

Immune system

Acknowledgement

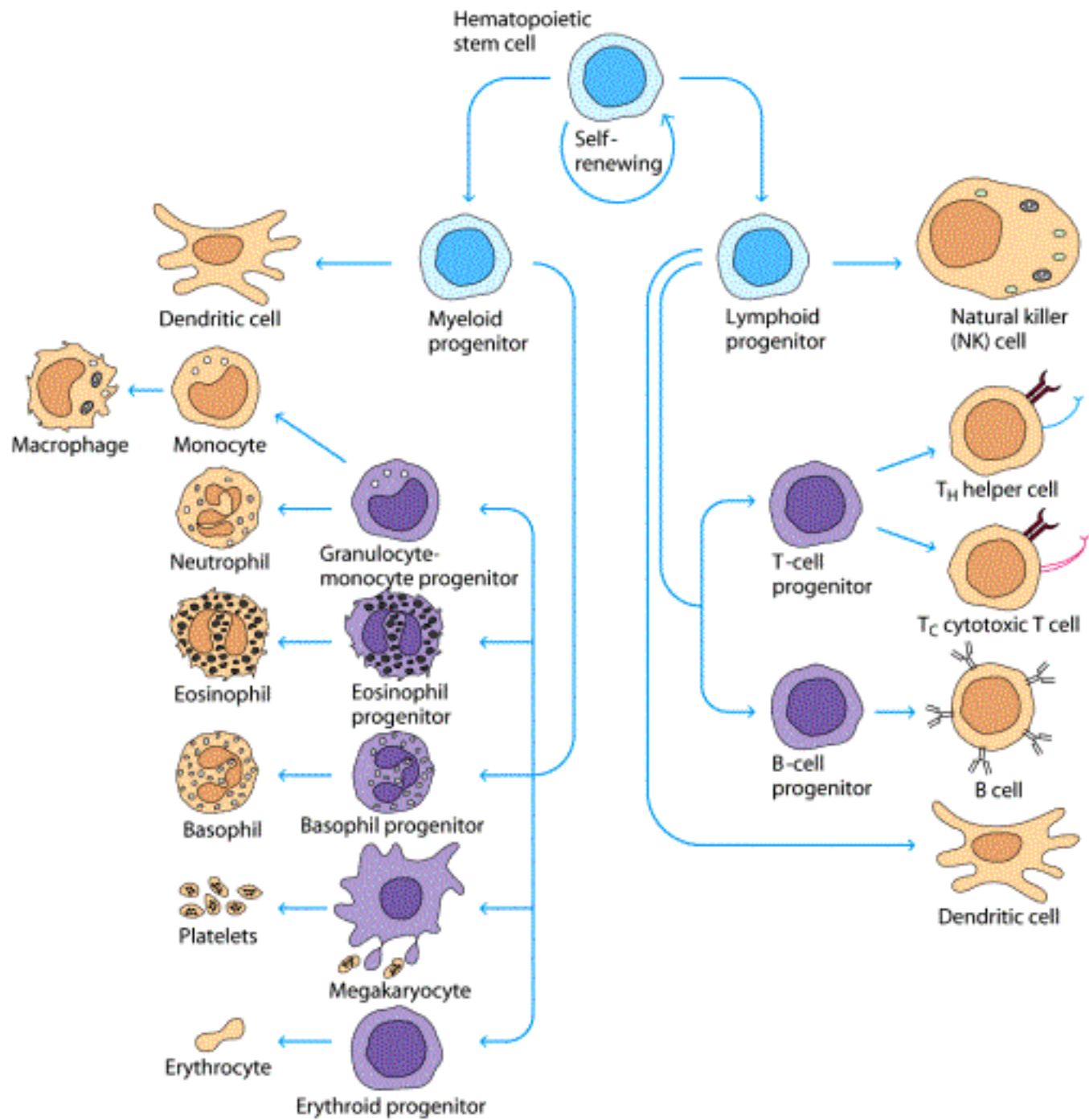
- Material used in some of the slides was taken from open websites and personnel communications.
- Help from these sites and providers is acknowledged.

THE IMMUNE SYSTEM

- Molecules, cells, tissues and organs which provide non-specific and specific protection against
 - Microorganisms
 - Microbial toxins
 - Tumor cells
- Crucial to human survival

ORIGIN OF CELLS OF THE IMMUNE SYSTEM

- Derived from common progenitor cell in bone marrow
 - Pluripotent hematopoietic stem cell
- Progenitor Stem Cells
 - Myeloid lineage
 - Monocyte/macrophage, dendritic cells, PMN's, mast cells
 - Erythroid : Erythrocytes and Megakaryocytes
 - Lymphoid lineage
 - Small and large lymphocytes



Regulation of Hematopoiesis

- Steady state synthesis and normal life span of red and white blood cells is controlled by four factors:
 - Levels and types of cytokines produced by bone marrow cells
 - Production of cytokines by T cells and macrophages
 - Expression of receptors for cytokines on HSC's
 - Apoptosis
- Importance of Regulation
 - Leukemias

TABLE 2-1

Some transcription factors essential for hematopoietic lineages

Factor	Dependent lineage
GATA-1	Erythroid
GATA-2	Erythroid, myeloid, lymphoid
PU.1	Erythroid (maturational stages), myeloid (later stages), lymphoid
BM11	Myeloid, lymphoid
Ikaros	Lymphoid
Oct-2	B lymphoid (differentiation of B cells into plasma cells)

- Genetic regulation of HSC differentiation

GATA transcription factors are a family of [transcription factors](#) characterized by their ability to bind to the [DNA](#) sequence "GATA"

Oct-2 is a [octamer transcription factor](#) which is part of the POU family.

POU (pronounced 'pow') is a family of [proteins](#) that have well-conserved [homeodomains](#). The acronym POU is derived from the names of three transcription factors:

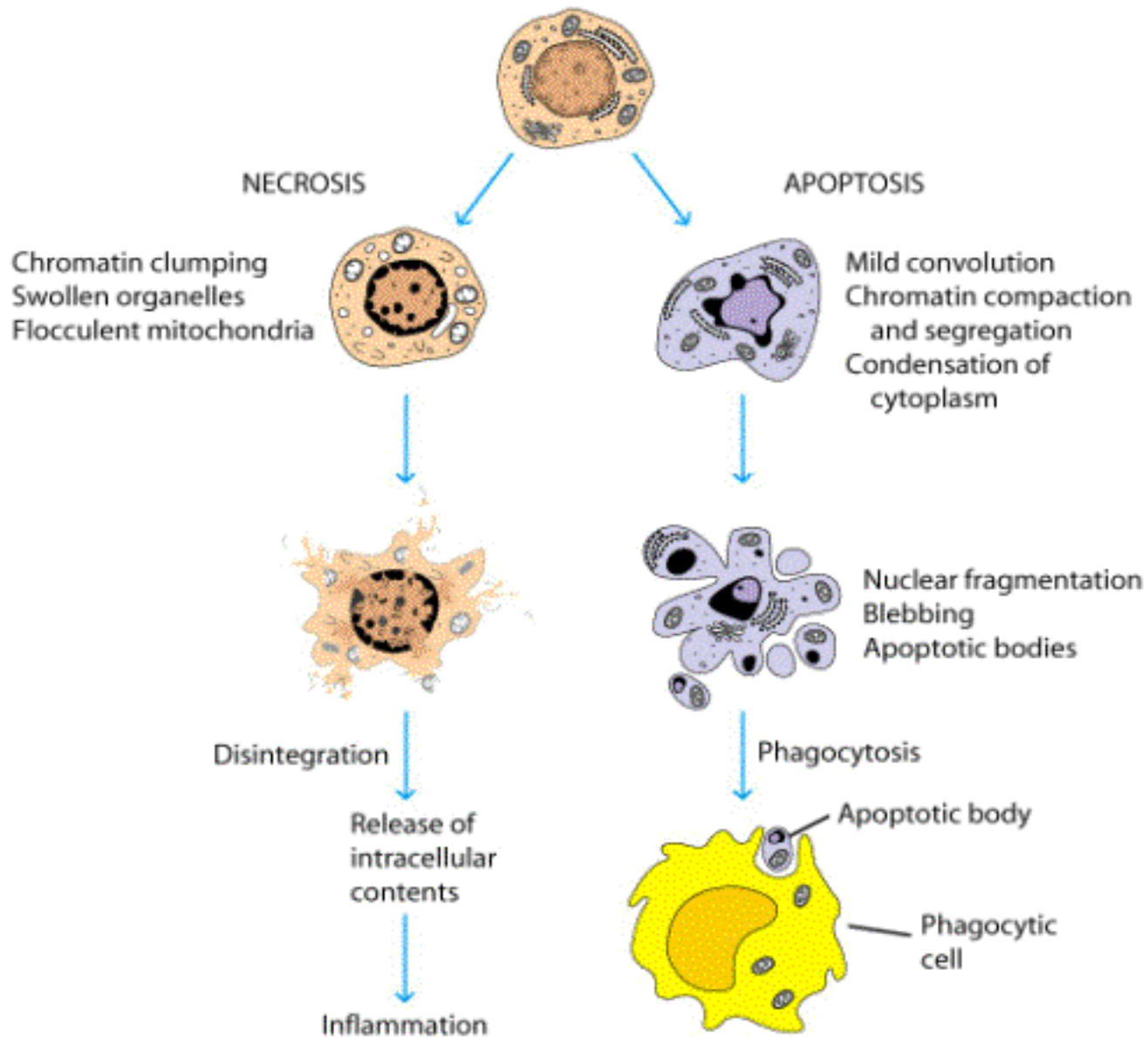
the [Pituitary](#)-specific [Pit-1](#)

the [Octamer transcription factor](#) proteins [Oct-1](#) and [Oct-2](#) (octamer sequence is ATGCAAAT)

the [neural](#) [Unc-86](#) transcription factor from [Caenorhabditis elegans](#).

TABLE 2-2**Genes that regulate apoptosis**

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



CELLS OF INNATE AND ADAPTIVE IMMUNITY

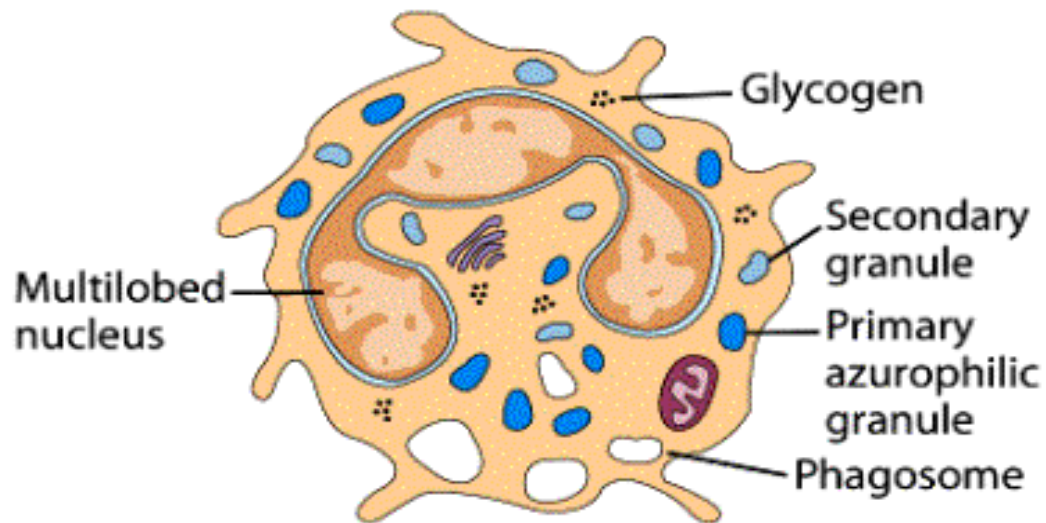
- Myeloid Lineage
- Referred to as
 - Polymorphonuclear leukocytes (PMN's)
 - Nuclei are multilobed (2 to 5)
 - Granulocytes
 - Cytoplasmic granules
- Neutrophil: Principal phagocytic cell of innate immunity
- Eosinophil: Principal defender against parasites
- Basophil: Functions similar to eosinophils and mast cells

Neutrophils and macrophages

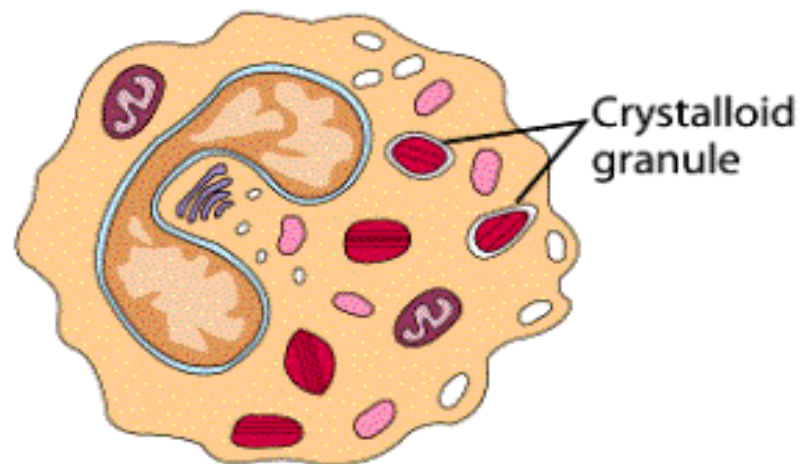
- Phagocytes - travel throughout body in pursuit of invading pathogens
- Neutrophils are found in bloodstream ; most abundant phagocyte, normally representing 50% to 60% of circulating leukocytes
- During acute phase of inflammation, particularly as a result of bacterial infection, neutrophils migrate toward site of inflammation in a process called chemotaxis, and are usually first cells to arrive at scene of infection
- Macrophages are versatile cells that reside within tissues and produce a wide array of chemicals including enzymes, complement proteins, and regulatory factors such as interleukin 1
- Macrophages also act as scavengers, ridding body of worn-out cells and other debris, and as antigen-presenting cells that activate adaptive immune system

Granulocytes

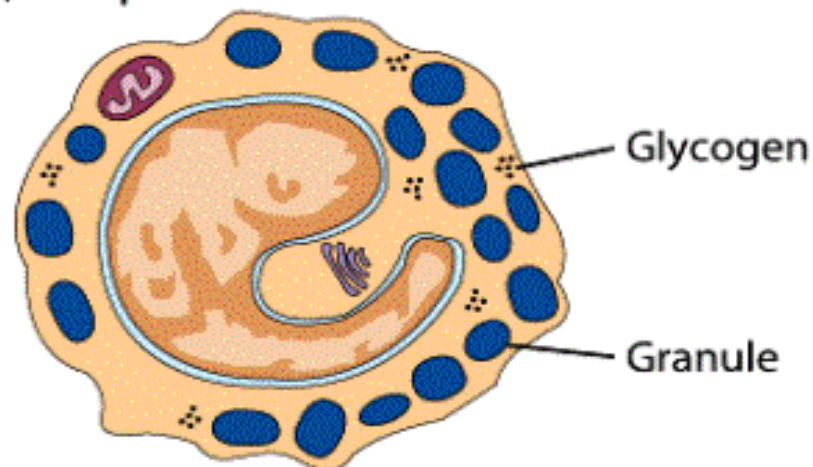
(a) Neutrophil



(b) Eosinophil

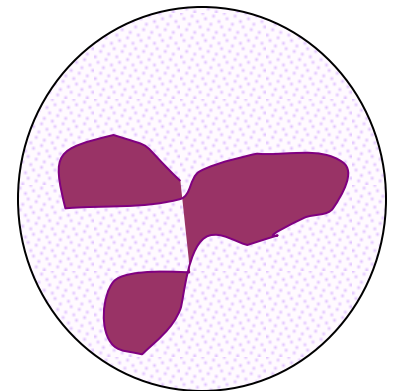
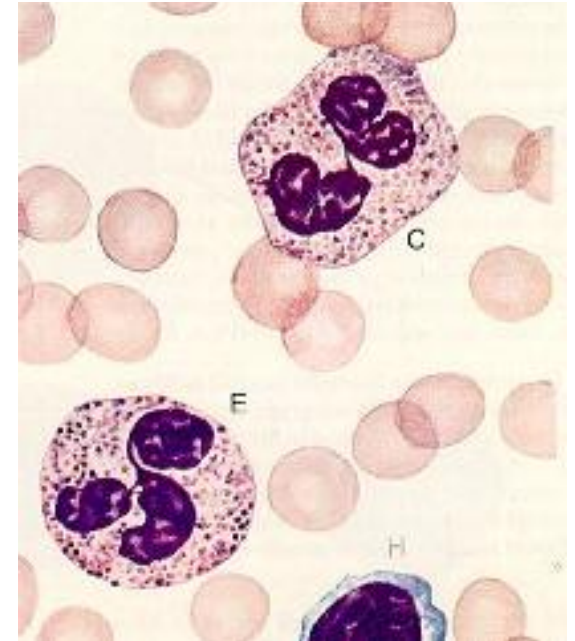


