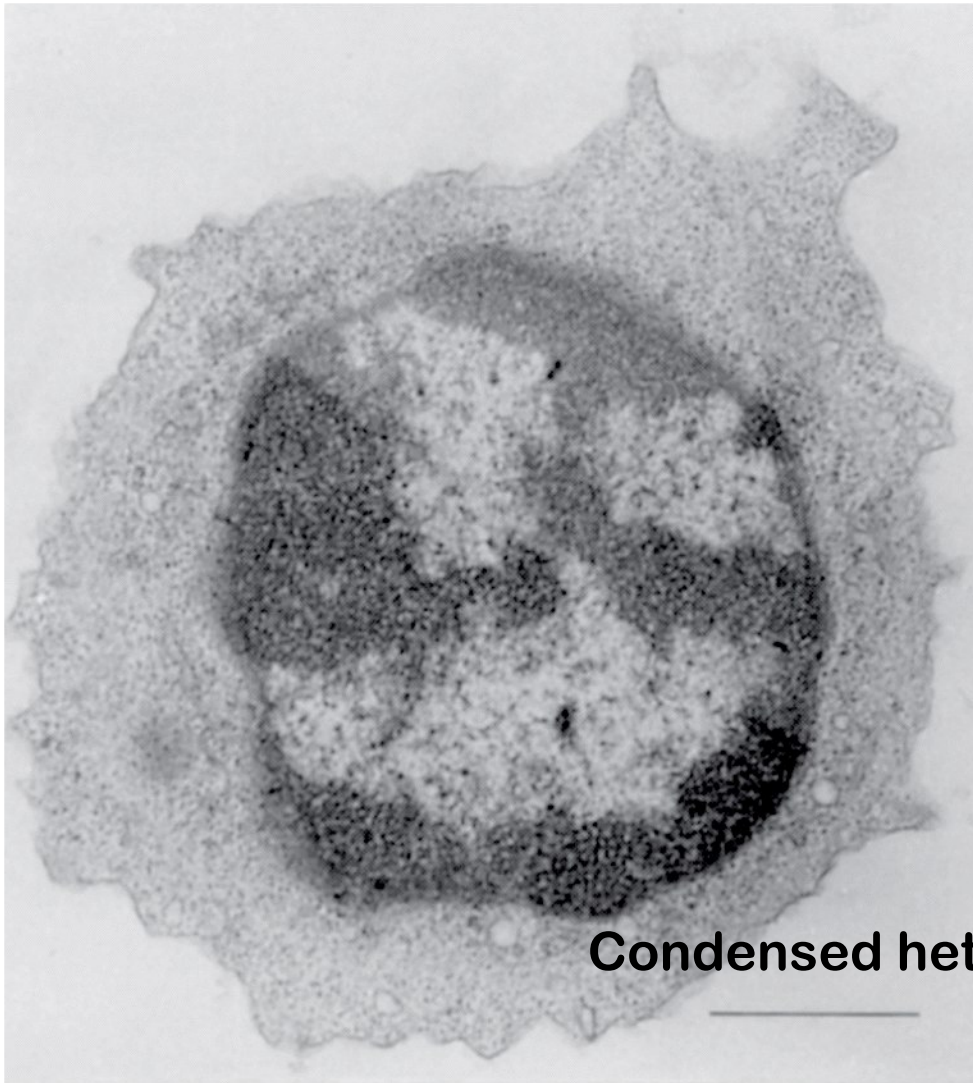
Figure 2-4

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

CD designation*	Function	B cell	T cell		NK cell
			T <sub>H</sub>	T <sub>C</sub>	
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 (Fc $\gamma$ RIII)	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 (Fc $\gamma$ RII)	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.