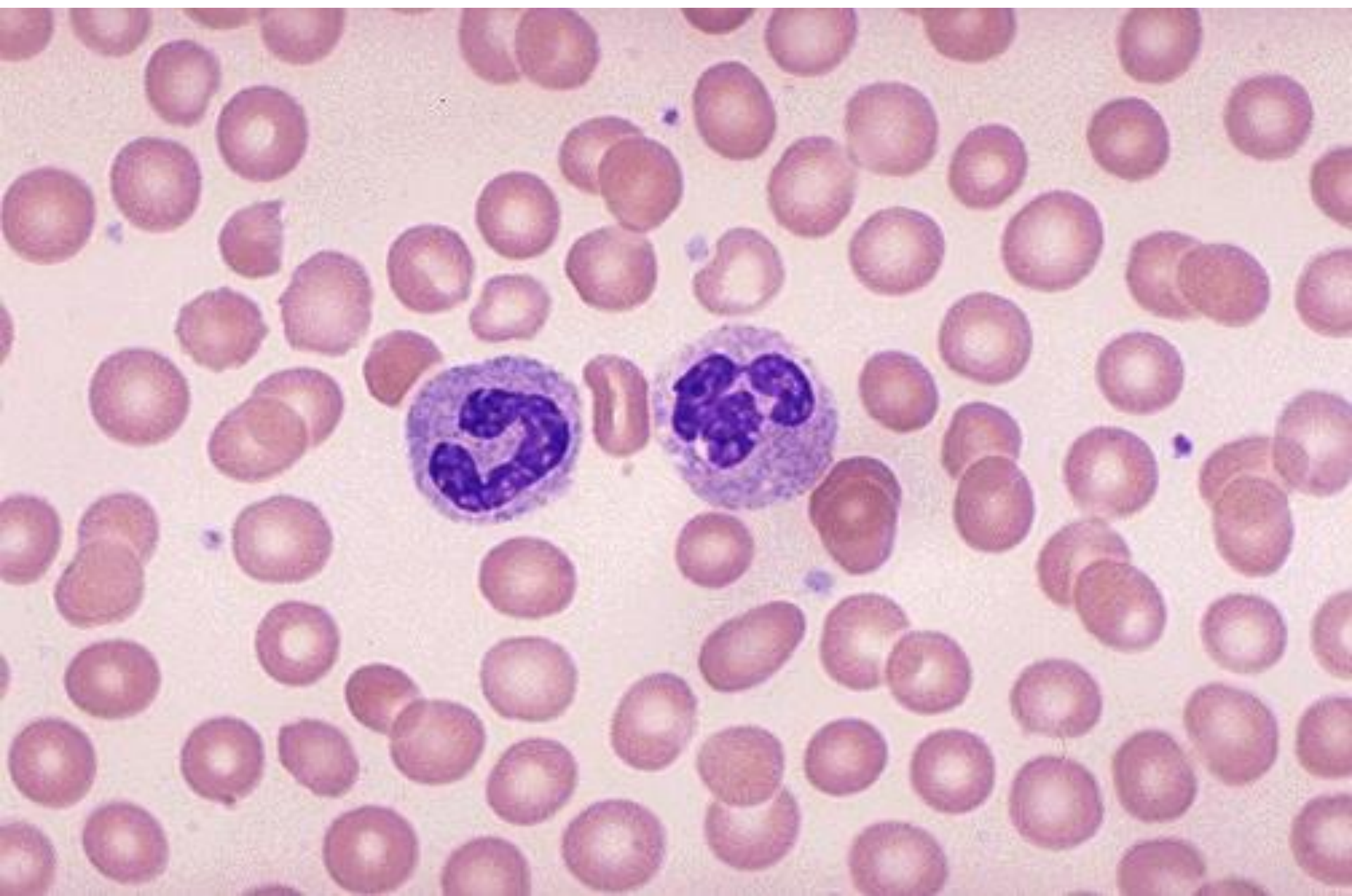
(c) Basophil

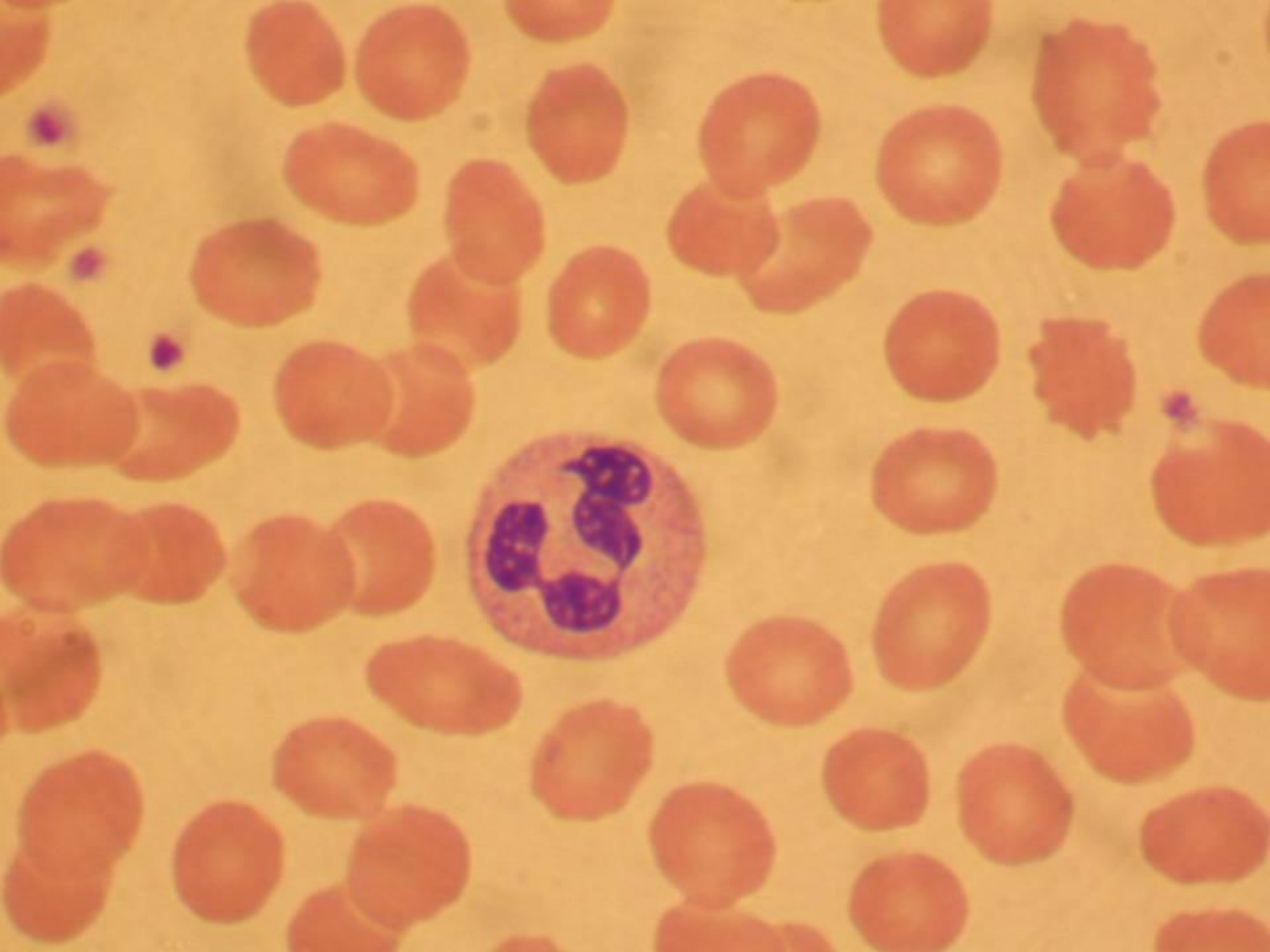


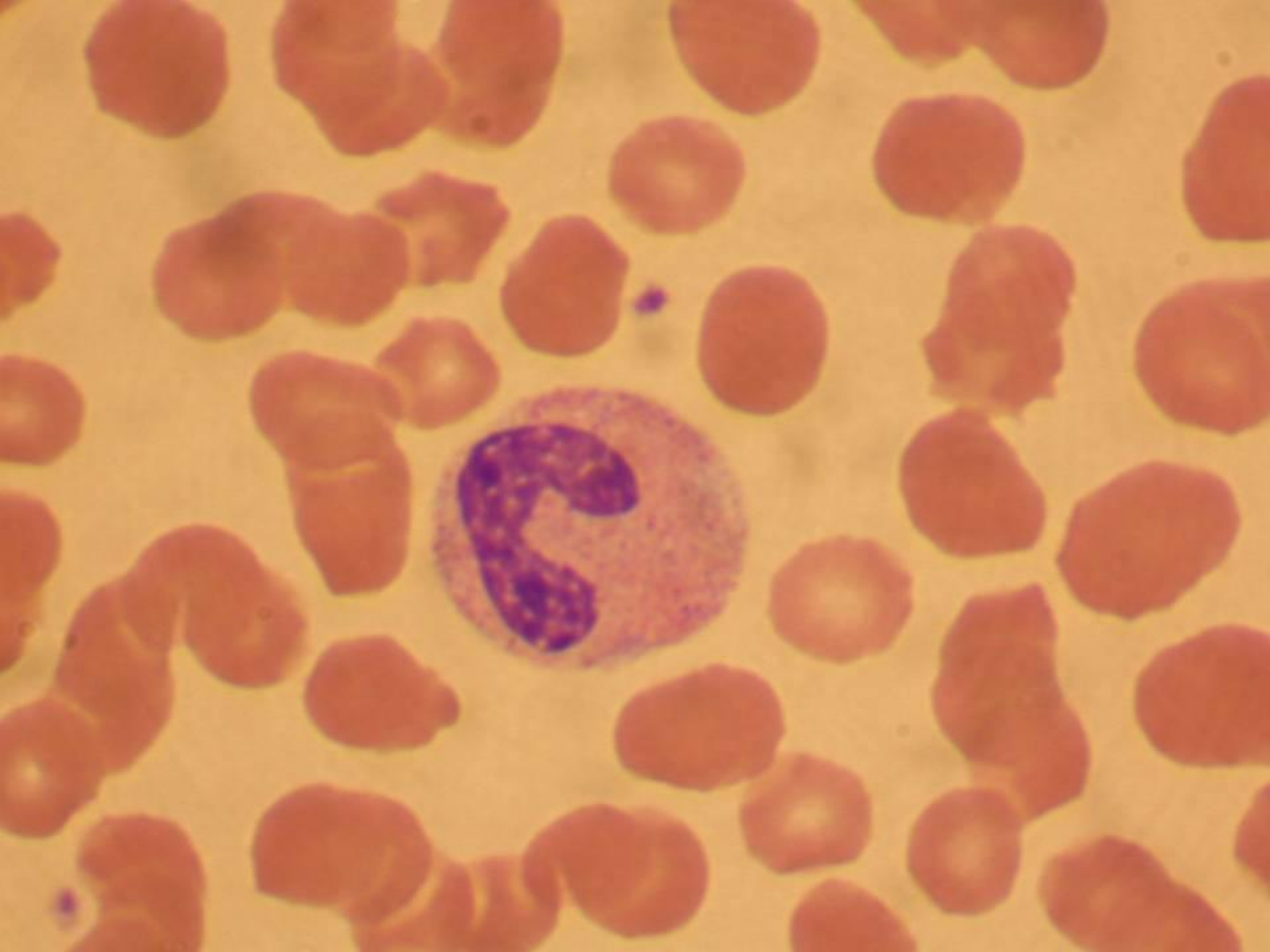
Neutrophil

- Granulocyte
 - Cytoplasmic granules
- Polymorphonuclear
- Phagocytosis
- Short life span (hours)
- Very important at “clearing” bacterial infections
- Innate Immunity



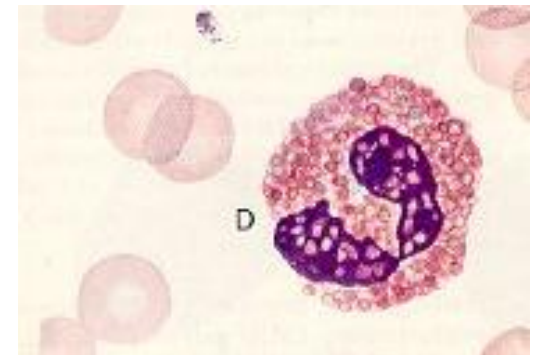
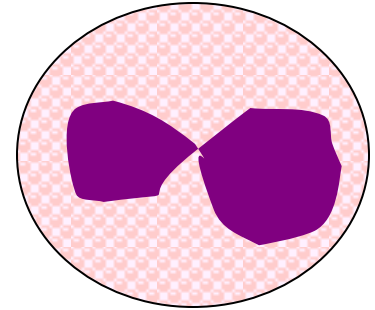


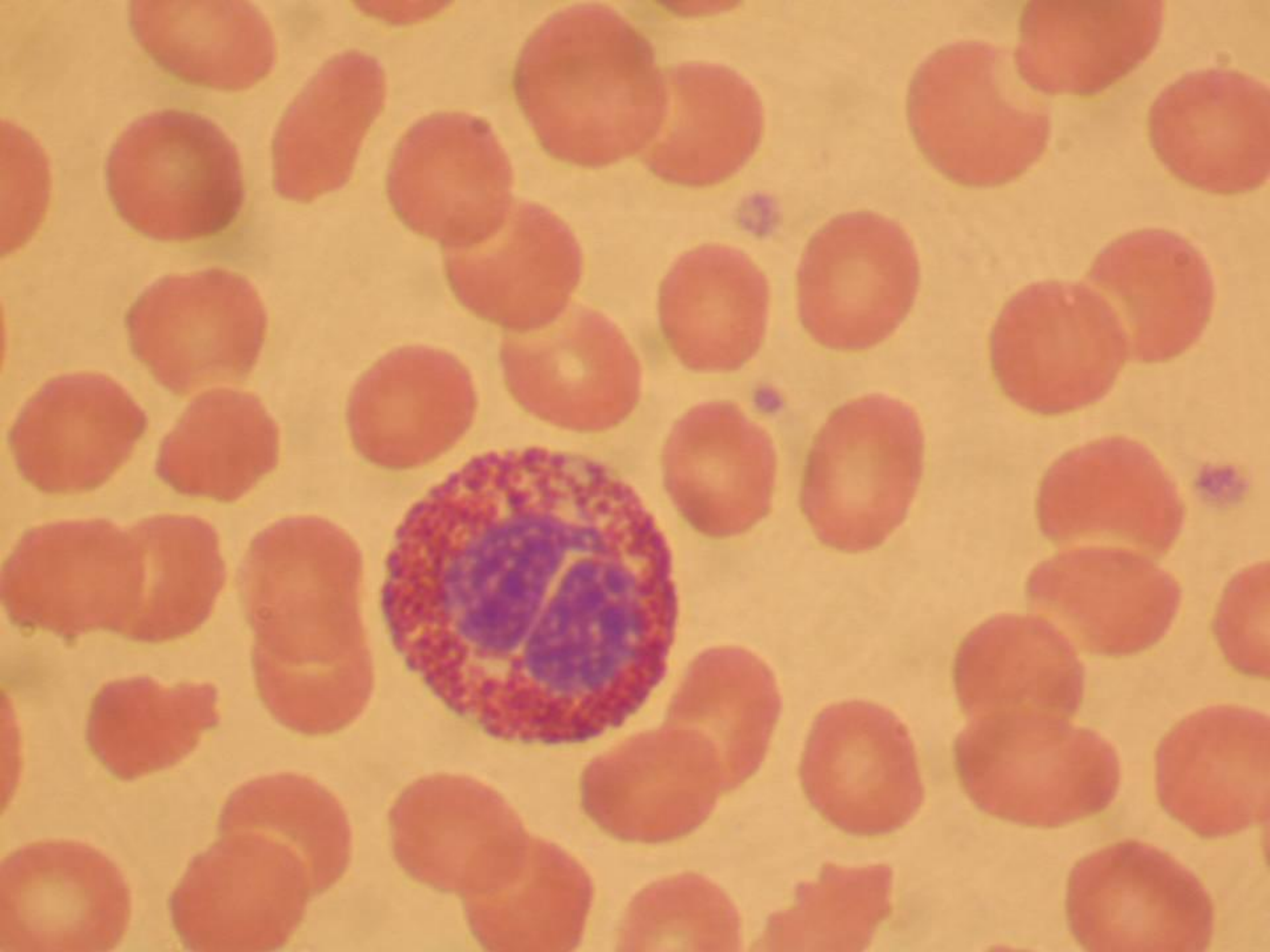


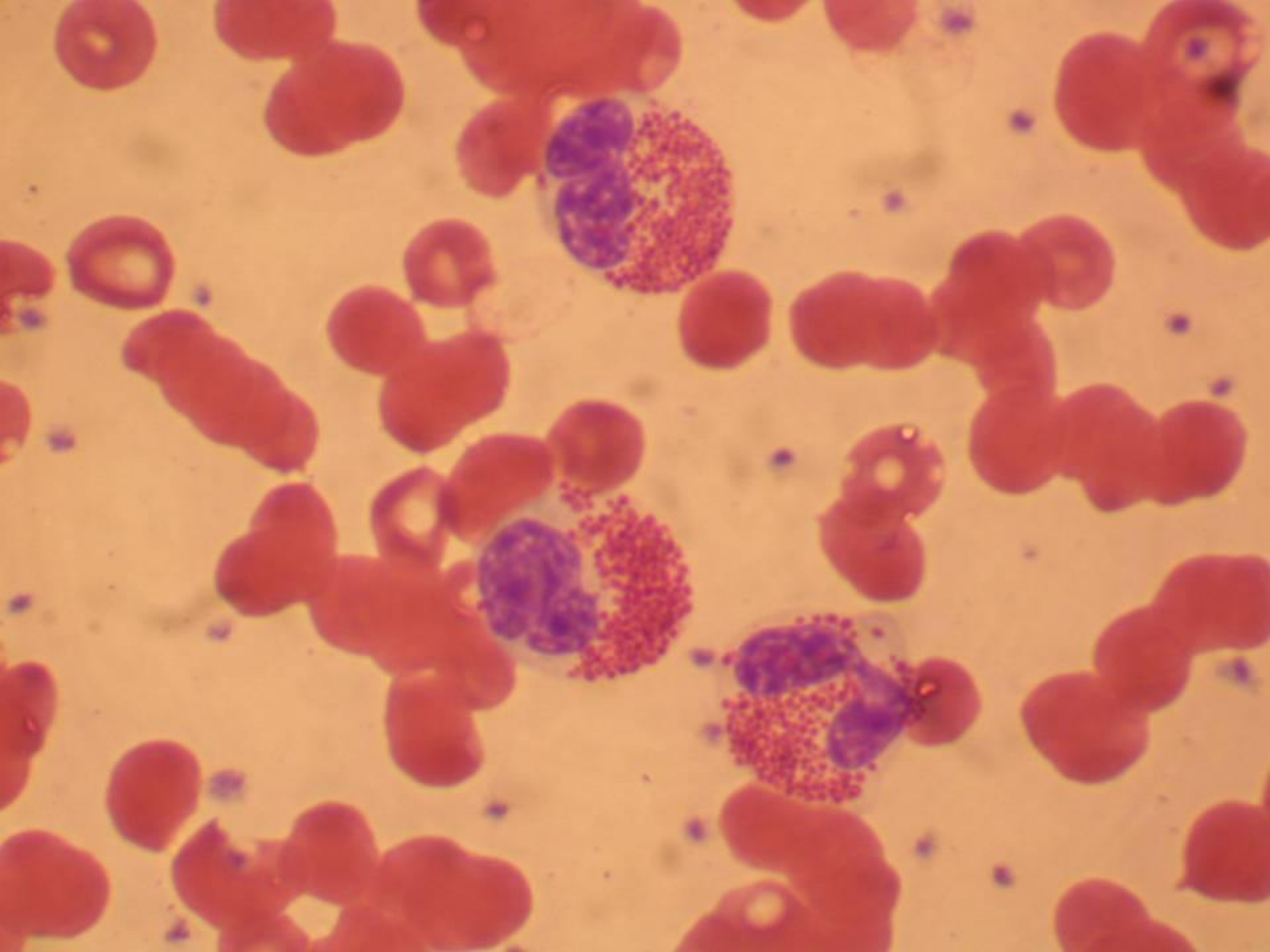


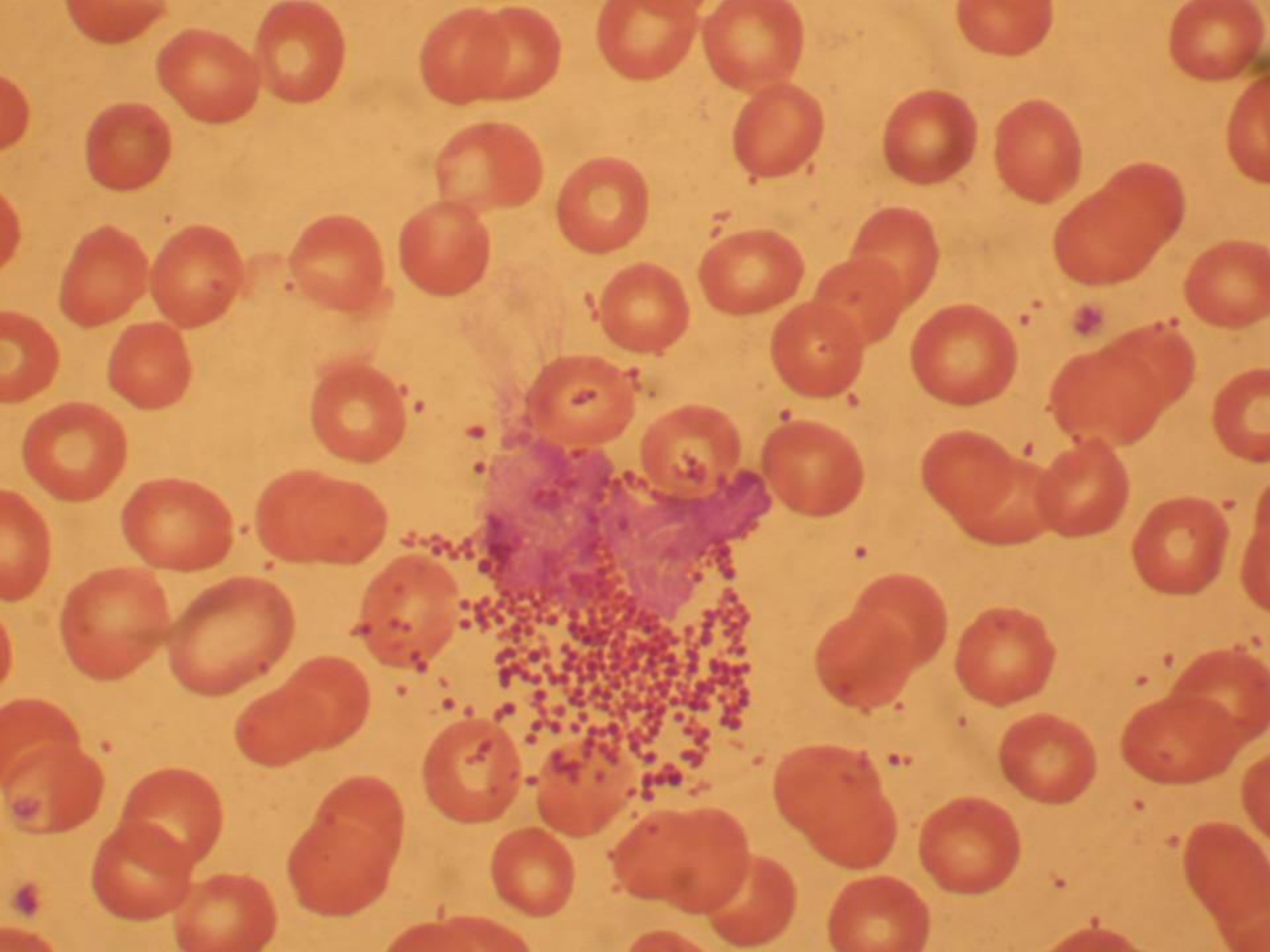
Eosinophils

- Kills Ab-coated parasites through degranulation
- Involved in allergic inflammation
- A granulocyte
- Double Lobed nucleus
- Orange granules contain toxic compounds



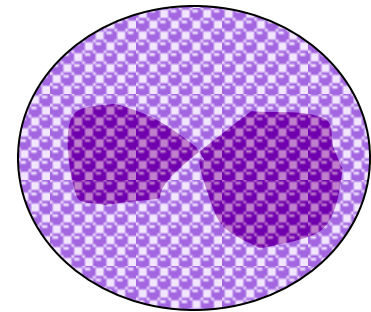


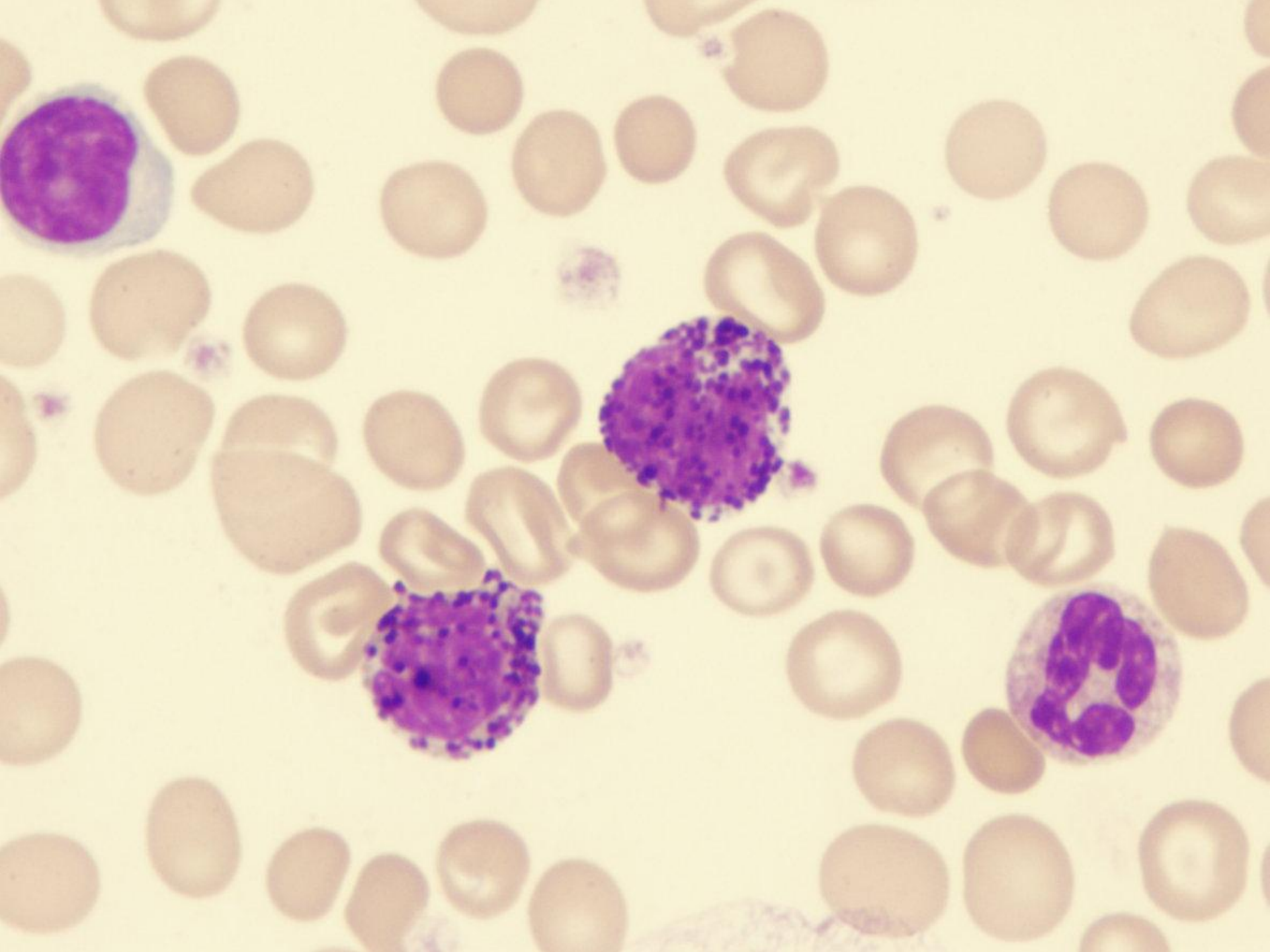




Basophils

- Might be “blood Mast cells’
- A cell-killing cells
 - Blue granules contain toxic and inflammatory compounds
- Important in allergic reactions

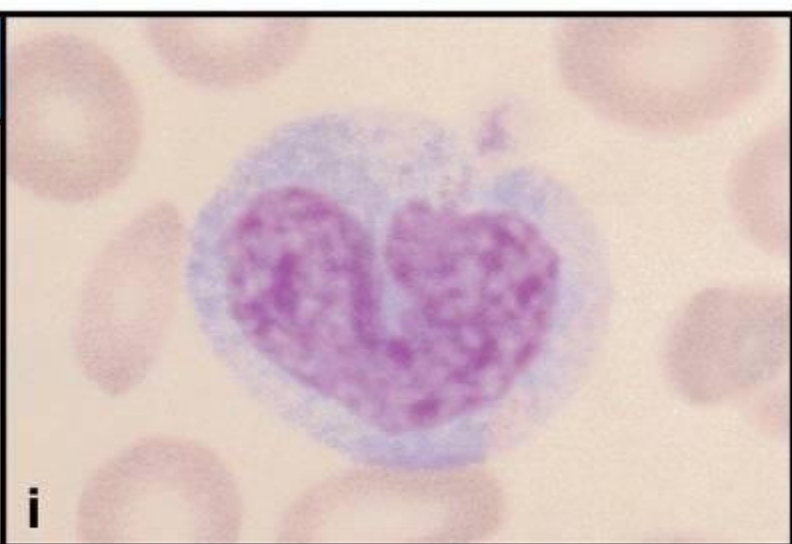




CELLS OF INNATE AND ADAPTIVE IMMUNITY

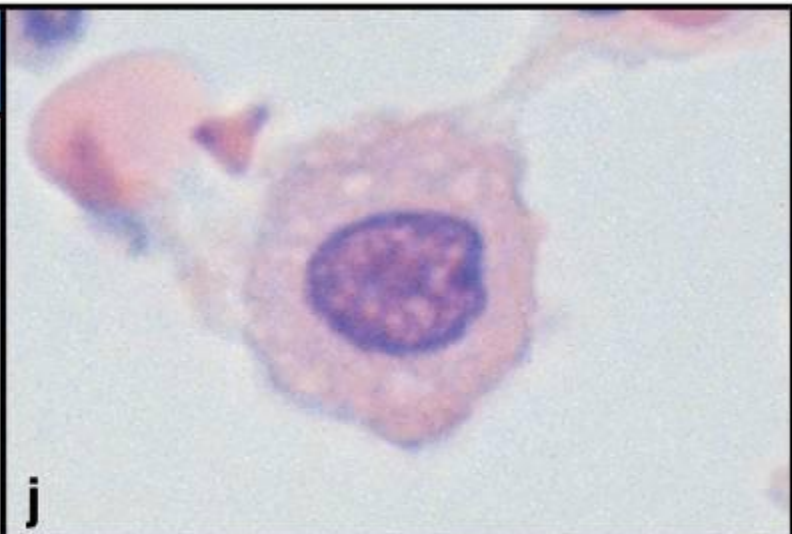
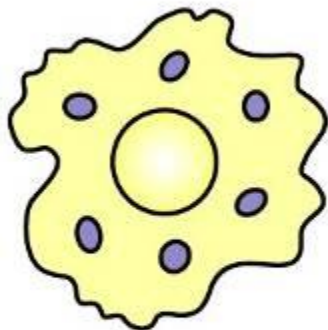
- Myeloid lineage
 - Monocytes
 - Leukocytes with bean shaped or brain-like convoluted nuclei
 - Circulate in blood with half life of 8 hours
 - Precursors of tissue macrophages
 - Macrophages
 - Mononuclear phagocytic cells in tissue
 - Derive from blood monocytes
 - Participate in innate and adaptive immunity

Monocyte



Circulating precursor cell to macrophage

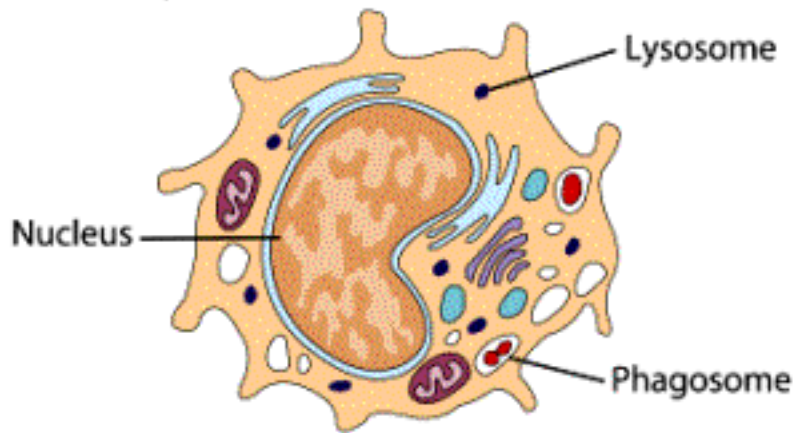
Macrophage



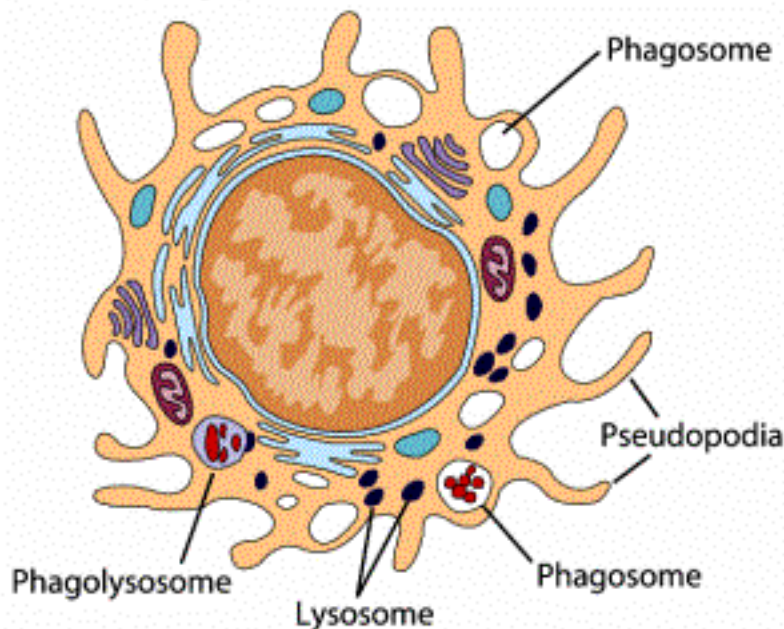
Phagocytosis and killing of microorganisms.
Activation of T cells and initiation of immune responses

Monocyte and Macrophage

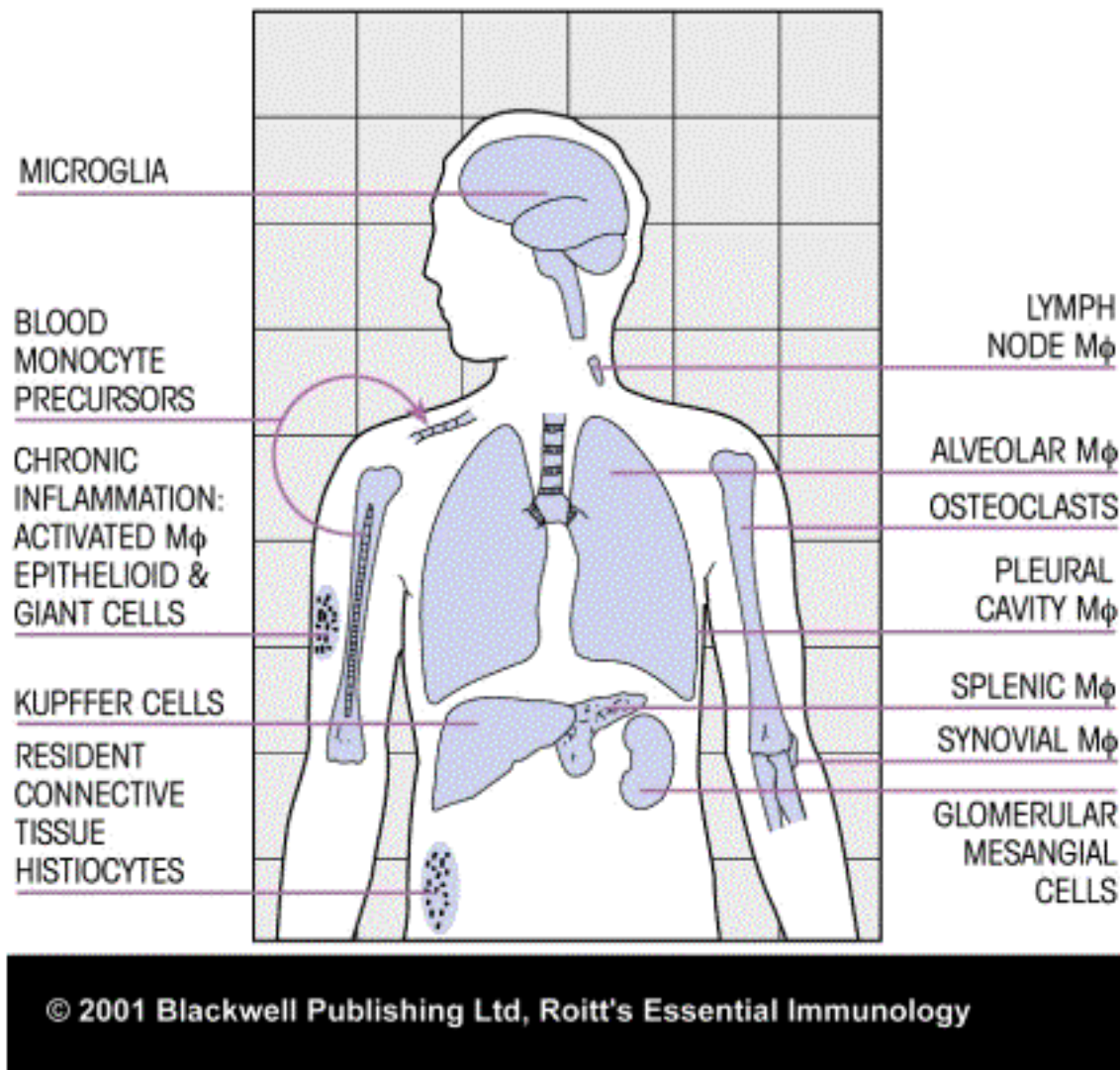
(a) Monocyte



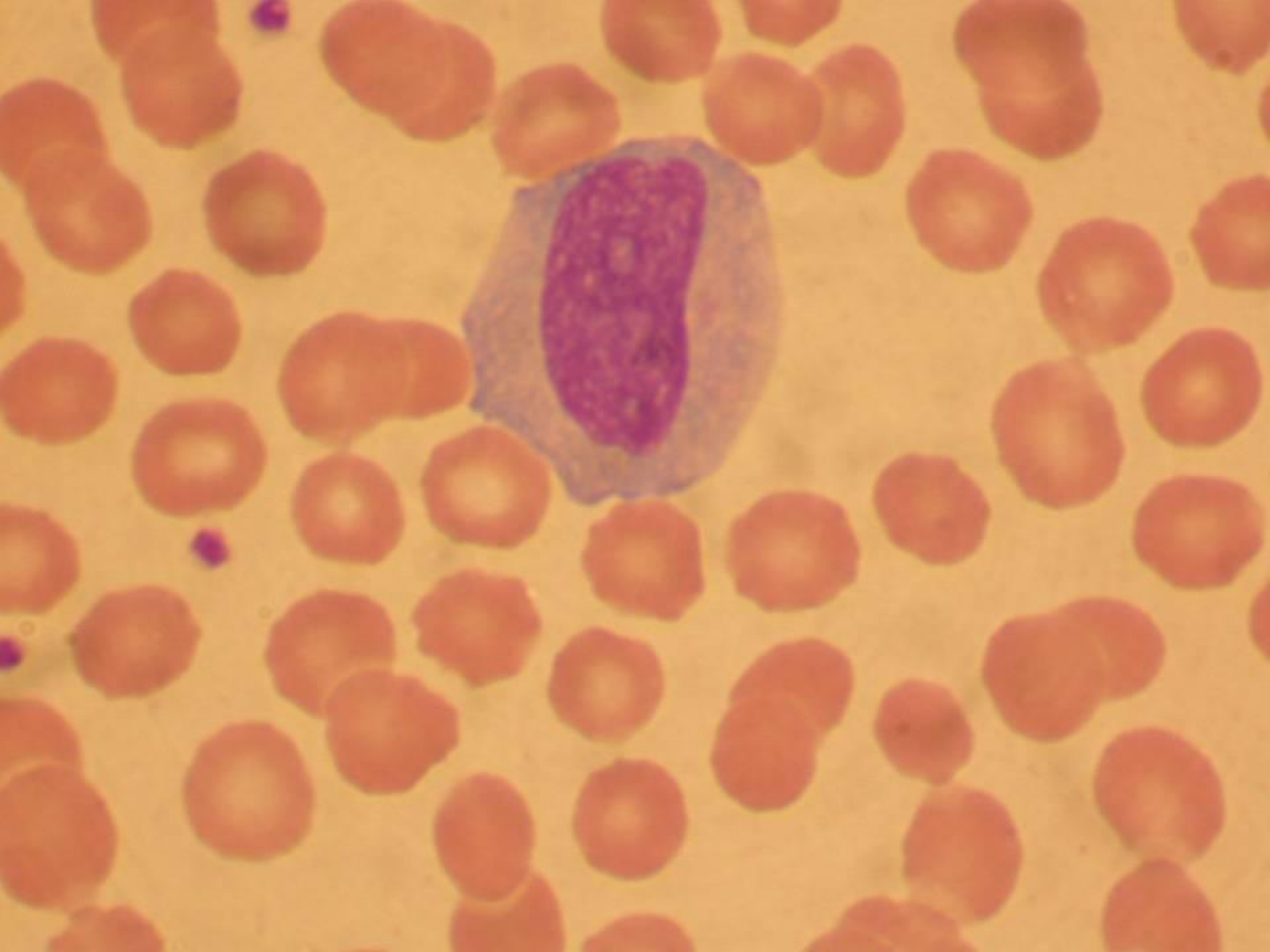
(b) Macrophage

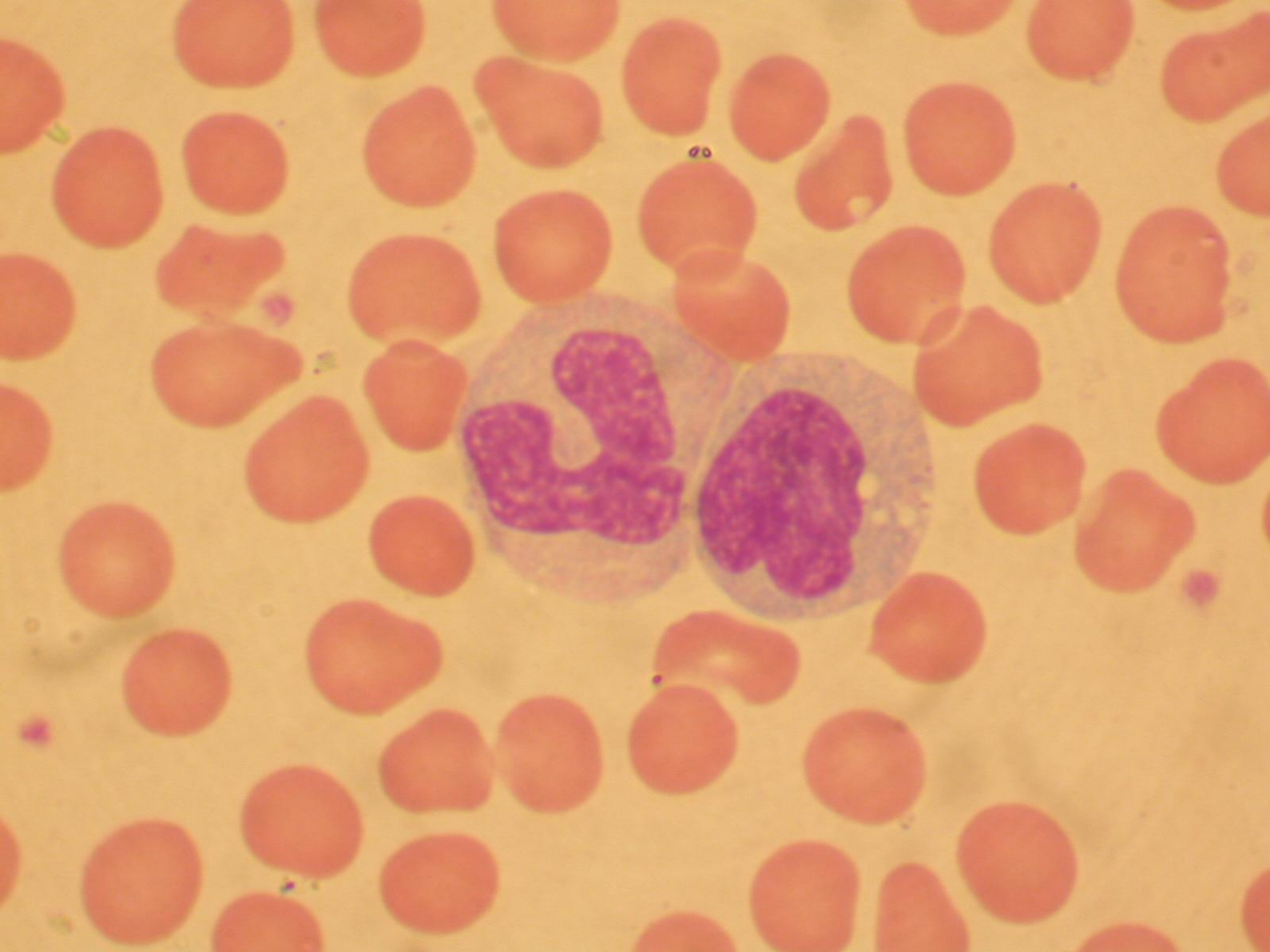


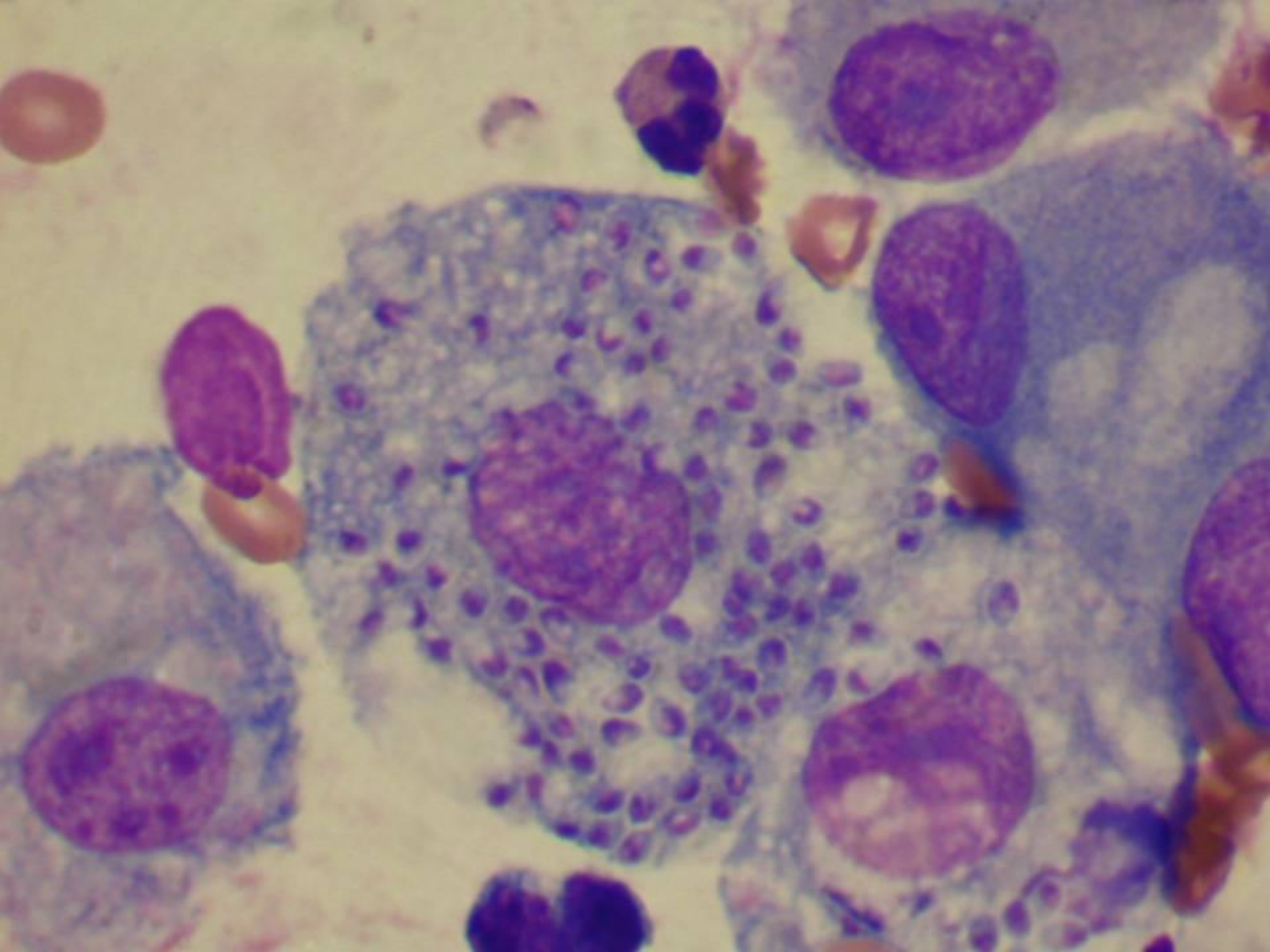
- Origin
- Migration maturation
- Morphological differences between monocytes and macrophage
- Activation of macrophages
- Macrophage function
 - Phagocytosis
 - Processing Antigen
 - Presenting antigenic peptide with class II MHC to T cells
 - Cytotoxic activity
 - Synthesis and release of cytokines