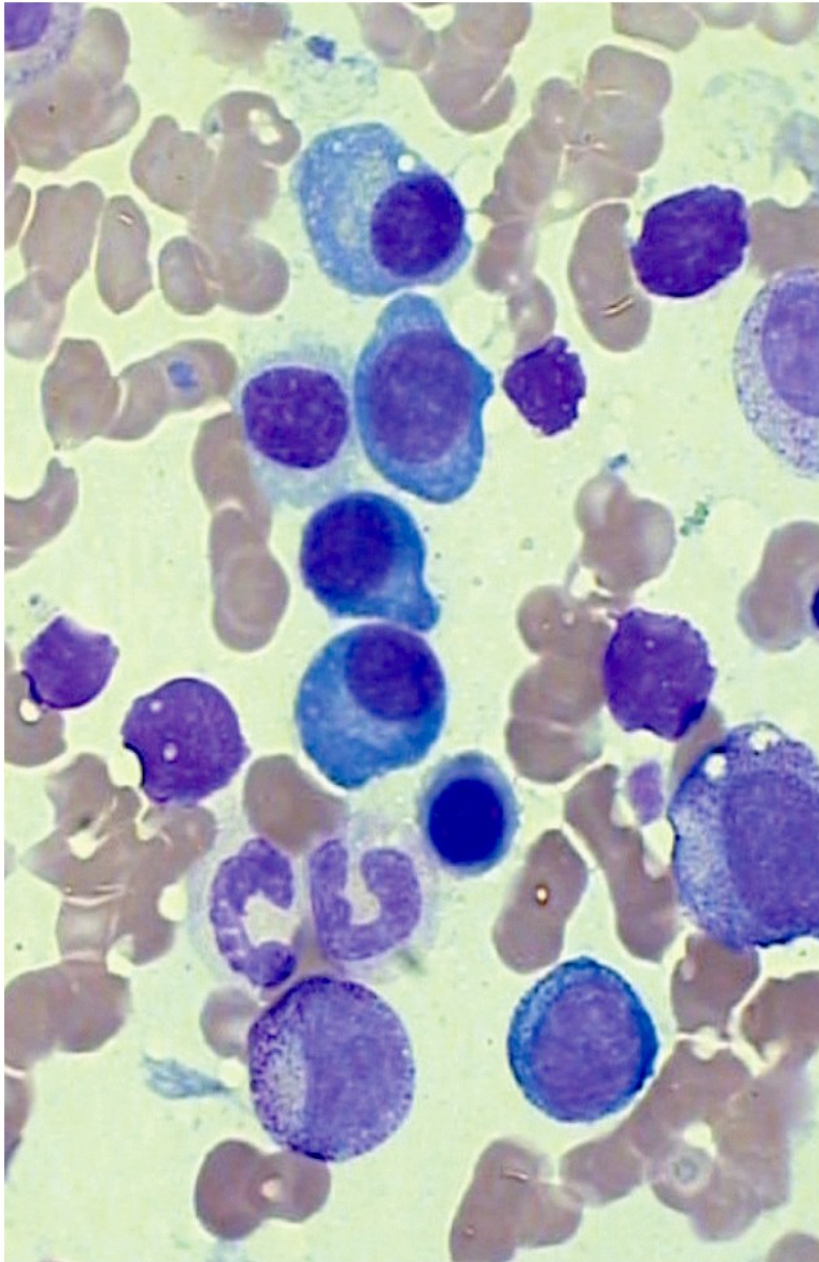
Condensed heterochromatin= resting

**Small lymphocyte (T or B)  
6  $\mu\text{m}$  diameter**



Decondensed chromatin= active

**Blast cell (T or B)**  
**15  $\mu\text{m}$  diameter**



**Plasma cell  
Perinuclear golgi  
and abundant  
layers of  
endoplasmic  
reticulum**





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

## **Plasma cell (B)** **15 $\mu\text{m}$ diameter**

# Mononucleosis



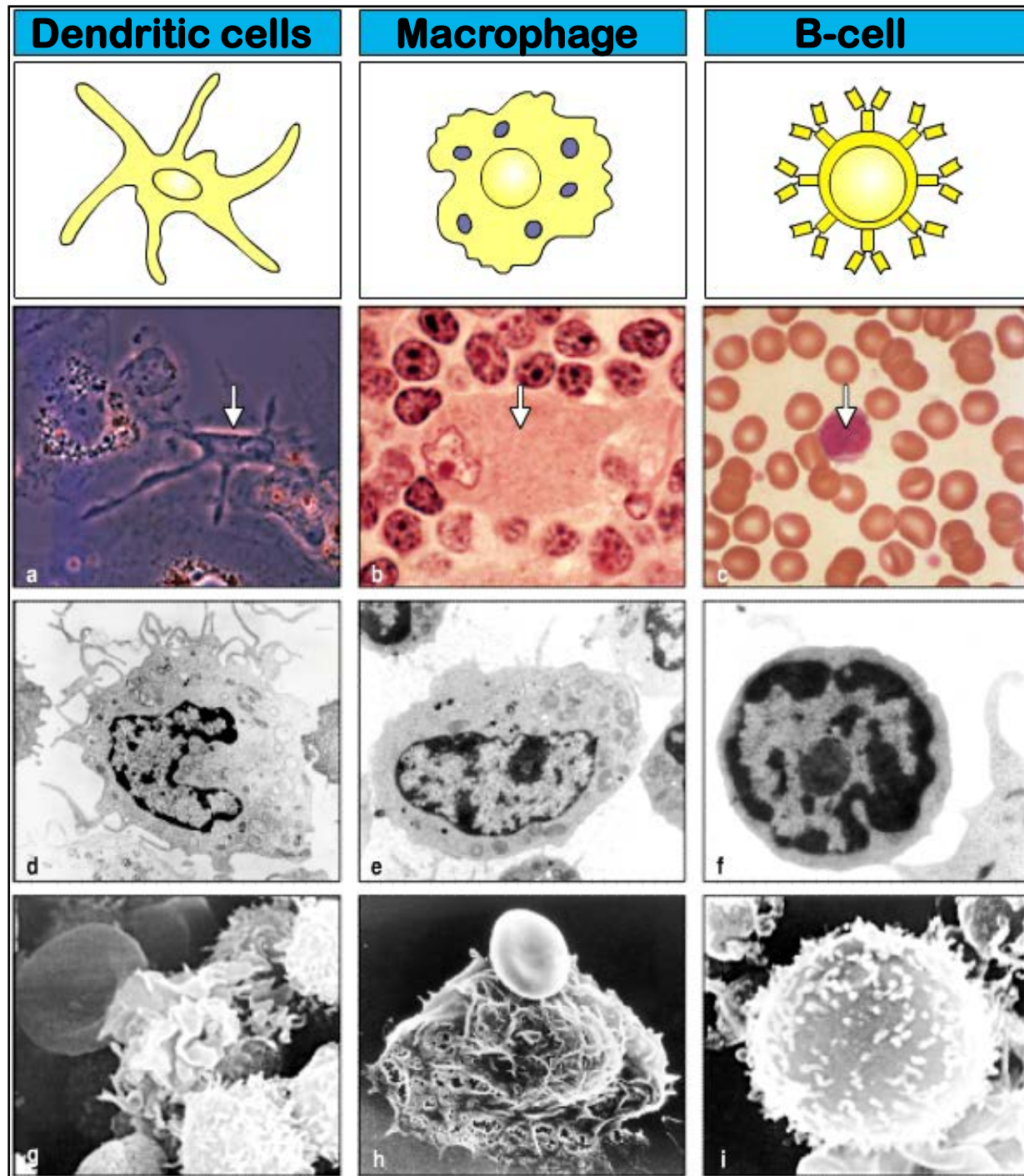
- **Caused by Epstein-Barr virus**
  - DNA herpes-types virus