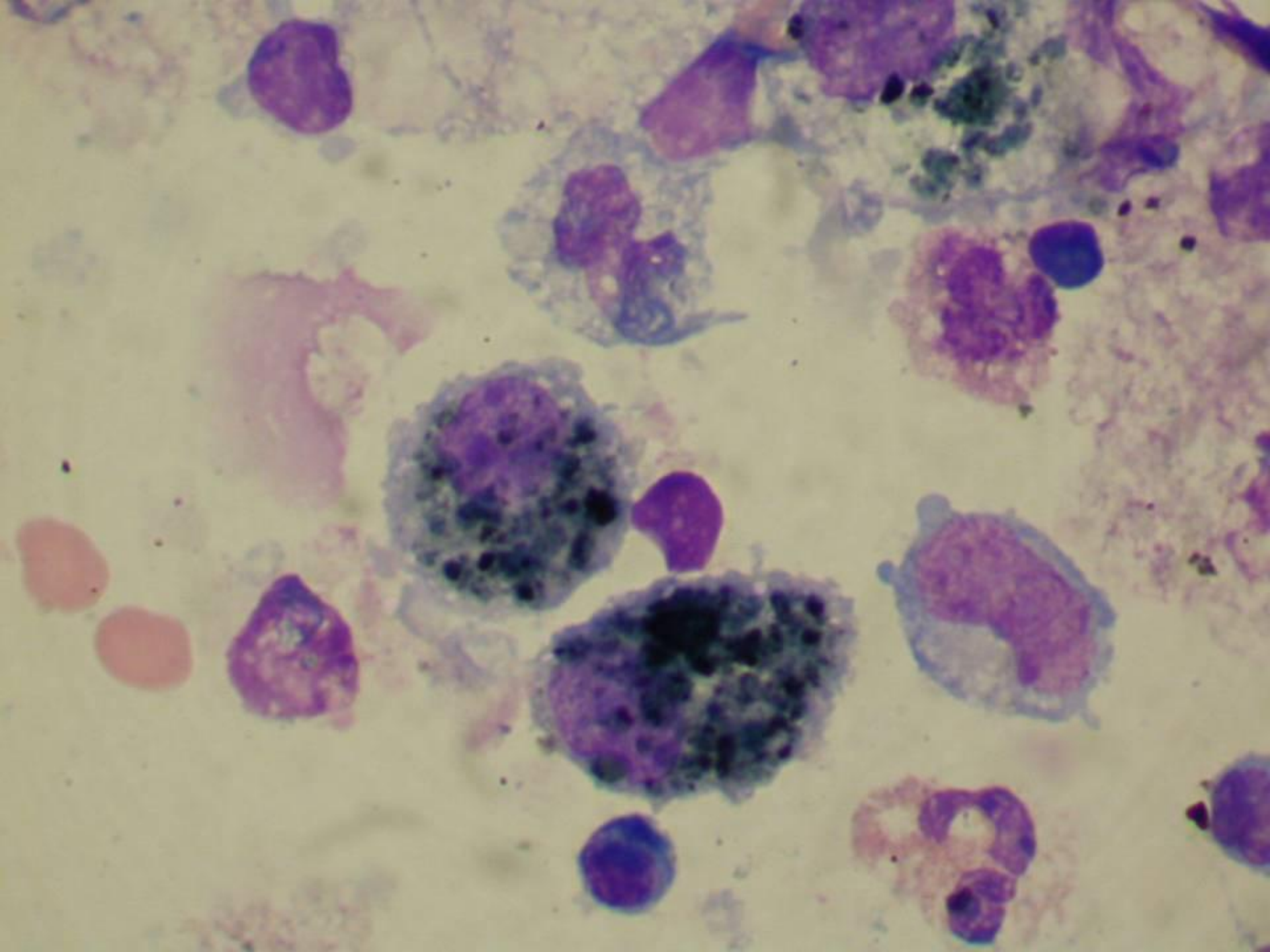


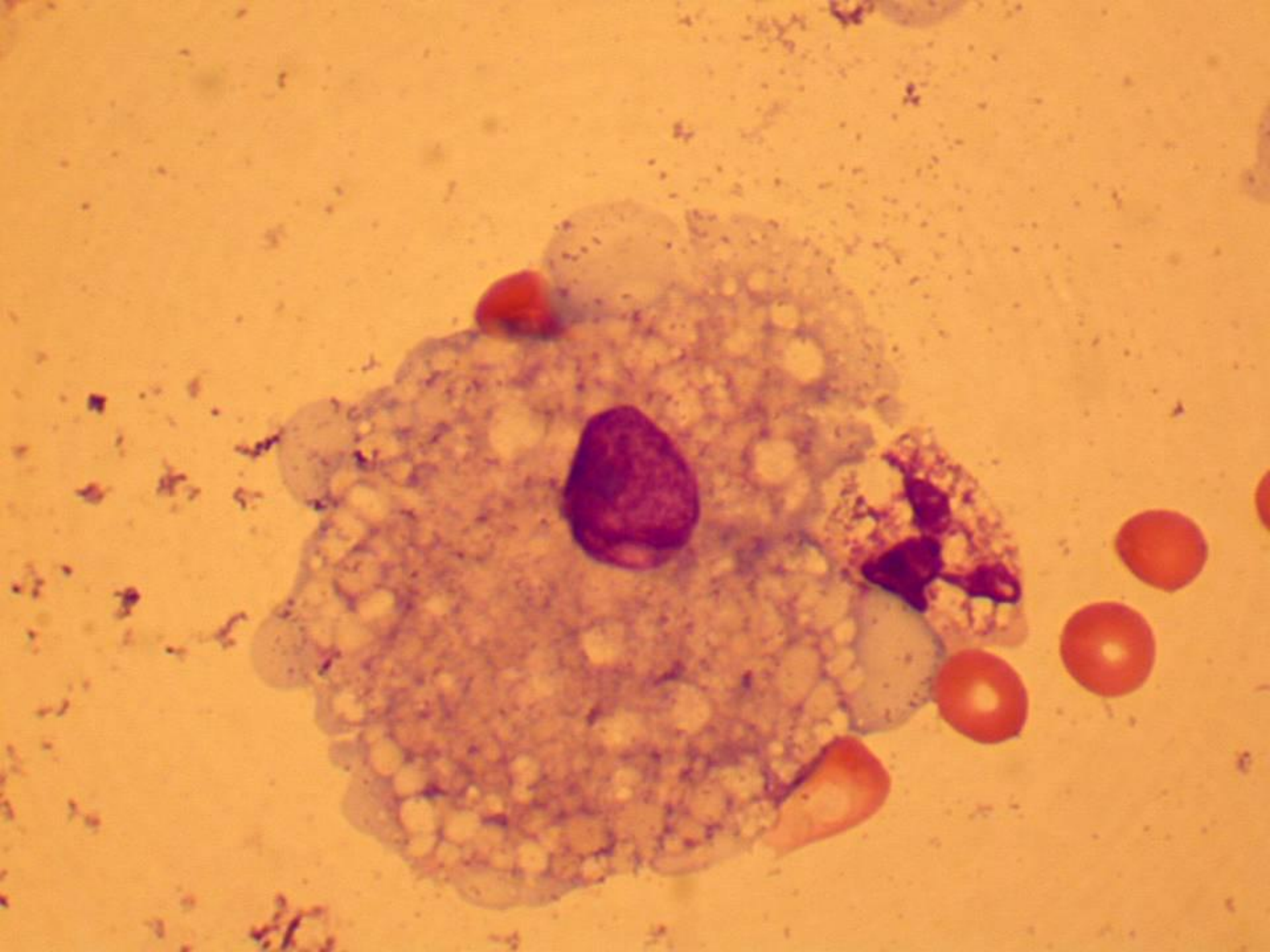
- Mononuclear Phagocyte System
 - Types of macrophages and their locations

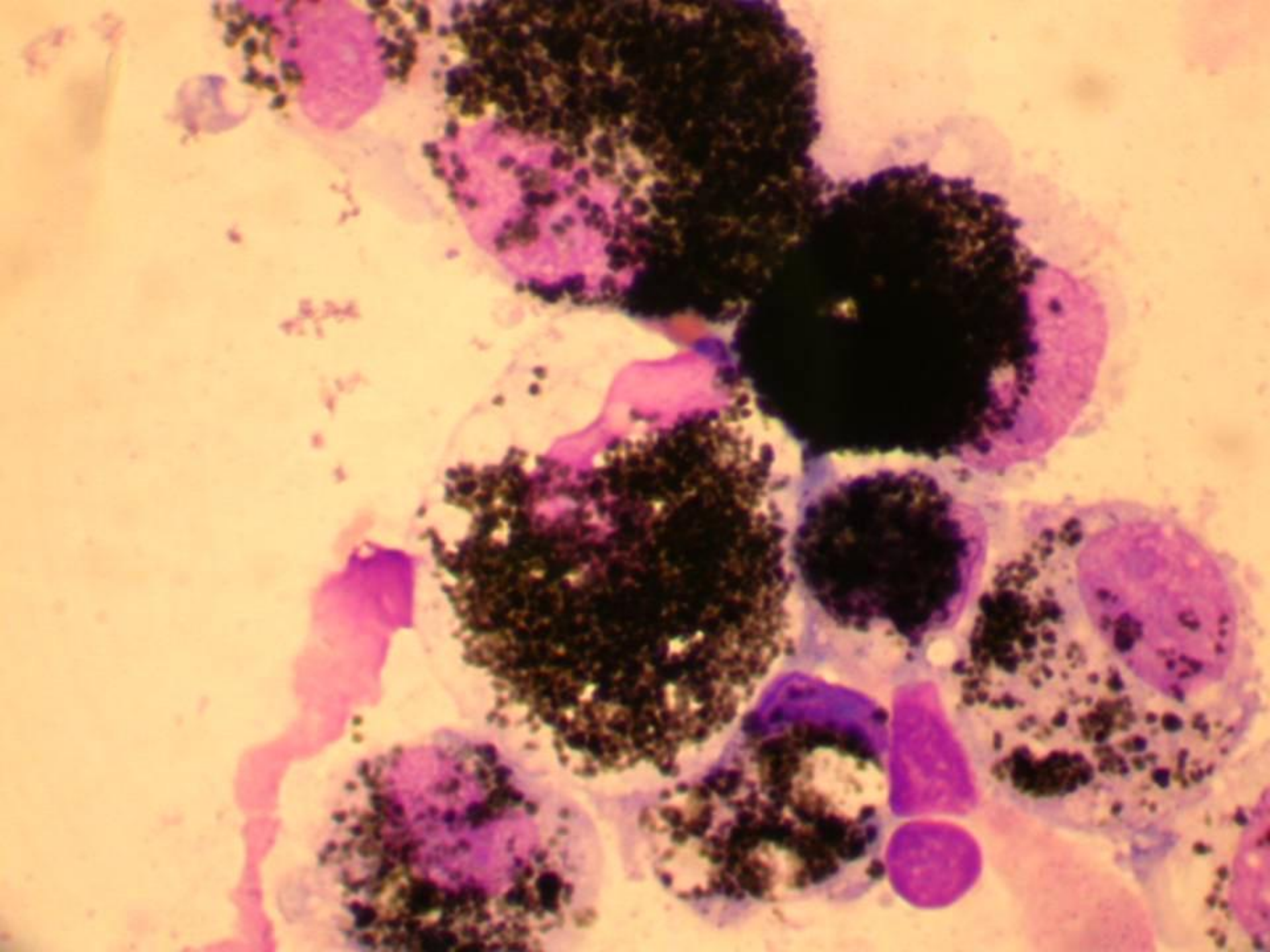


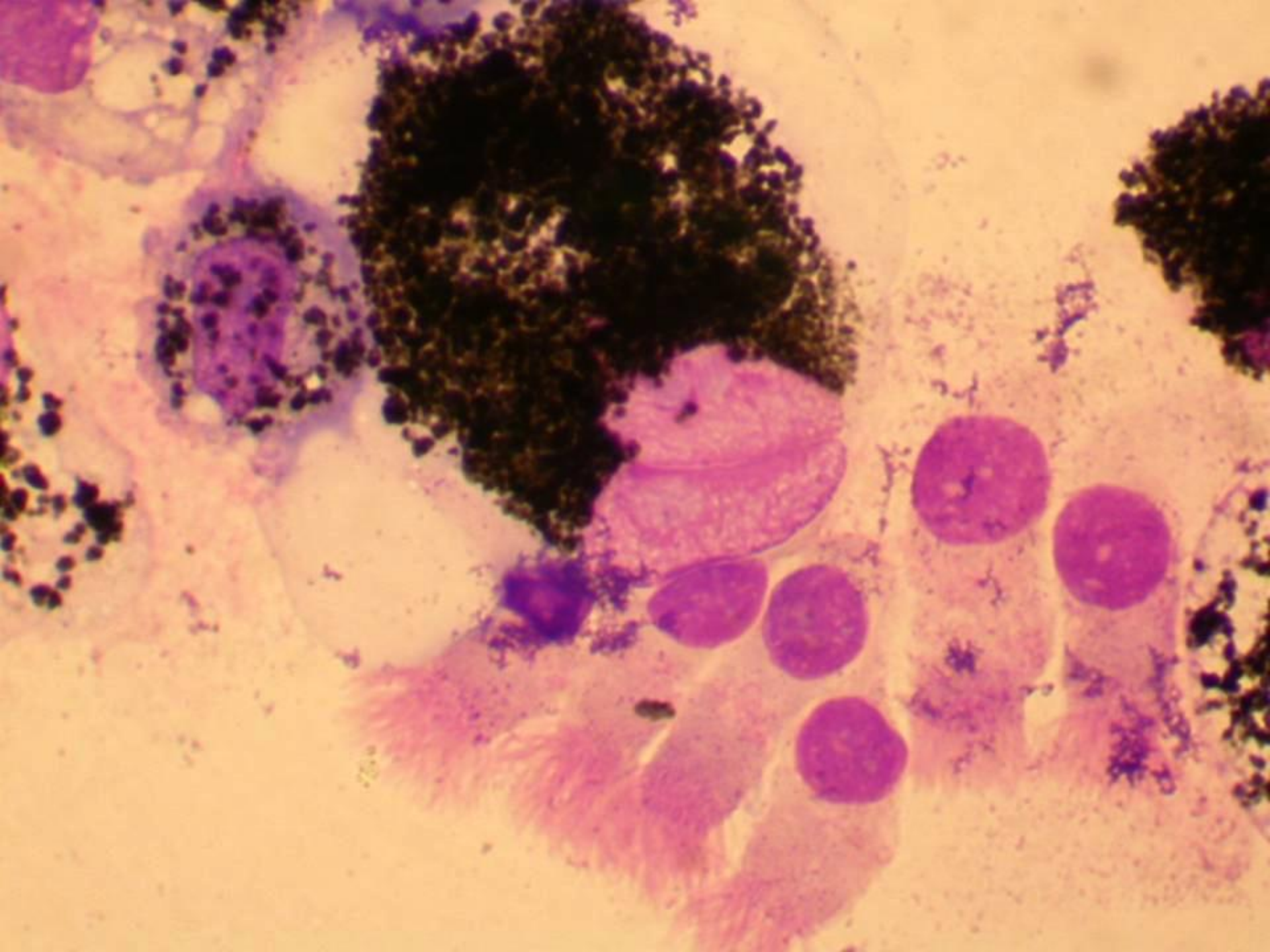












CELLS OF INNATE AND ADAPTIVE IMMUNITY

- Myeloid lineage
 - Dendritic cells
 - Cells with dendriform (star shaped) morphology
 - Interdigitating reticular cells (synonym)
 - Capture and present antigens to T lymphocytes
 - Mast cells
 - Located in mucous membrane and connective tissue throughout body
 - Major effectors cell in allergy
 - Modulation of initial immune response

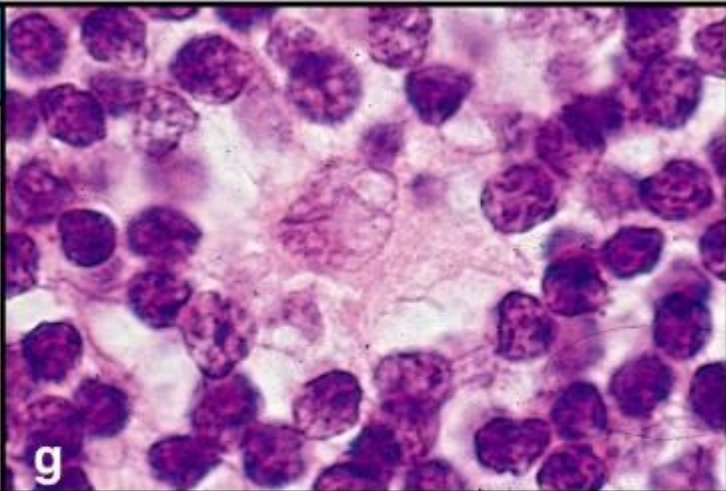
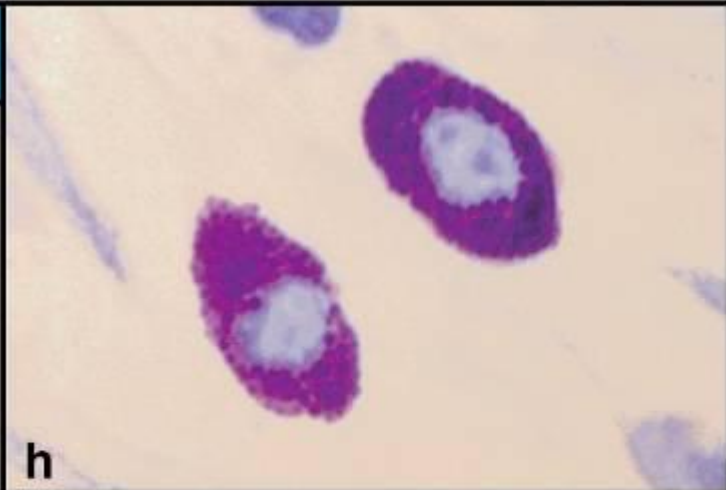
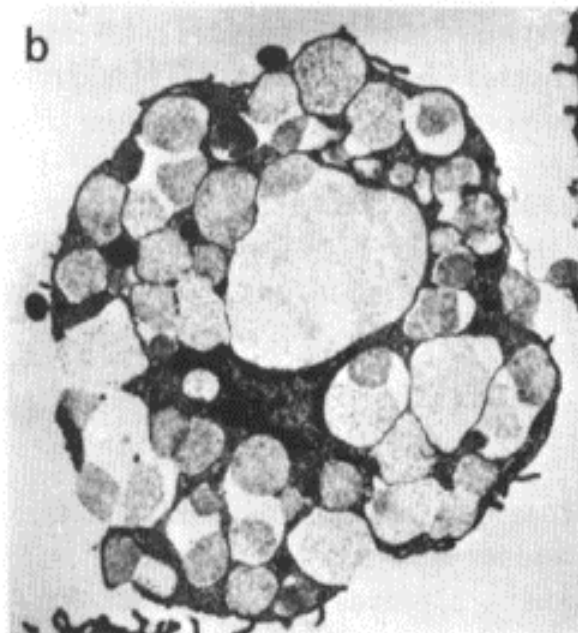
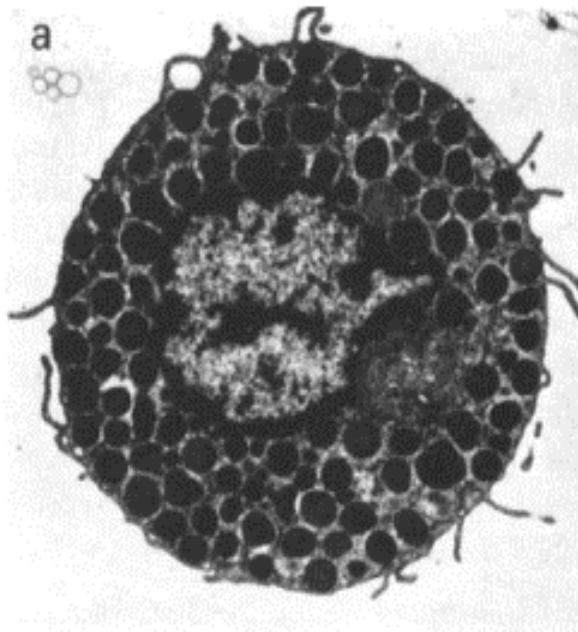
<p>Dendritic cell</p>	 <p>g</p>
<p>Activation of T cells and initiation of adaptive immune responses</p>	
<p>Mast cell</p>	 <p>h</p>
<p>Expulsion of parasites from body through release of granules containing histamine and other active agents</p>	

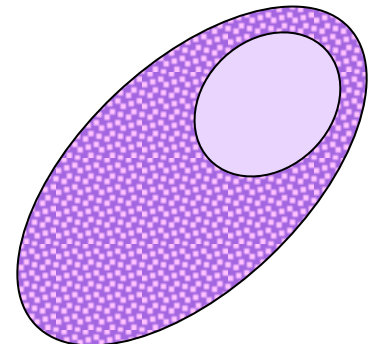
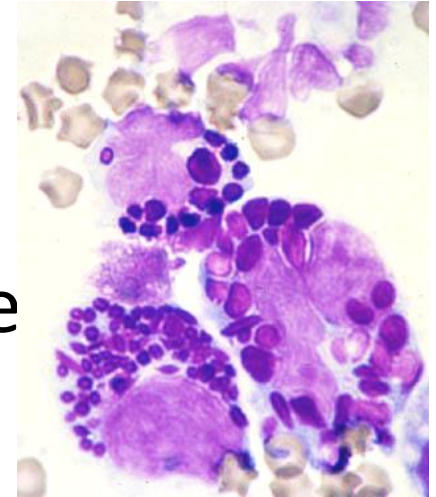
Figure 1-9 part 4 of 6 The Immune System, 2/e (© Garland Science 2005)

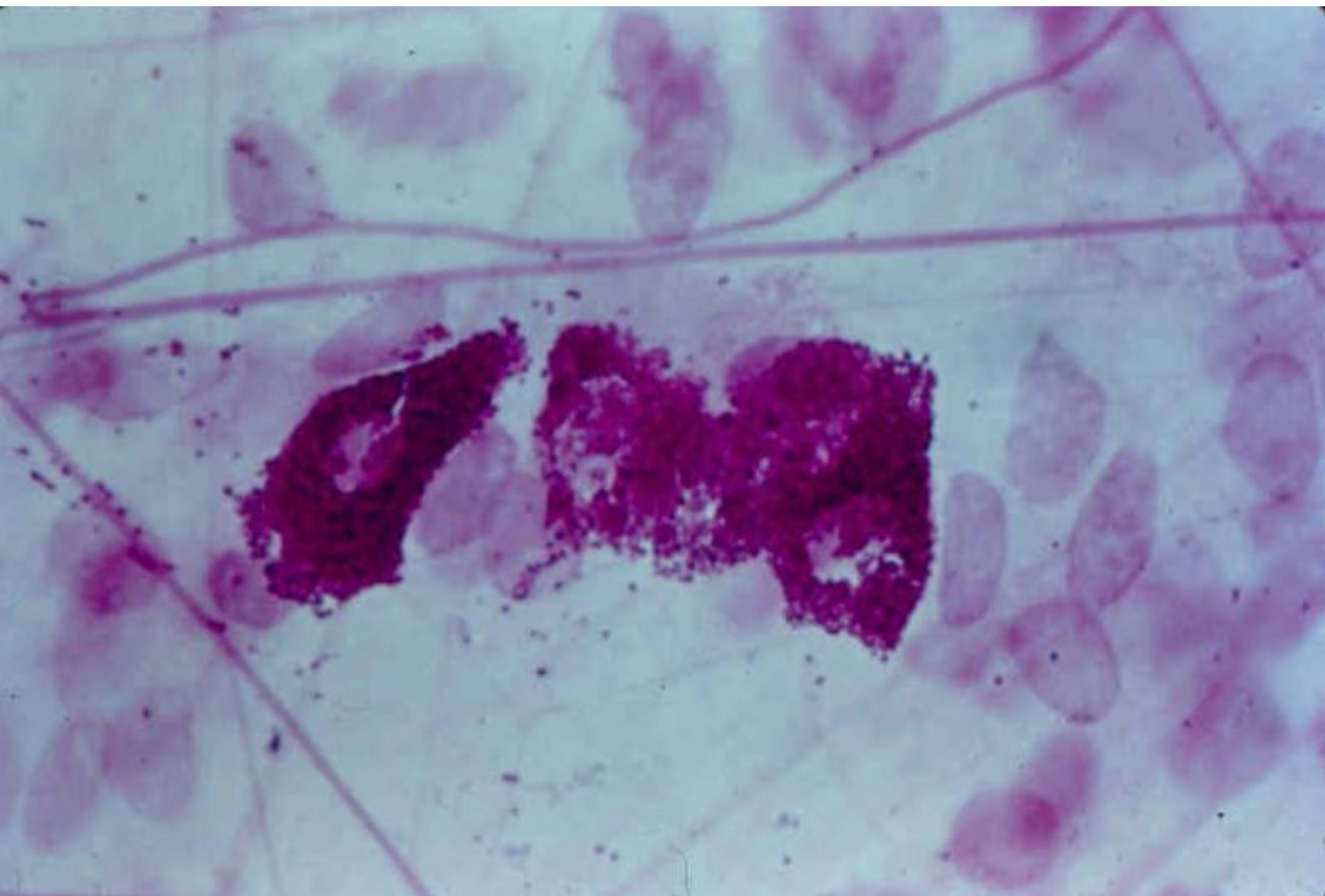


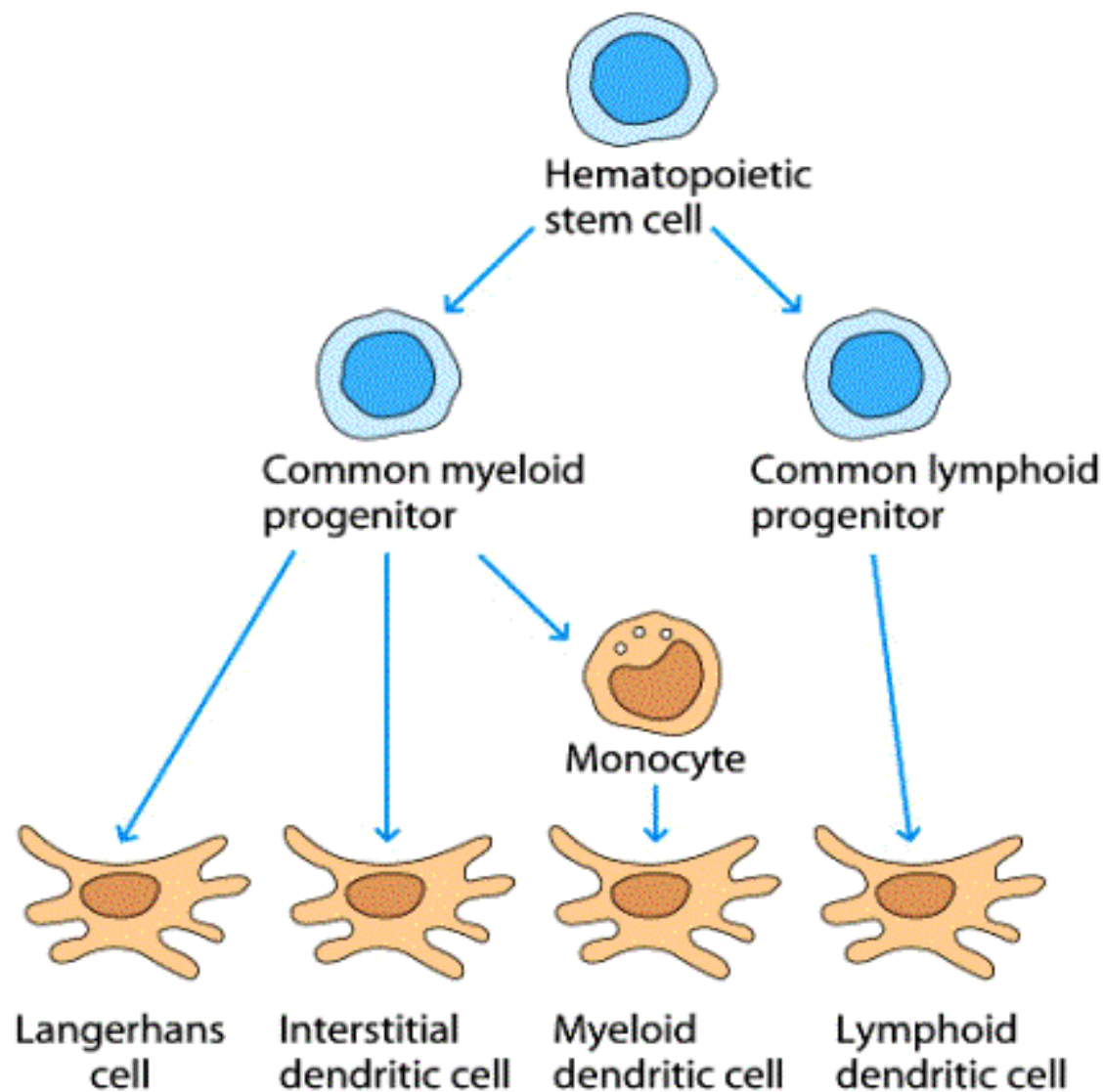
- Mast Cells
 - Origin
 - Location
 - Function
 - Importance in allergic responses

Mast Cells

- Expulsion of parasites through release of granules
- Histamine, leukotrienes, chemokine cytokines
- Also involved in allergic responses







- Dendritic cells

- Morphology

- Origin

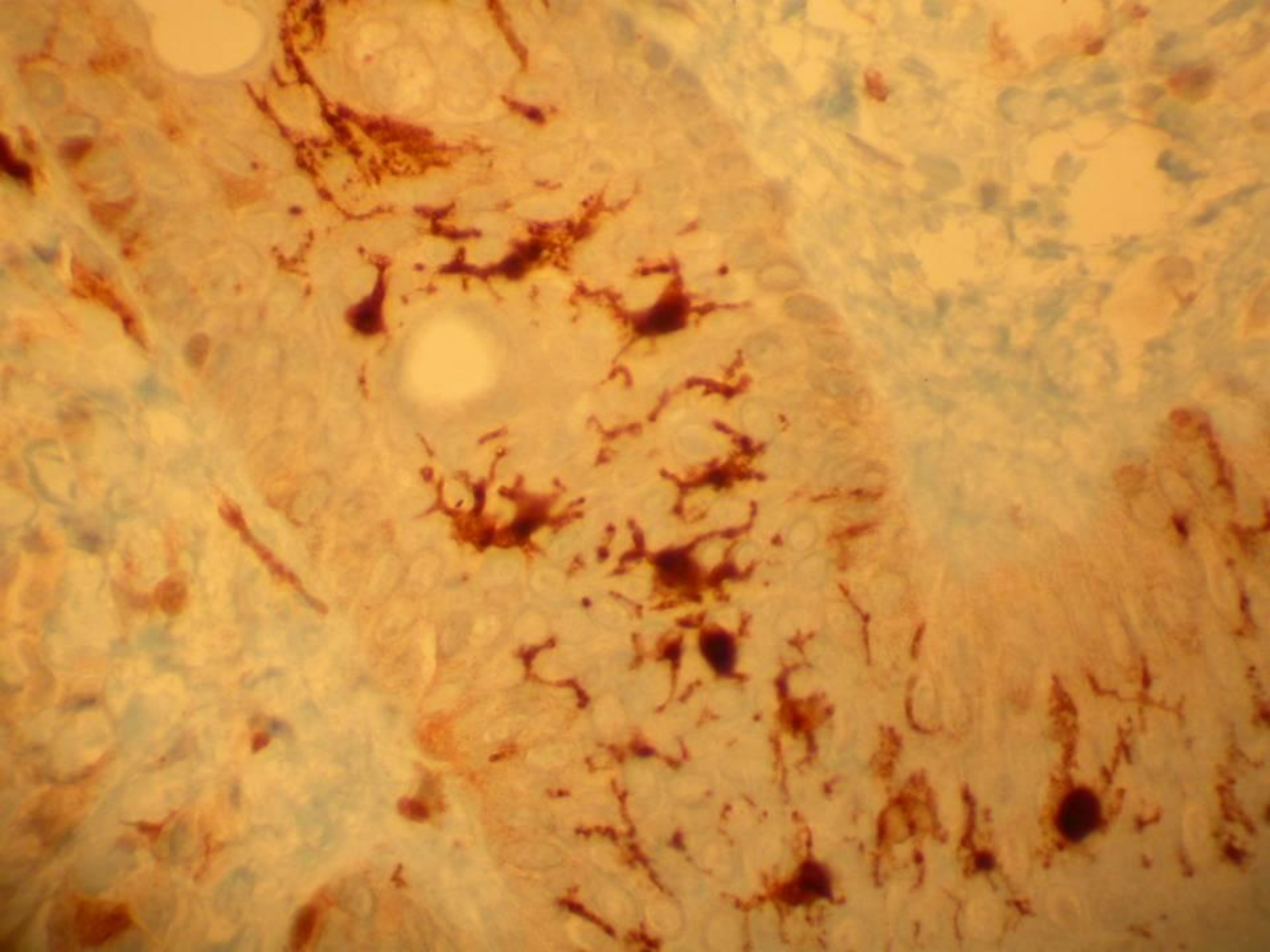
- Types

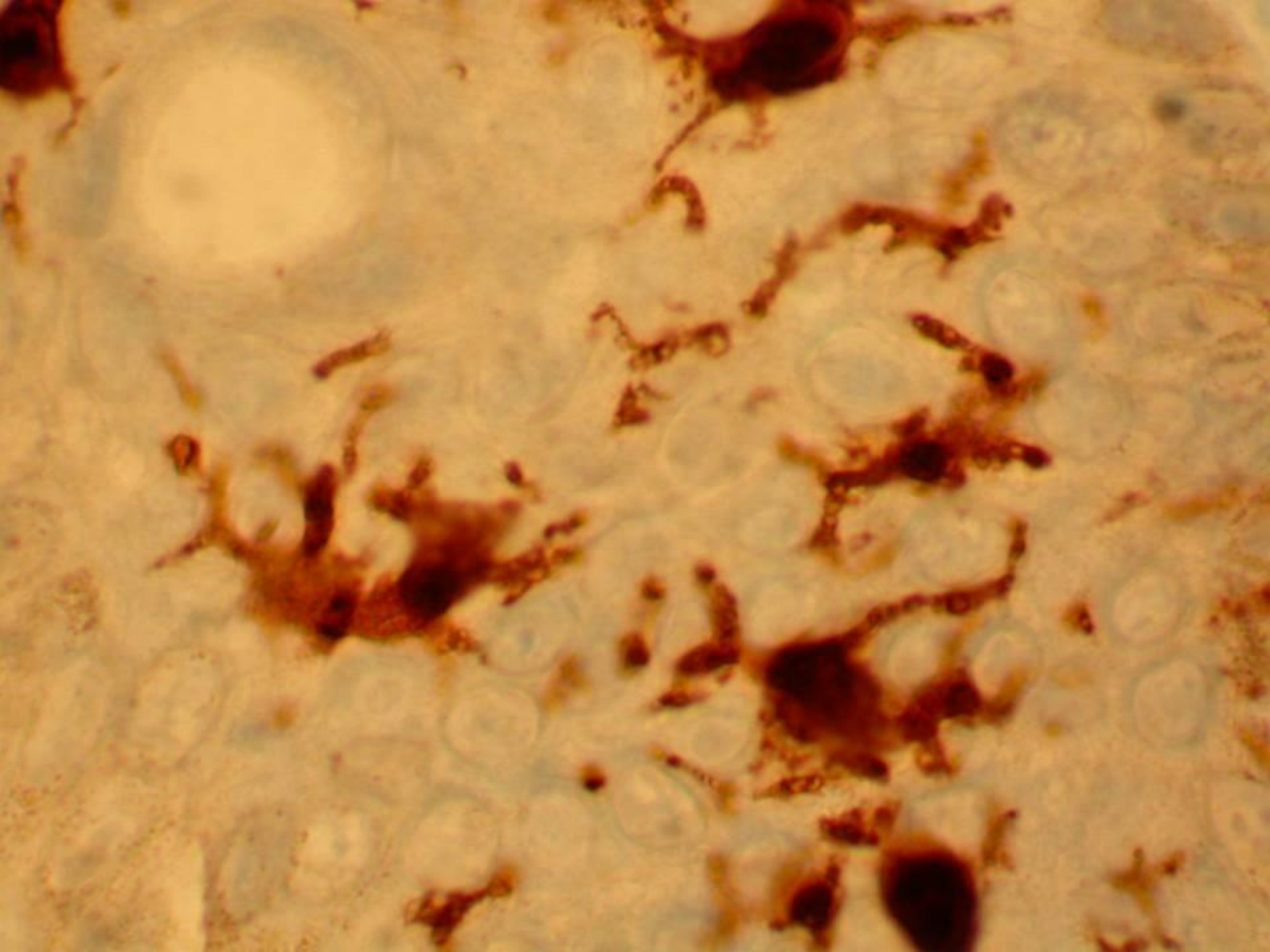
- Function

- Follicular dendritic cell

Dendritic cells (DC)

- are phagocytes in tissues that are in contact with the external environment; therefore, they are located mainly in the skin, nose, lungs, stomach, and intestines
- named for their resemblance to neuronal dendrites, as both have many spine-like projections, but dendritic cells are in no way connected to the nervous system
- serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigen to T cells, one of the key cell types of the adaptive immune system





CELLS OF INNATE AND ADAPTIVE IMMUNITY

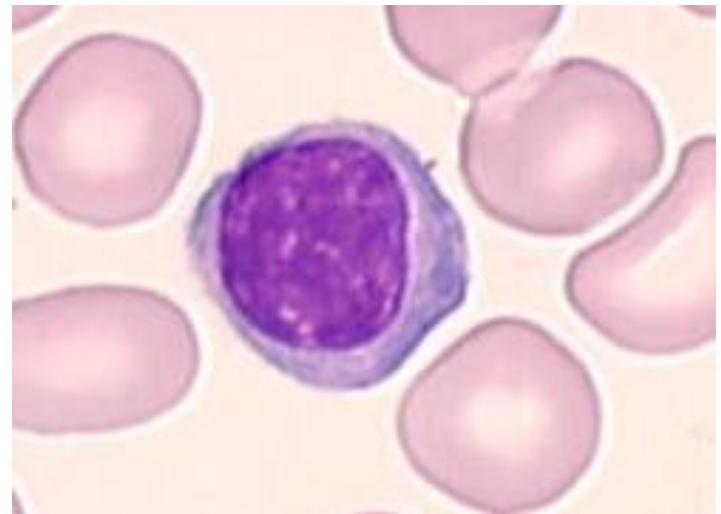
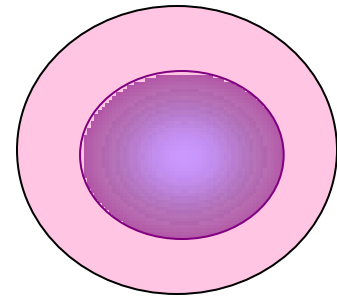
- Lymphoid Lineage
 - Large lymphocytes (large granular lymphocytes)
 - Natural killer (NK) cells (CD16, CD56)
 - Innate immunity to viruses and other intracellular pathogens
 - Participate in antibody-dependent cell-mediated cytotoxicity (ADCC)
 - Small lymphocytes
 - B cells (CD19)
 - T cells (CD3, CD4 or CD8)
 - Adaptive immunity
 - Lymphocytes refers to small lymphocytes

Lymphocytes; B cells T cells

- B cells & T cells carry receptor molecules that recognize specific targets
- T cells recognize a “non-self” target, such as a pathogen, only after antigens (small fragments of the pathogen) have been processed and presented in combination with a “self” receptor called a major histocompatibility complex (MHC) molecule
- There are two major subtypes of T cells: the killer T cell and the helper T cell
- Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells only recognize antigens coupled to Class II MHC molecules
- A third, minor subtype are the $\gamma\delta$ T cells that recognize intact antigens that are not bound to MHC receptors
- In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture

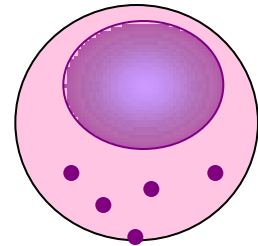
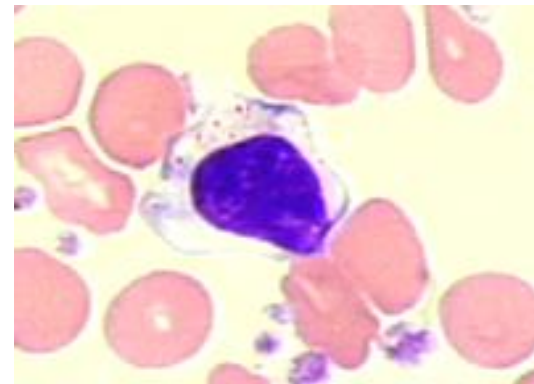
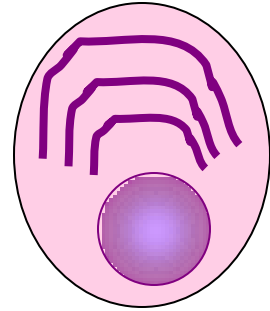
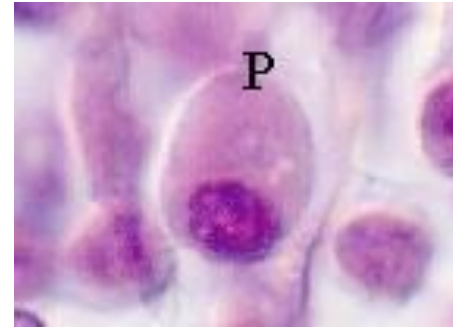
Lymphocytes