- **Infects 2 cell types**
  - First epithelial cells of salivary gland- virus released in saliva
  - Then B lymphocytes via CD21
- **Circulating B cells spread virus**
  - to “reticuloendothelial system (liver, spleen, lymph nodes)
- **Symptoms**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

# Antigen Presenting Cells

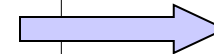
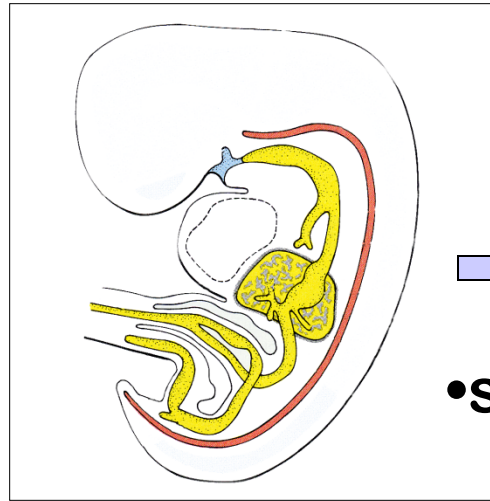
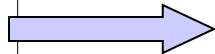
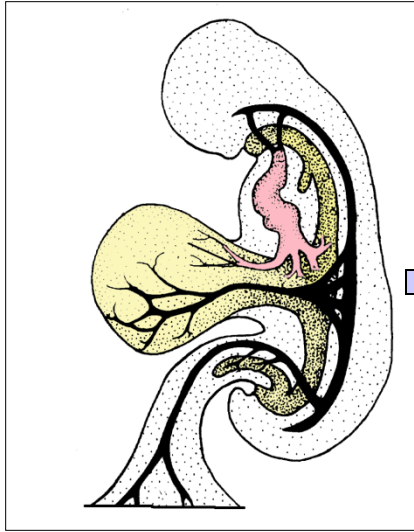
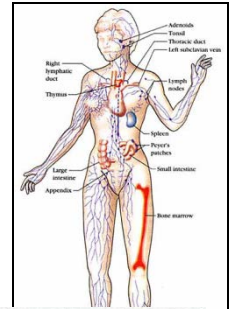
3 kinds of cells present Ag to T-cells

Dendritic cells:  
Several types

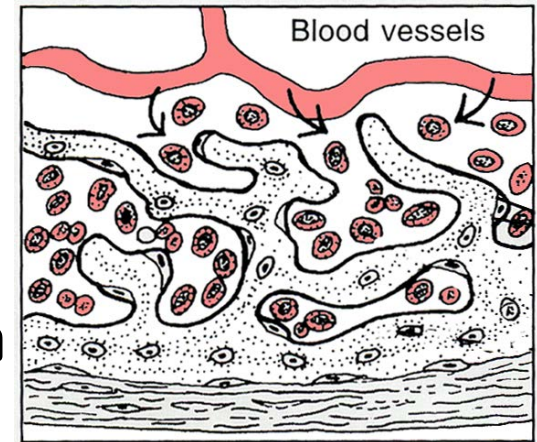
Capture, process,  
present Ag



# Organs of Hematopoiesis...



•spleen



## Yolk Sac

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

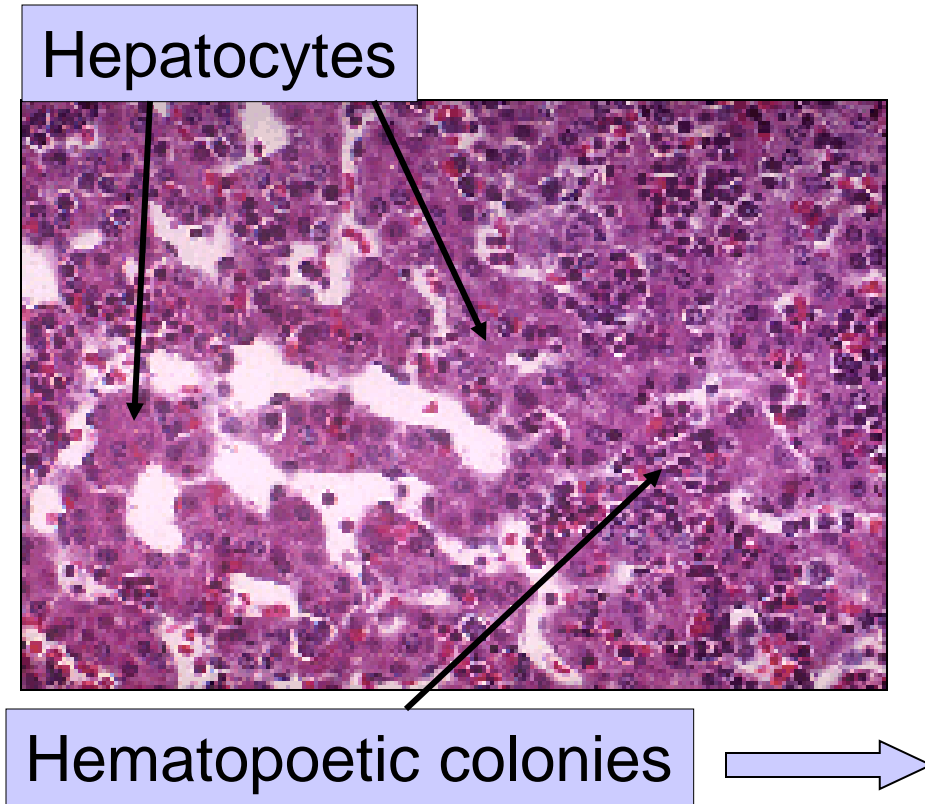