- Many types; important in both humoral and cell-mediated immunity
- B-cells produce antibodies
- T- cells
 - Cytotoxic T cells
 - Helper T cells
- Memory cells

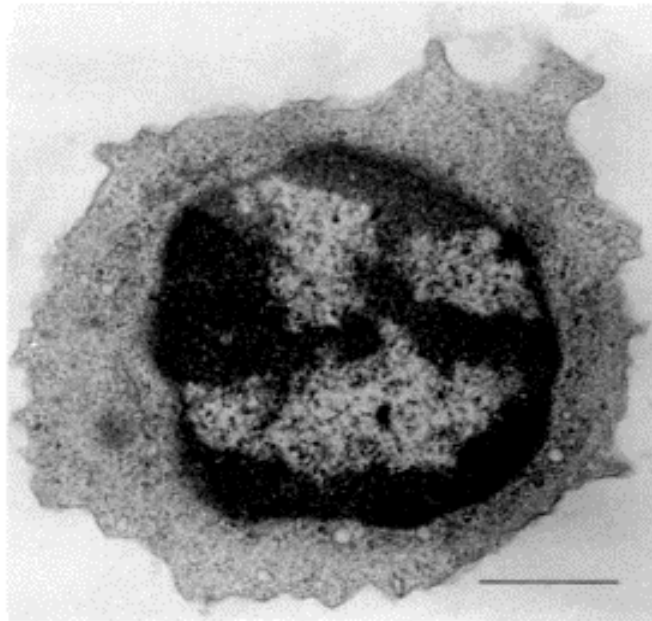


Lymphocytes

- Plasma Cell (in tissue)
 - Fully differentiated B cells, secretes Ab
- Natural Killer cells
 - Kills cells infected with certain viruses
 - Both innate and adaptive
 - Antigen presentation



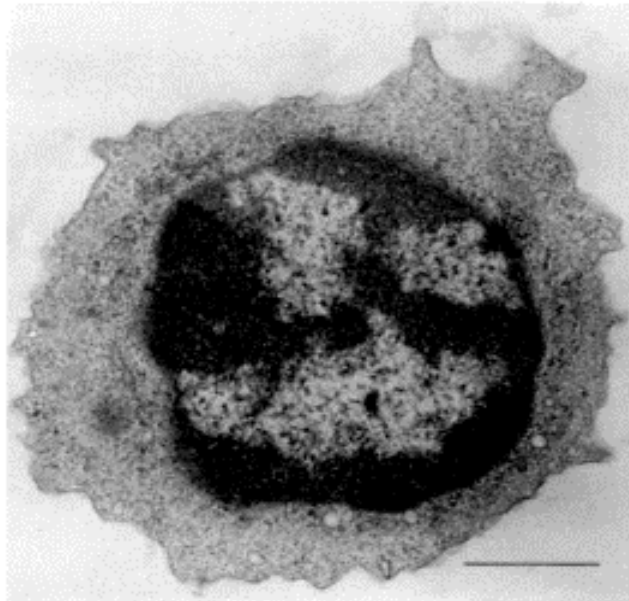
B Lymphocytes



Small lymphocyte (T or B)
6 μm diameter

- Site of maturation
- Membrane receptors
 - Membrane bound immunoglobulin
- Markers of a mature B cell
 - Class II MHC
 - B220
 - CR1 and CR2
 - Fc γ RII
 - B7-1, B7-2
 - CD40

T Lymphocytes



Small lymphocyte (T or B)
6 μm diameter

- Site of maturation
- Membrane receptors
 - T Cell Receptor (TCR)
 - CD4
 - CD8
 - CD28
 - CD45
- Classes of T cells
 - T helper cells (T_H)
 - T cytotoxic cells (T_C)
 - Function of T_H and T_C
- Class restriction

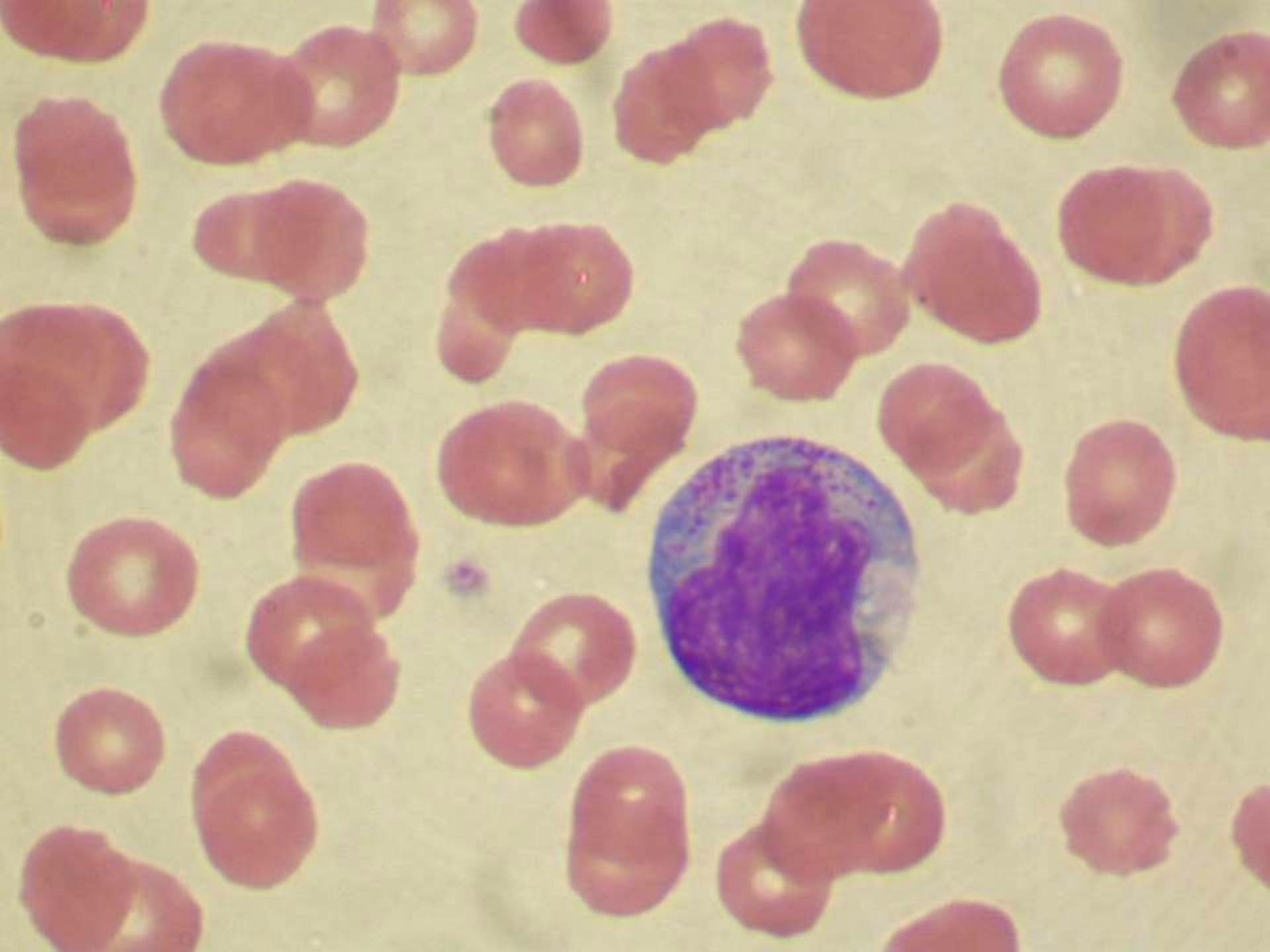
Comparison of T and B cells

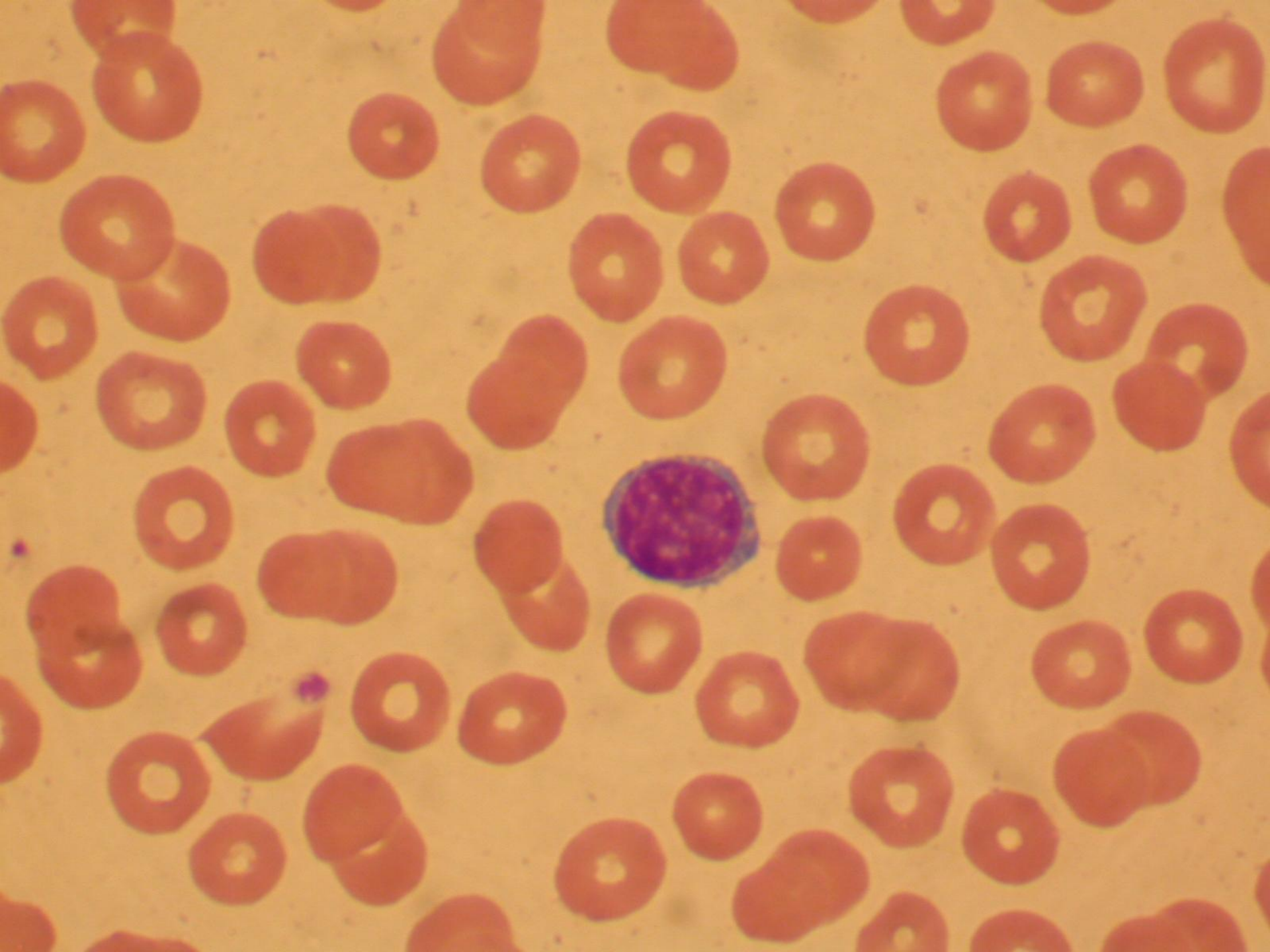
T-cells

- responsible for cell mediated immunity
- Life span is long
- Differentiate inside Thymus Gland
- Absence of surface antibodies
- Transformed in small lymphocytes by antigens
- secrete Lymphokines
- sub population are Cytotoxic T, Helper cells and suppressor cells.
- stimulate phagocytes and B-cells into activity.

B-cells

- responsible for Humoral immunity
- Life span is short
- Differentiate inside Bone Marrow
- Surface Antibodies present
- Transformed to plasma cells by antigens
- secrete antibodies
- sub population are memory cells and plasma cells
- B-cells or B-lymphocytes produce antibodies



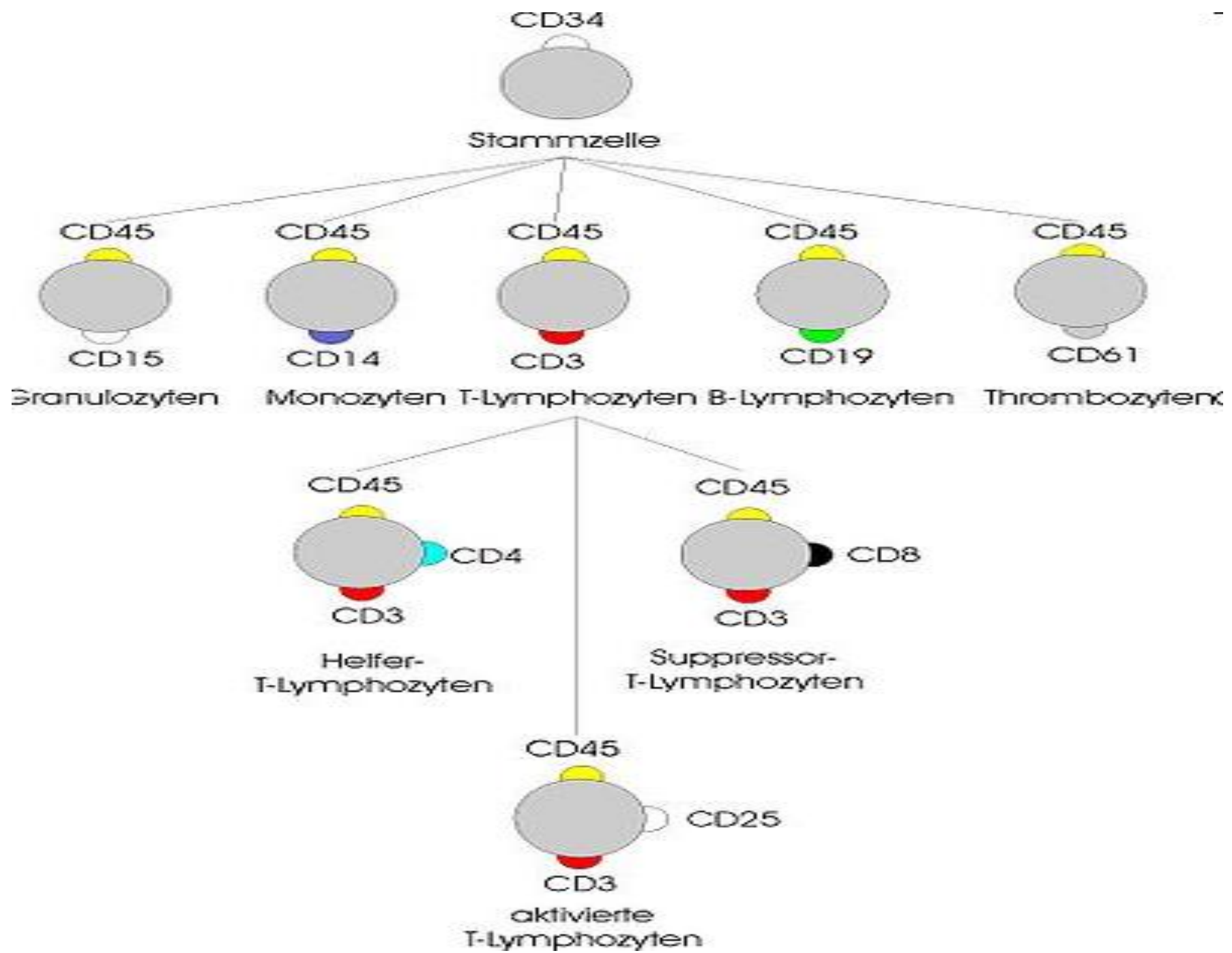


THE CLUSTER OF DIFFERENTIATION (CD)

- CD nomenclature established in 1982
 - 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (HLDA) held in Paris
- protocol for identification and investigation of cell surface molecules
- intended for classification of many monoclonal antibodies generated by different laboratories around the world against epitopes on the surface molecules of leukocytes
- CD number assigned on basis of 1 cell surface molecule recognized by 2 specific m Ab

cluster of differentiation

- The (**cluster of designation**) (often abbreviated as **CD**) is a protocol used for the identification and investigation of cell surface molecules present on White blood cells
- CD molecules can act in numerous ways, often acting as receptors or ligands (the molecule that activates a receptor) important to the cell
- A signal cascade is usually initiated, altering the behavior of the cell
- Some CD proteins do not play a role in cell signaling, but have other functions, such as cell adhesion
- CD for humans is numbered up to 350 most recently (as of 2009).
- If the molecule has not been well-characterized, or has only one mAb, it is usually given the provisional indicator "w" (as in "CDw186")



THE CLUSTER OF DIFFERENTIATION (CD)

- CD markers on leukocytes

Granulocyte	CD45+, CD15+
Monocyte	CD45+, CD14+
T lymphocyte	CD45+, CD3+
T helper lymphocyte	CD45+, CD3+, CD4+
T cytotoxic lymphocyte	CD45+, CD3+, CD8+
B lymphocyte	CD45+, CD19+
Natural killer cell	CD45+, CD16+, CD56+, CD3-

TABLE 2-5

Common CD markers used to distinguish functional lymphocyte subpopulations

CD designation*	Function	T CELL			
		B cell	T _H	T _C	NK cell
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 co-stimulatory 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.

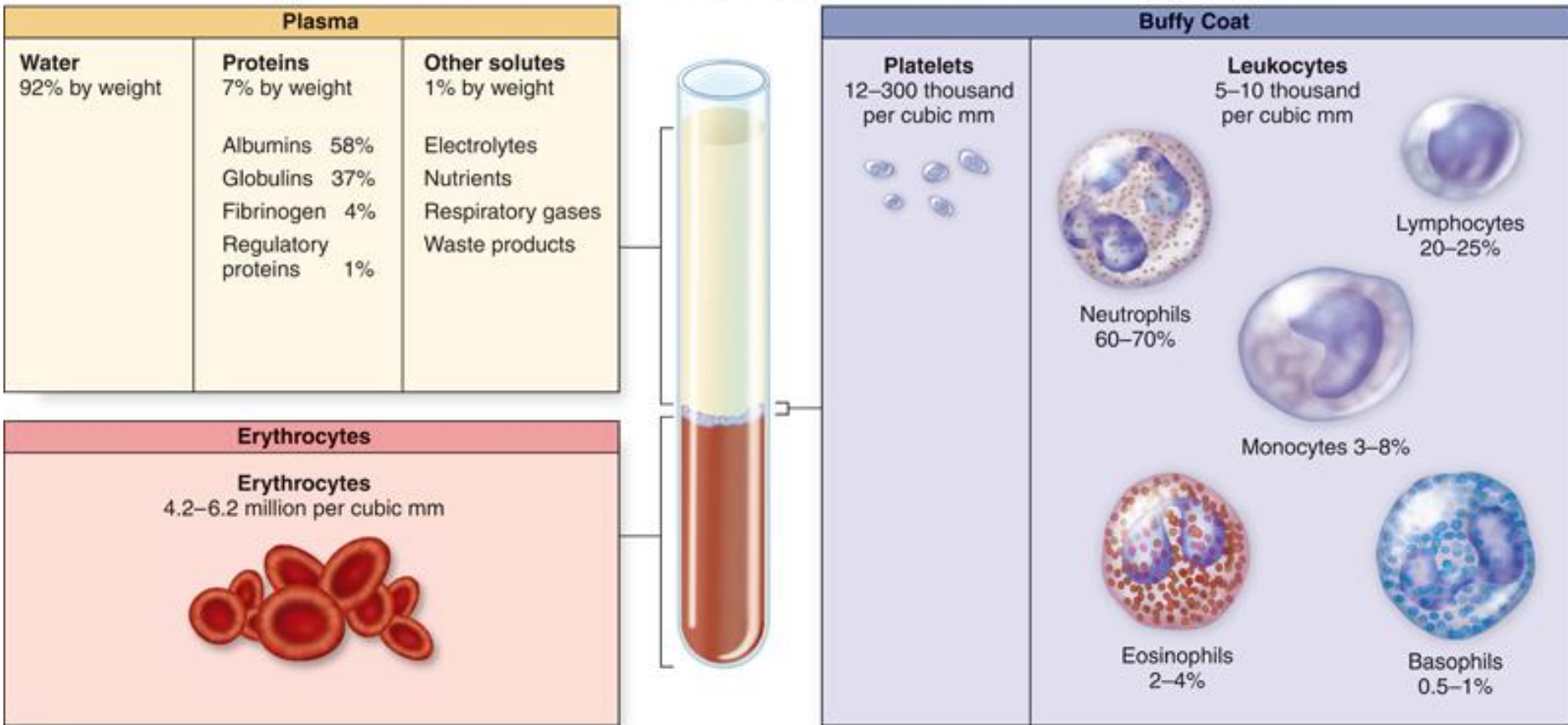
Components of blood

Serum vs. Plasma

- Serum: cell-free liquid, minus the clotting factors
- Plasma: cell-free liquid with clotting factors in solution (must use an anticoagulant)

Components of blood

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COMPLETE BLOOD COUNT WITH DIFFERENTIAL (CBC WITH DIFF)