## Fetal Liver

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

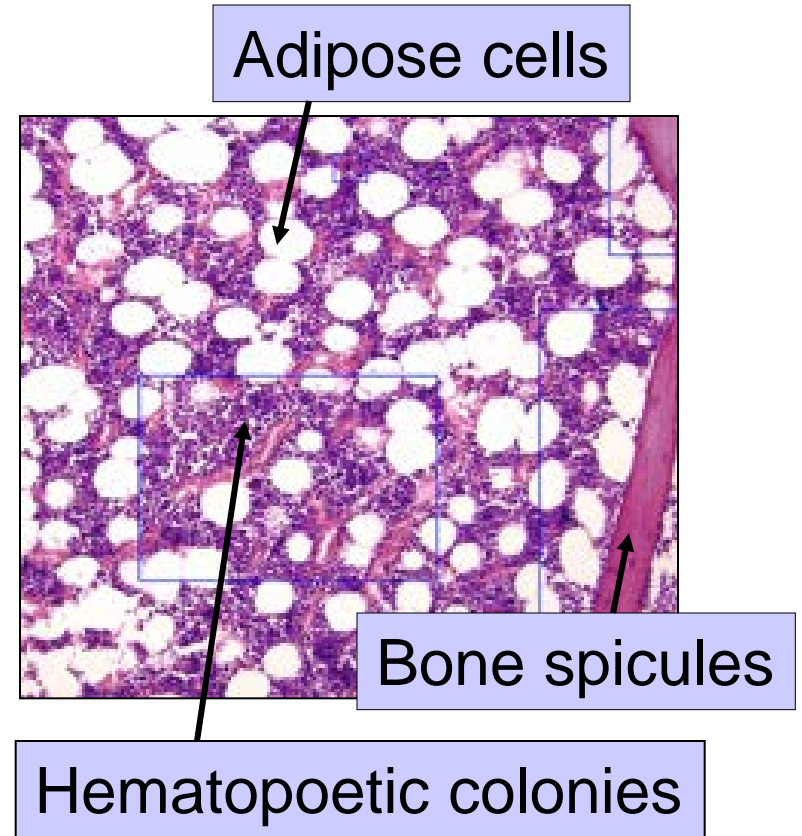
## Bone Marrow

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

# Organs of Hematopoiesis



Fetal Liver



Bone Marrow

# Organs of the Immune System

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

2. Distribution to Secondary lymphoid organs for engagement with antigens

T lymphocytes

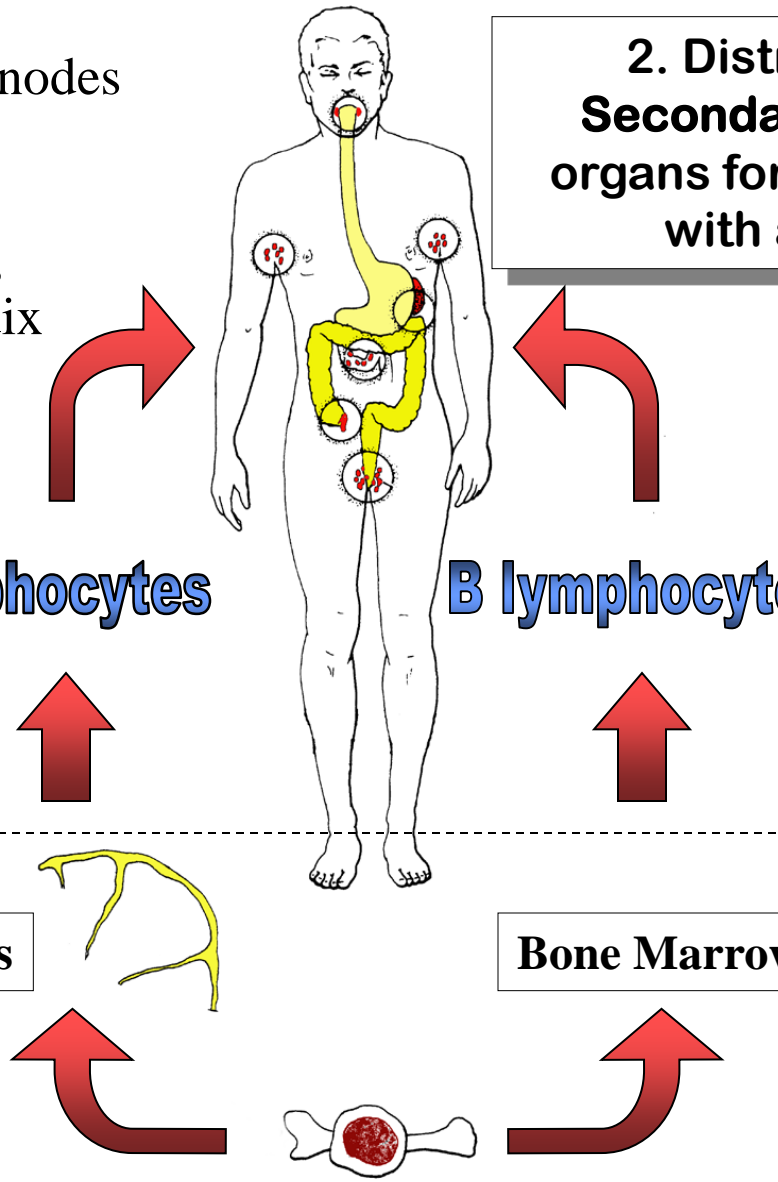
B lymphocytes

Thymus

Bone Marrow

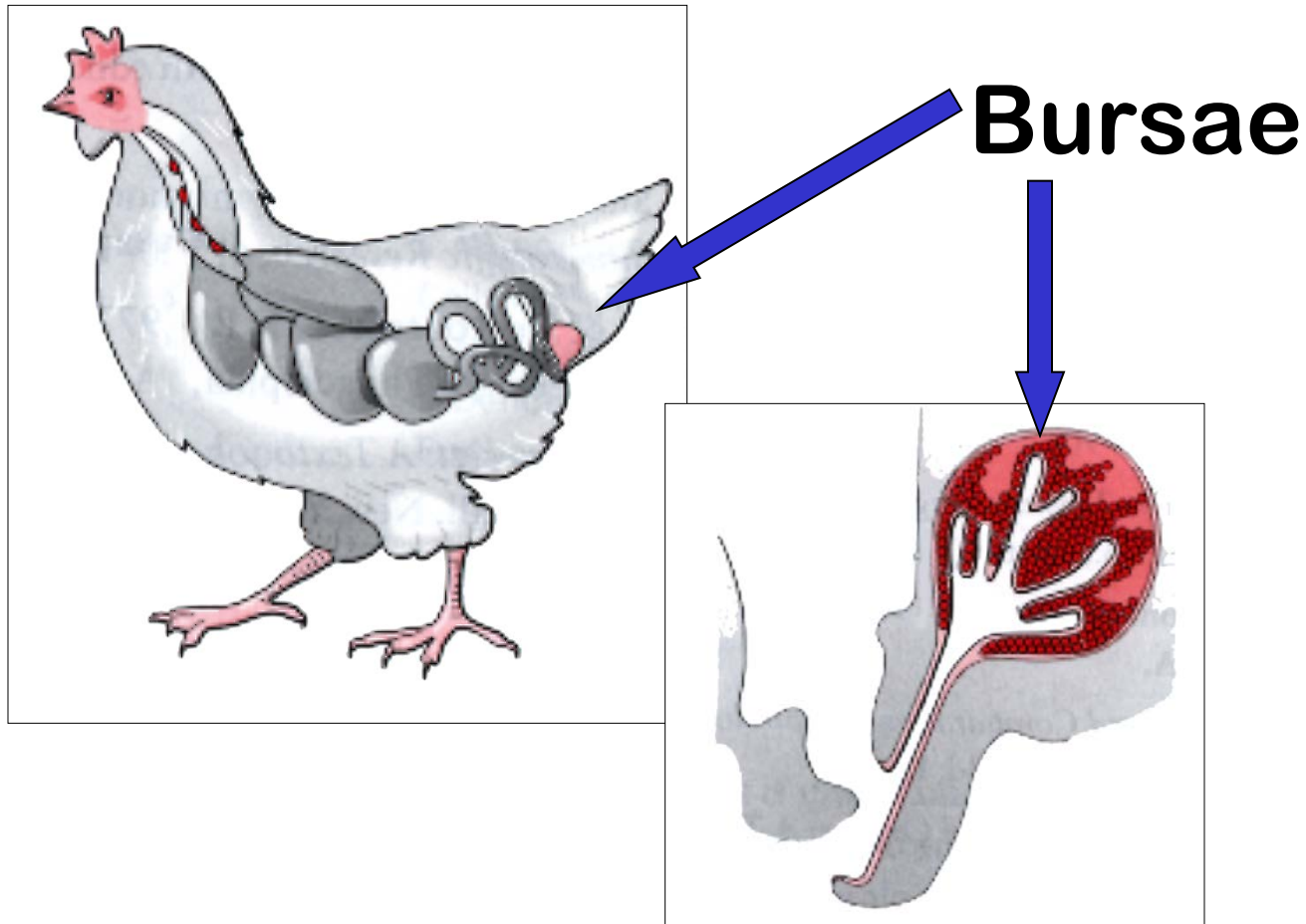
1. Development & maturation in primary lymphoid organs