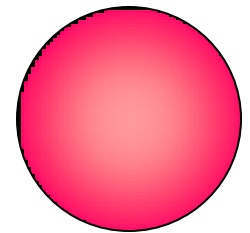
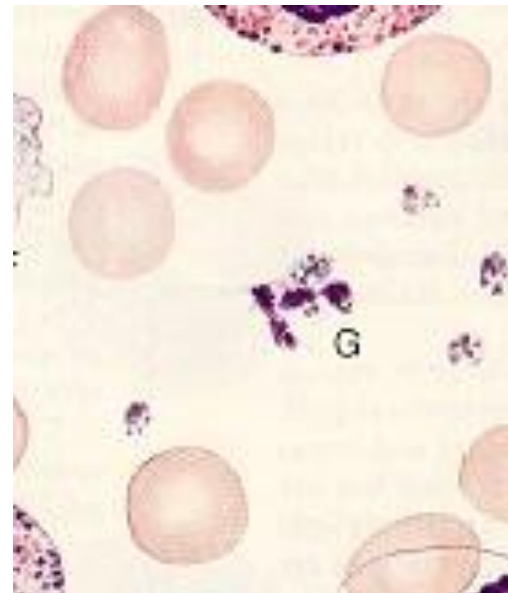
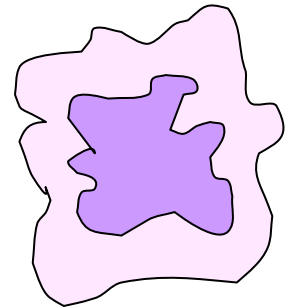
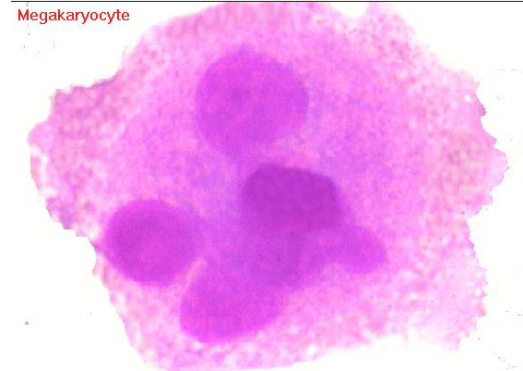
	References	Ranges
Erythrocytes (RBC)	4.0 to 5.4	M/uL
Thrombocytes (Platelets)	145 to 400	K/uL
Leukocytes (WBC)	4.8 to 10.8	K/uL
Neutrophils	40 to 74	%
Band neutrophils	0 to 9	
Eosinophils	0 to 6	
Basophils	0 to 1	
Lymphocytes	15 to 47	
Monocytes	0 to 12	

Cell type	Proportion of leukocytes (%)
Neutrophil	40–75
Eosinophil	1–6
Basophil	<1
Monocyte	2–10
Lymphocyte	20–50

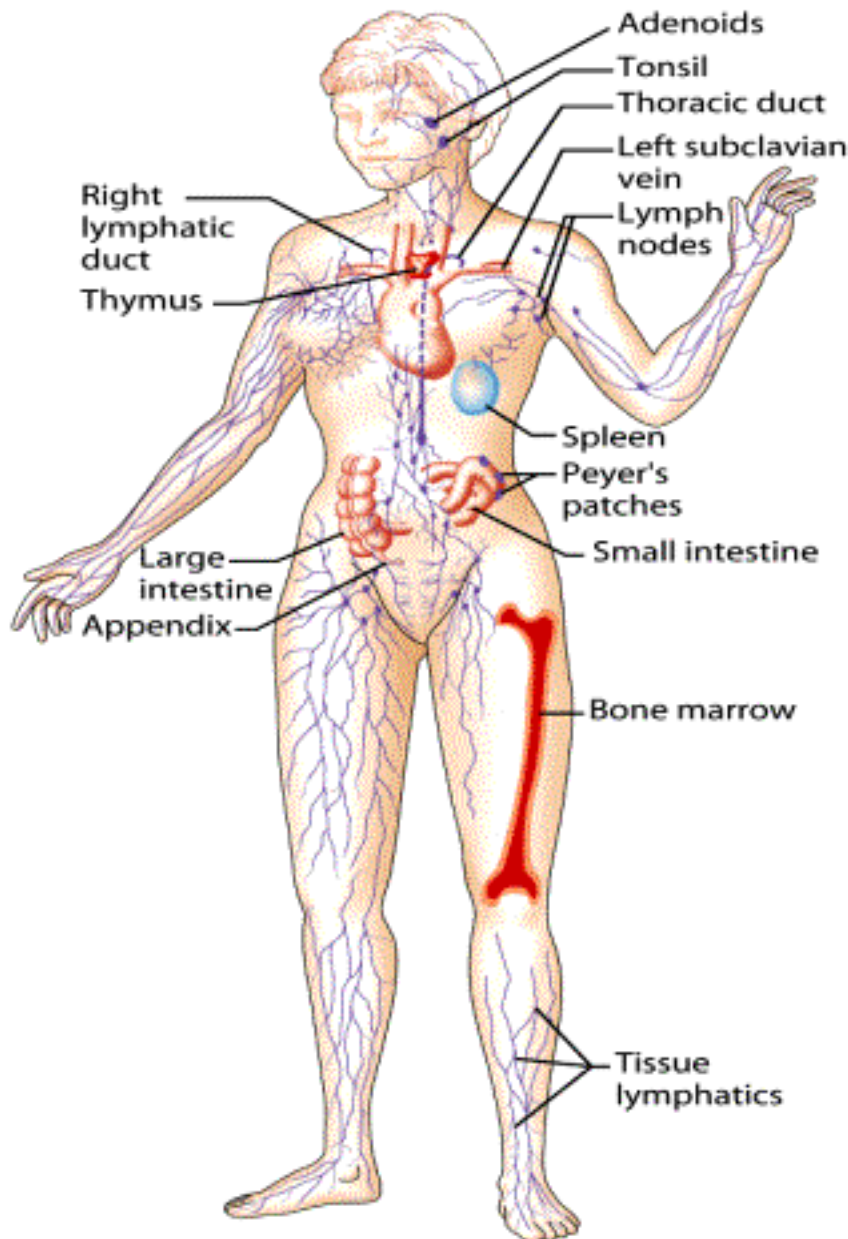
Figure 1-12 The Immune System, 2/e (© Garland Science 2005)

Other Blood Cells

- Megakaryocyte
 - Platelet formation
 - Wound repair
- Erythrocyte
 - Oxygen transport



Organs of the Immune System



- Primary lymphoid organs
 - Bone marrow
 - Thymus gland
- Secondary lymphoid organs
 - Lymph nodes
 - Spleen
 - MALT
- Tertiary lymphoid organs
 - Cutaneous associated lymphoid tissue

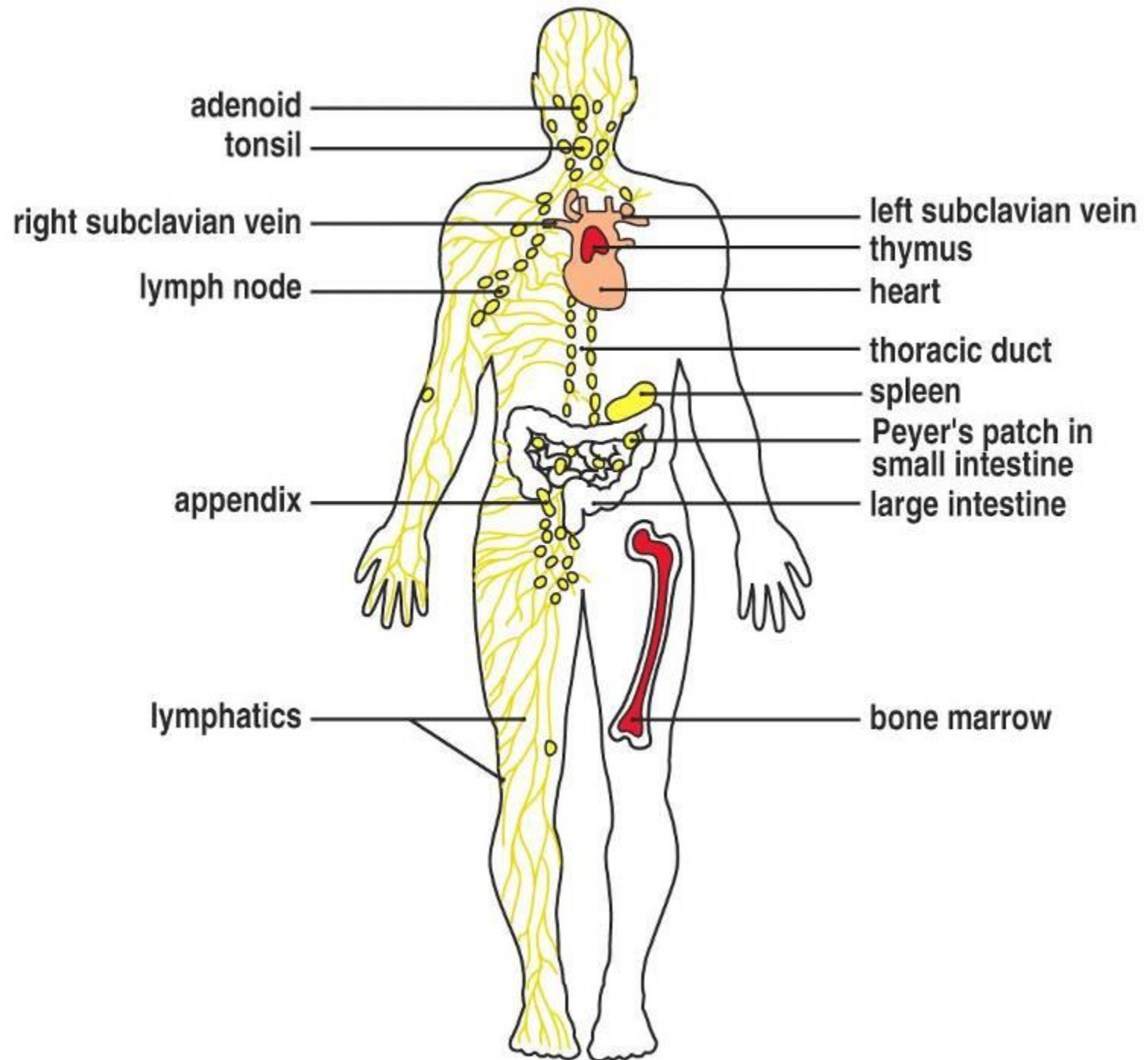


Figure 1-15 The Immune System, 2/e (© Garland Science 2005)

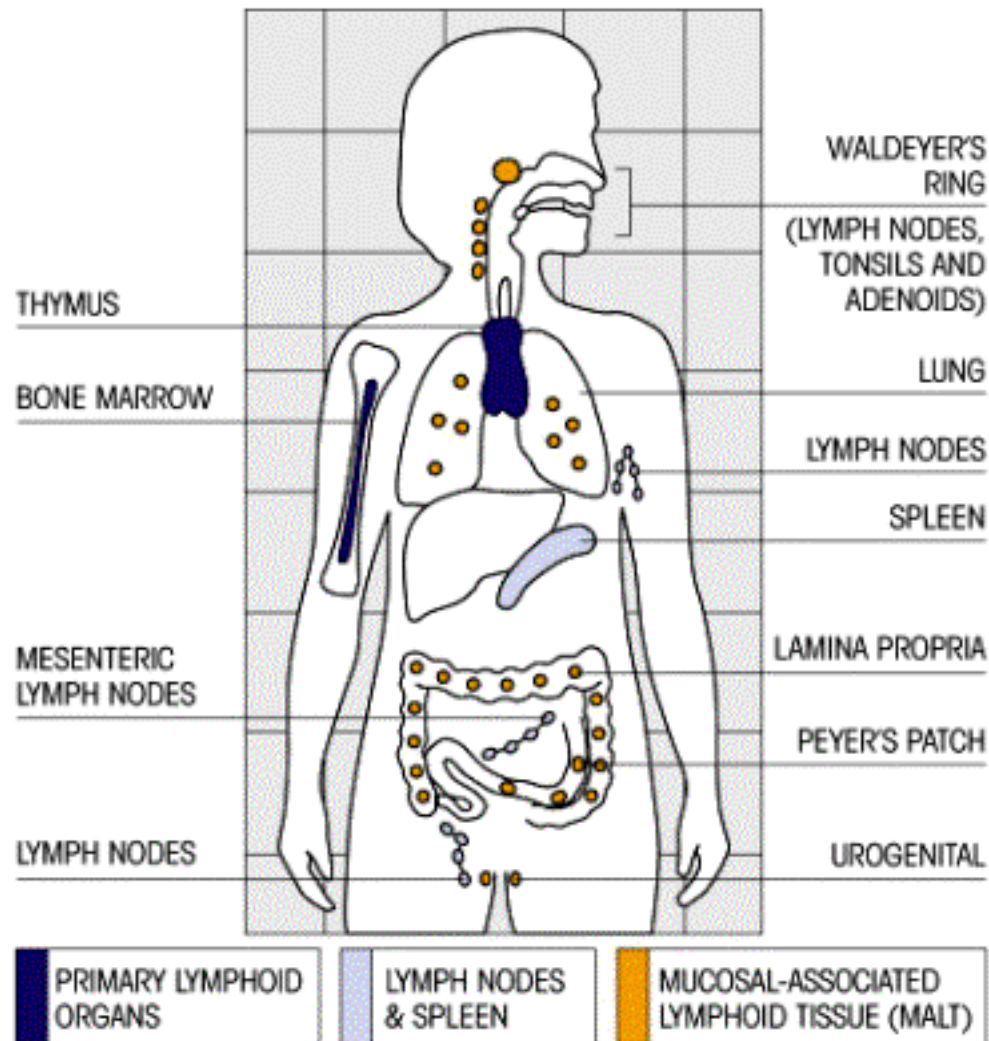
LYMPHOCYTES, LYMPHOID TISSUES AND ORGANS

- Lymphocytes originate in bone marrow
- Lymphoid tissues and organs
 - Primary
 - Development and maturation of lymphocytes
 - Bone Marrow (B cells) and thymus gland (T cells)
 - Secondary
 - Mature lymphocytes meet pathogens
 - Spleen, adenoids, tonsils, appendix, lymph nodes, Peyer's patches, mucosa-associated lymphoid tissue (MALT)

THE LYMPHATIC SYSTEM

- Lymph
 - Fluid and cells in lymphatic vessels
- Lymphatic vessels
 - Collect and return interstitial fluid to blood
 - Transport immune cells throughout body
 - Transport lipid from intestine to blood
- Lymph nodes
 - Kidney shaped organs at intervals along lymphatic vessels
- Other secondary lymphatic tissues and organs

Lymphoid Organs



LYMPHOCYTES AND THE LYMPH NODES

- Naïve lymphocytes circulate between blood, lymph and secondary lymph nodes
- Pathogens from infected tissue sites are picked up by lymphatic vessels and arrive at closest lymph node
- T and B cells congregate at specific regions of nodes
- Architecture and size of nodes change in response to activation of lymphocytes

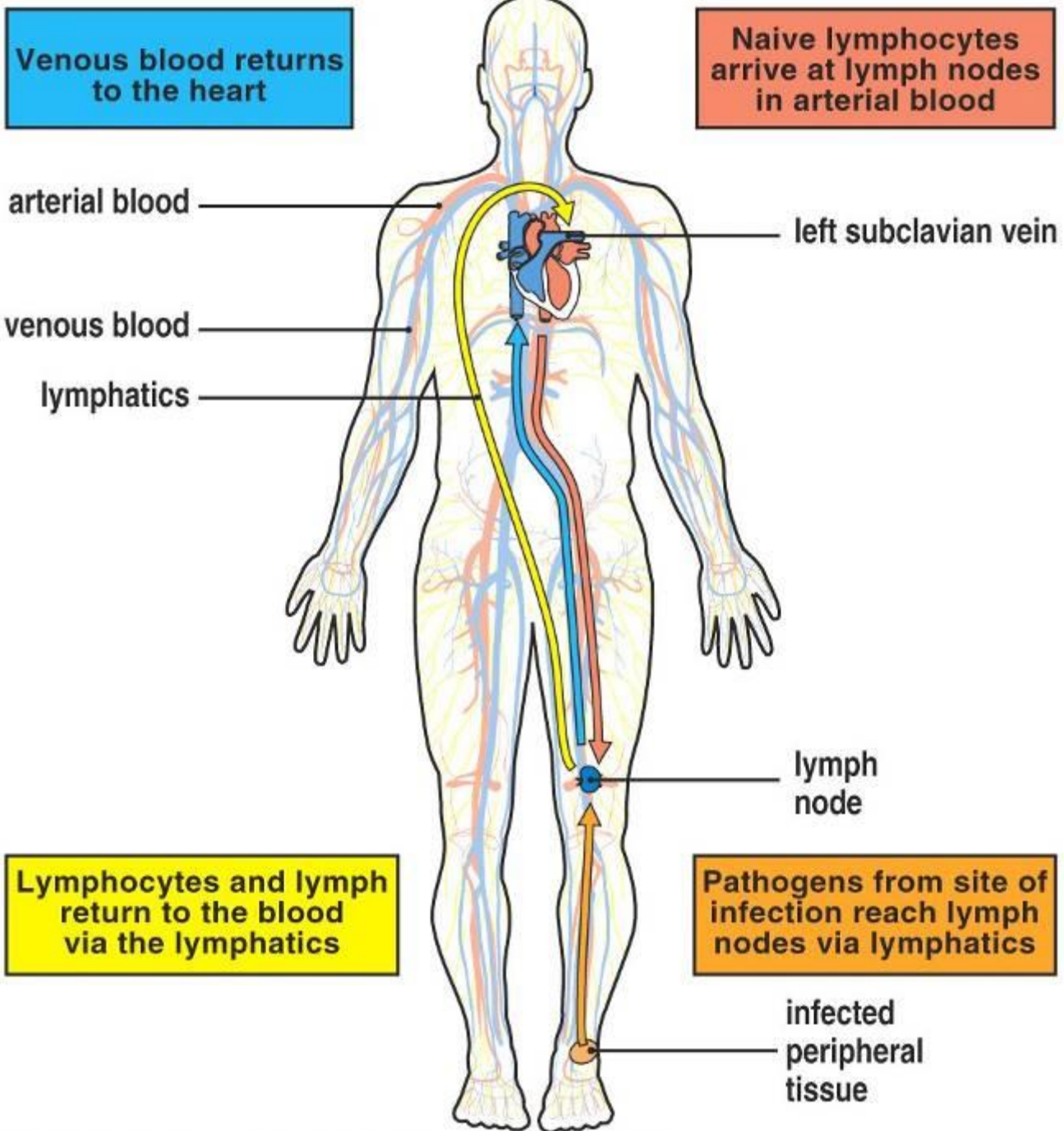
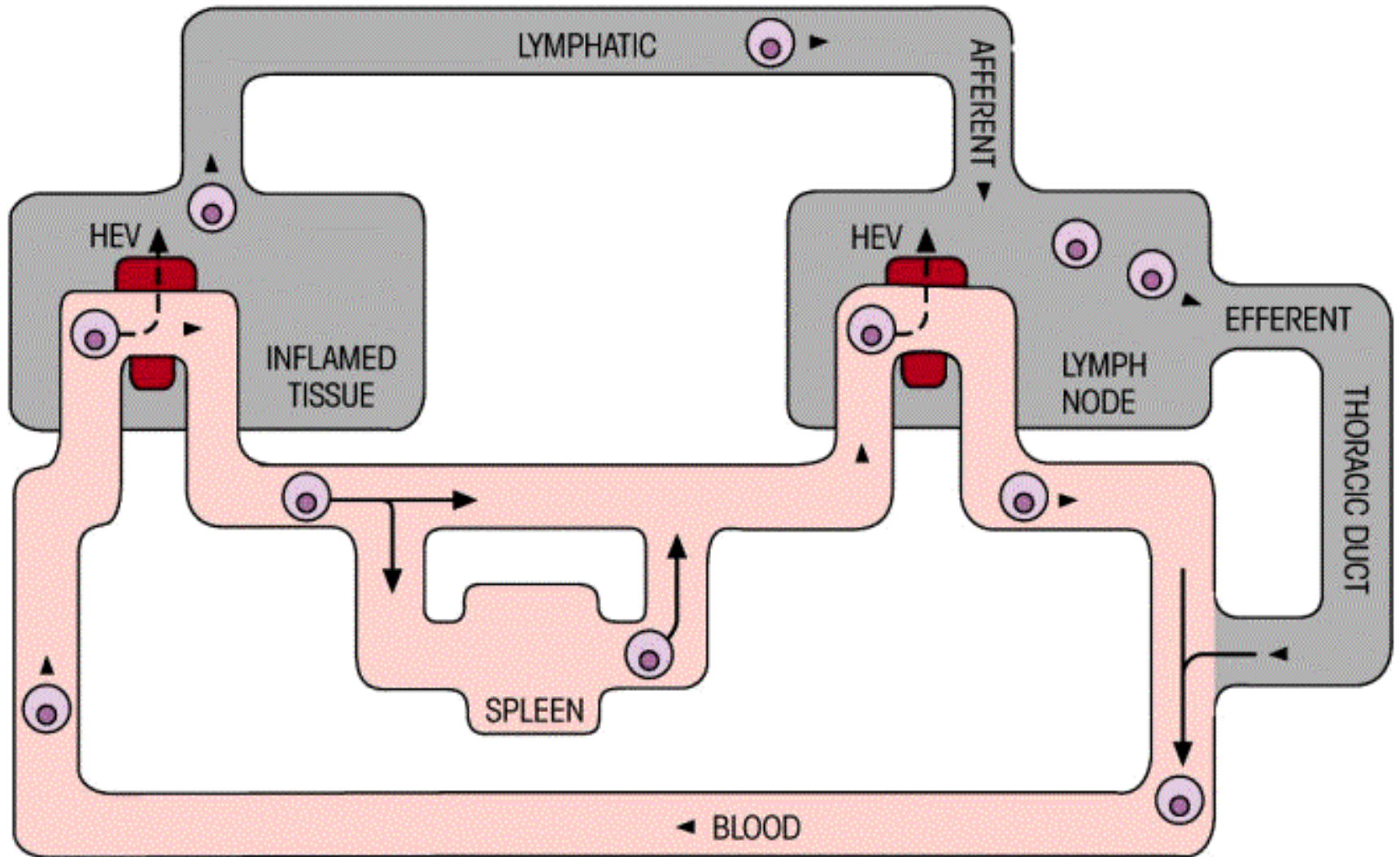
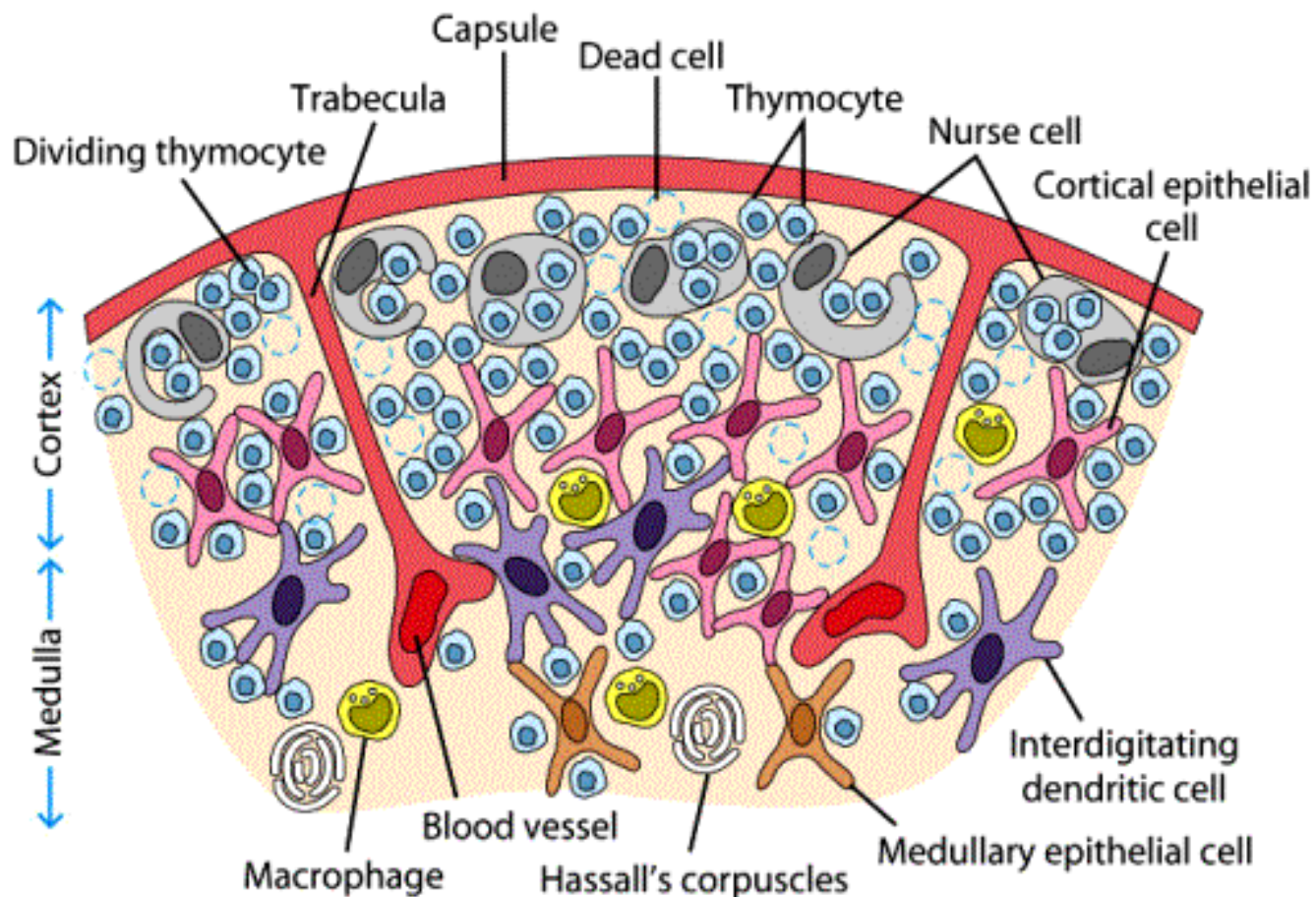
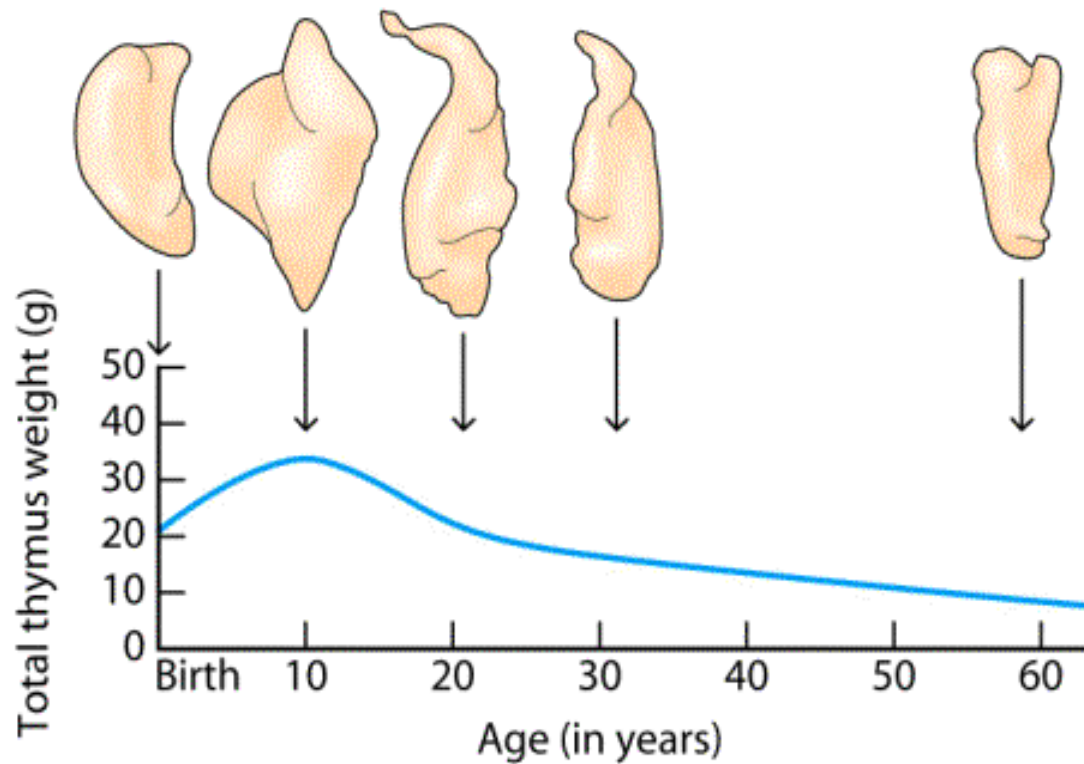