Stem cell  
(in bone marrow)

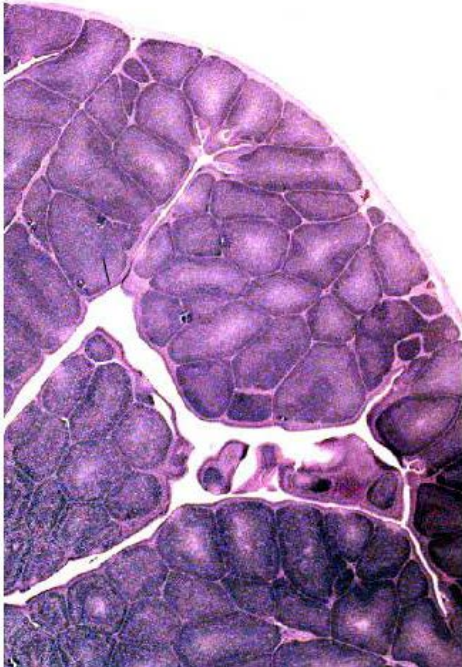


# In birds, the *Bursae of Fabricius* is the site of B-cell maturation

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



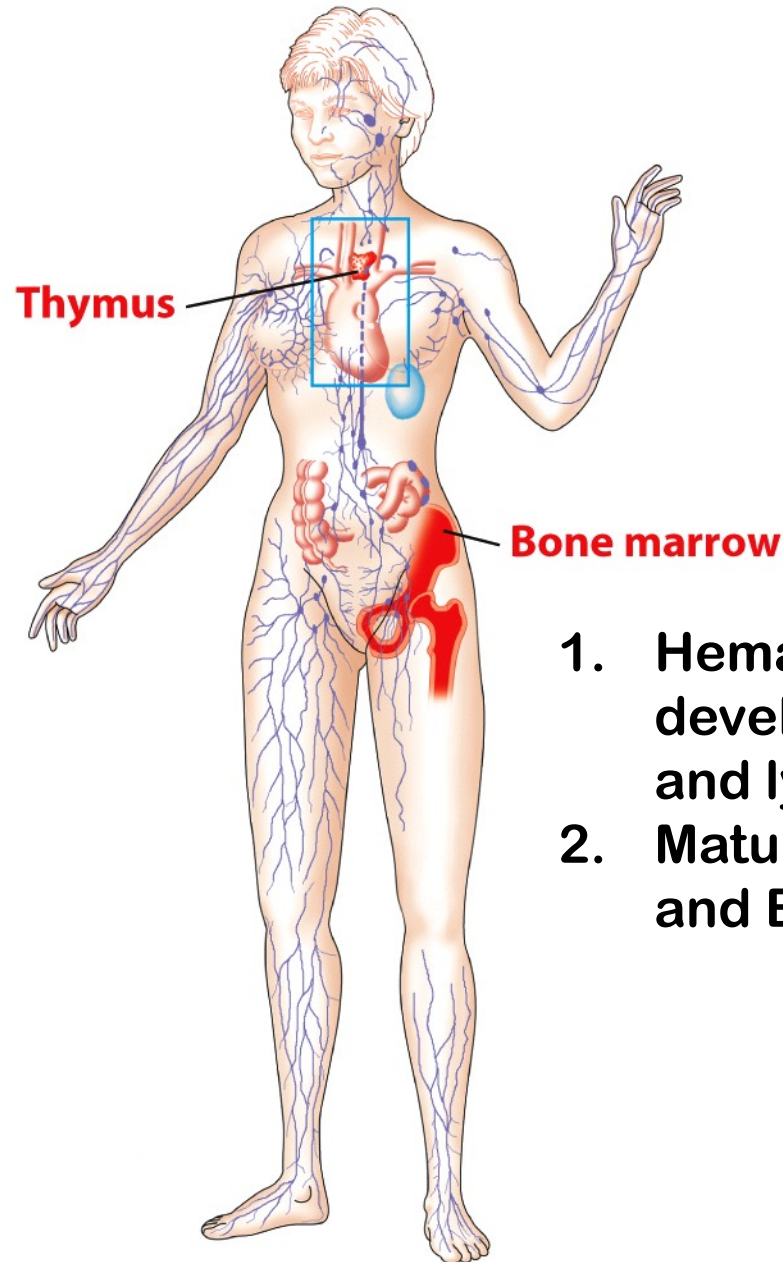
# Bursae of Fabricius



- *In mammals*, B-cell maturation occurs in fetal liver and *bone marrow* after birth

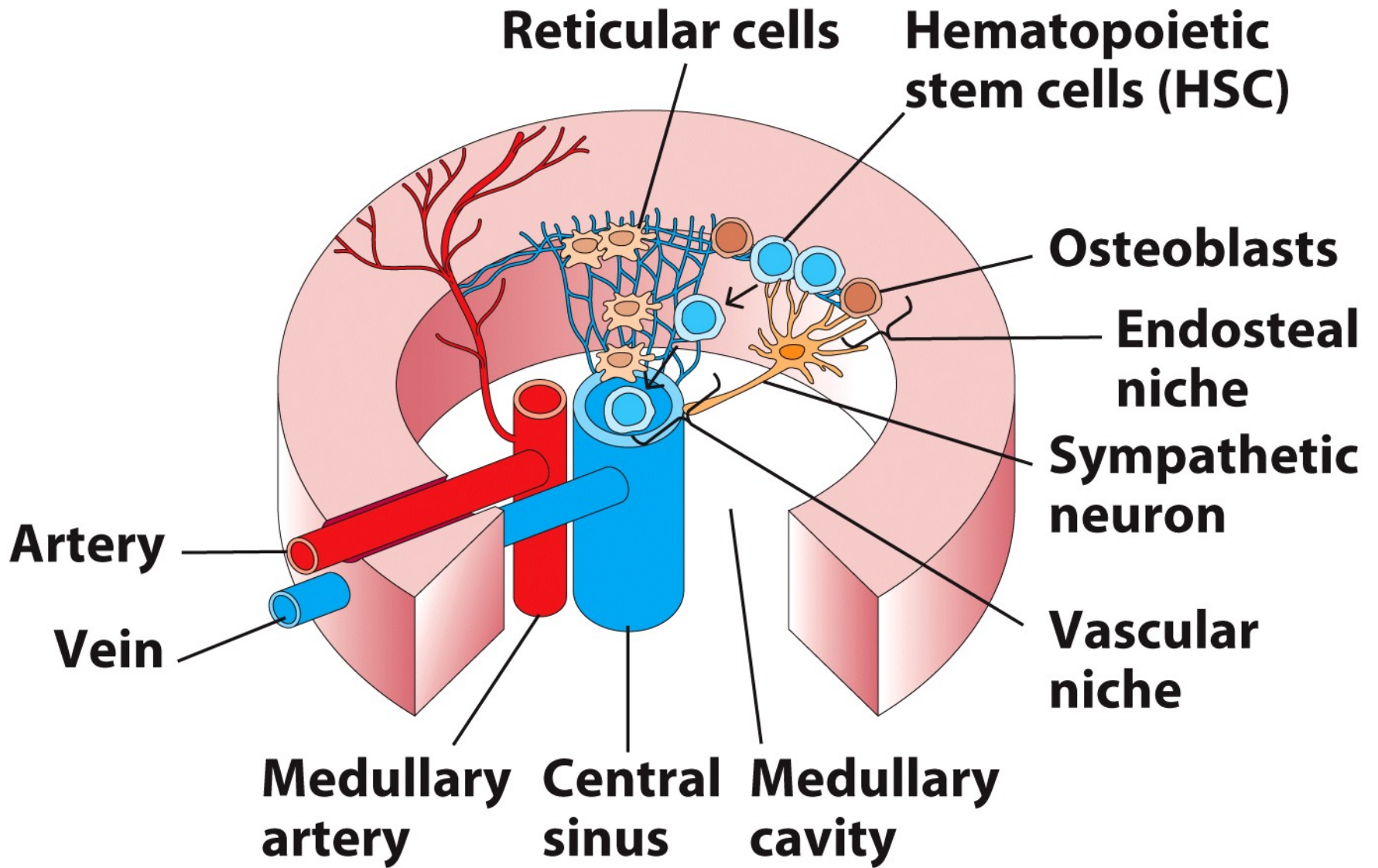


## Maturation of T cells-



1. Hematopoiesis/ development of myeloid and lymphoid cells
2. Maturation of myeloid and B-cells

**Figure 2-6a**  
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**Figure 2-5c**  
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