Figure 1-16 The Immune System, 2/e (© Garland Science 2005)





- Thymus
 - Site of T cell development and maturation
 - Anatomical structure
 - Role in immune function
 - Result of dysfunction, DiGeorge's Syndrome



- Age, thymus size and function of the immune system

The lymph node

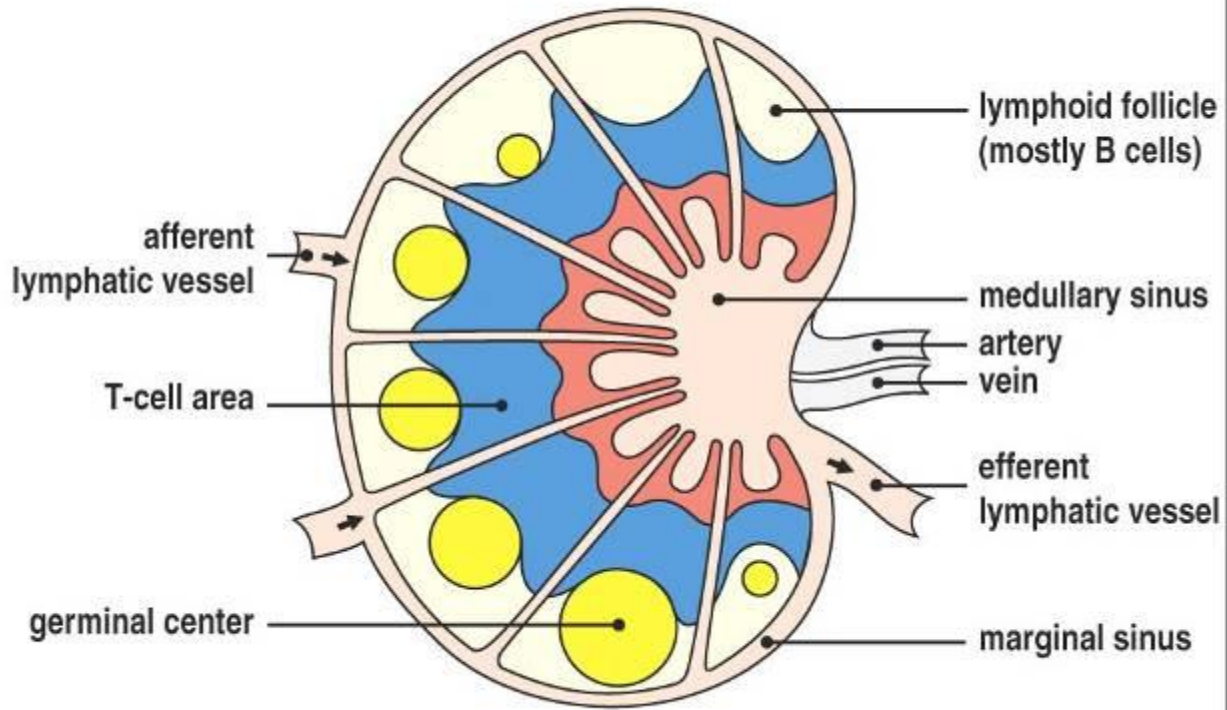
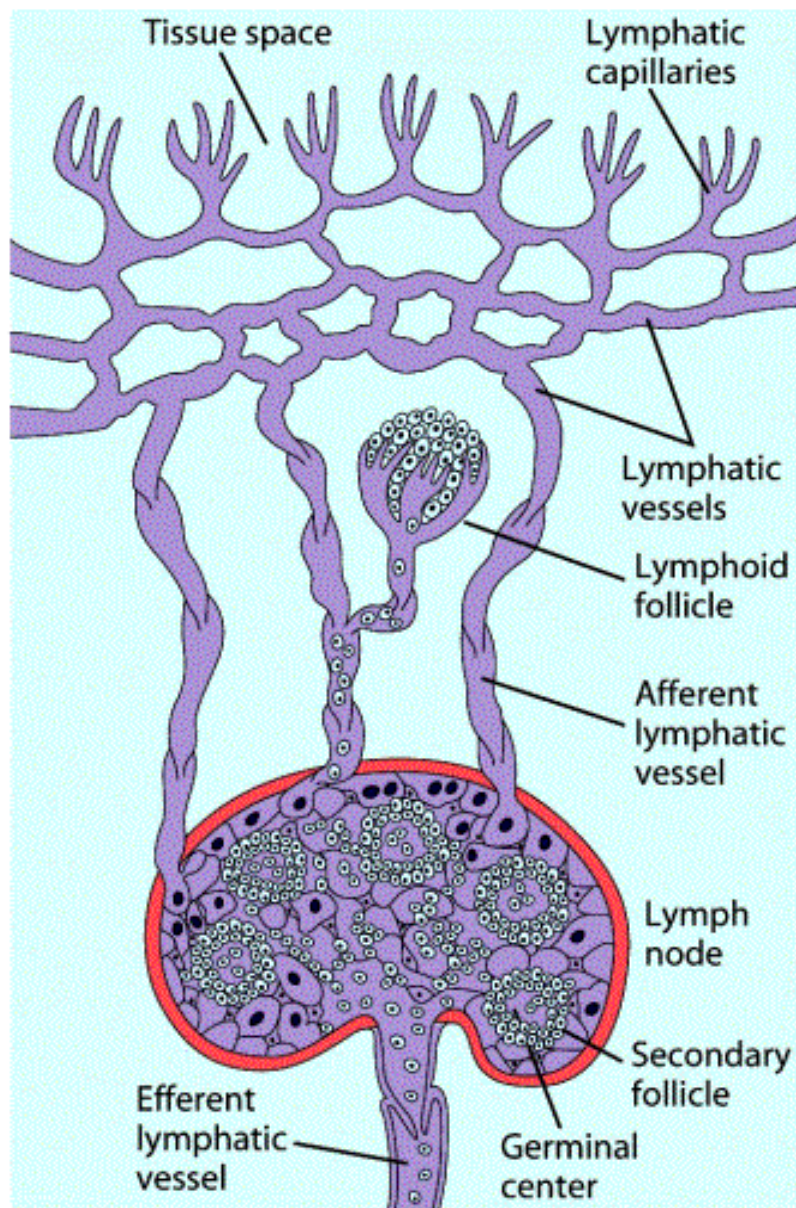


Figure 1-17 The Immune System, 2/e (© Garland Science 2005)

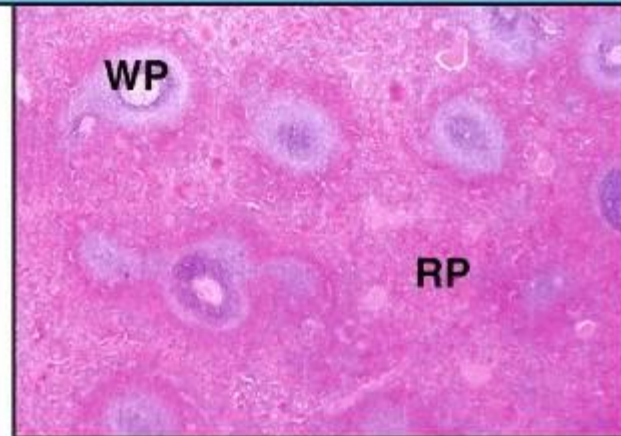
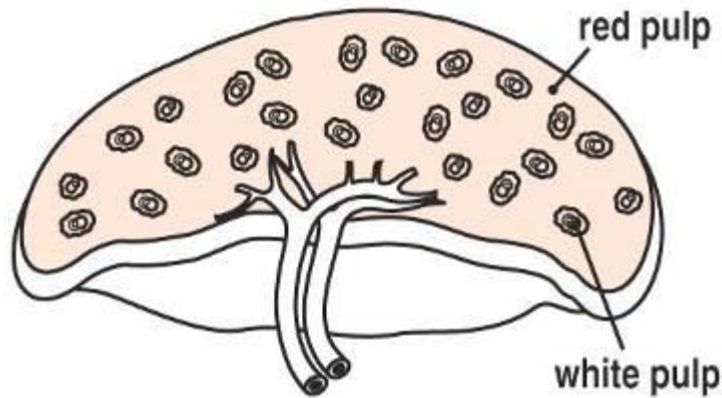


- Lymphatic System and function of lymph nodes
 - Circulation of lymphocytes
 - Interstitial fluid
 - Route of lymph in the lymph node
 - Follicle
 - Germinal center

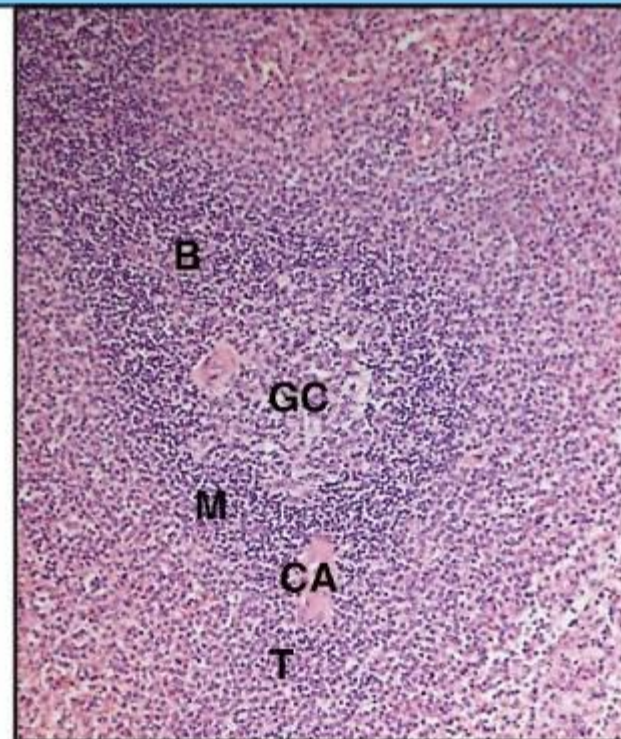
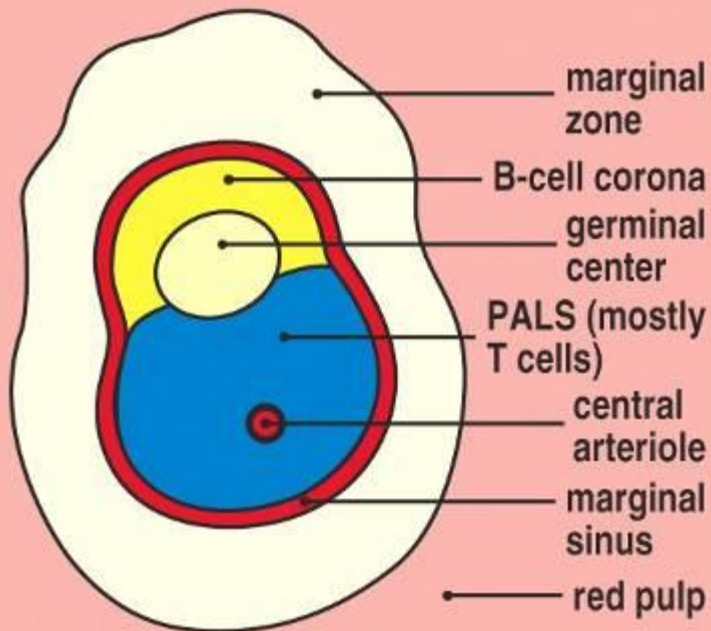
LYMPHOCYTES AND THE SPLEEN

- Spleen
 - Lymphoid organ in upper left abdomen
 - Functions
 - Remove damaged or old erythrocytes
 - Activation of lymphocytes from blood borne pathogens
- Architecture of Spleen
 - Red pulp
 - Erythrocytes removed
 - White pulp
 - Lymphocytes stimulated

The spleen



Transverse section of white pulp of spleen



SECONDARY LYMPHOID TISSUES ASSOCIATED WITH MUCOUS MEMBRANES

- Primary portals of entry for pathogens
 - Respiratory tract
 - Gastrointestinal tract
- Secondary lymphoid tissues
 - Bronchial-associated lymphoid tissue (BALT)
 - Gut-associated lymphoid tissues (GALT)
 - Tonsils, adenoids, appendix, Peyer's patches
- Pathogens are directly transferred across mucosa by “M” cells

Gut-associated lymphoid tissue

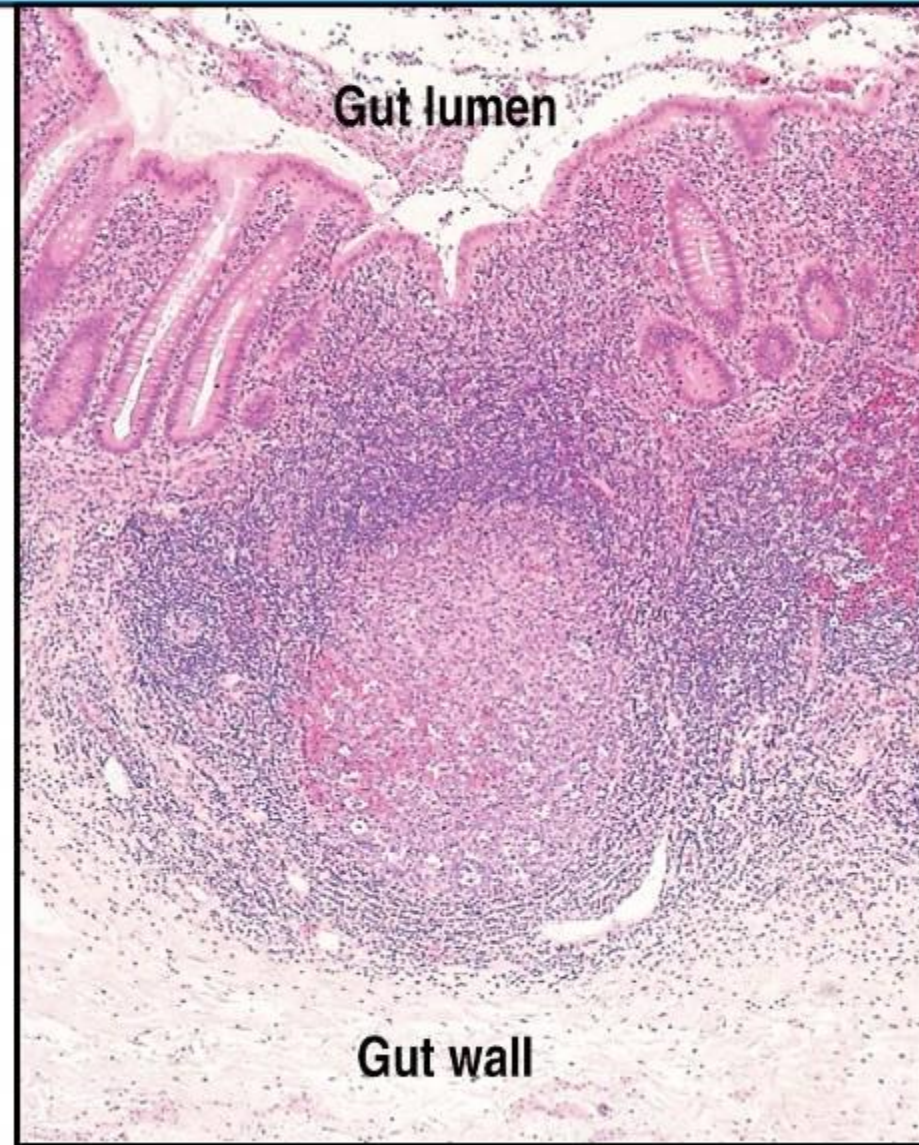
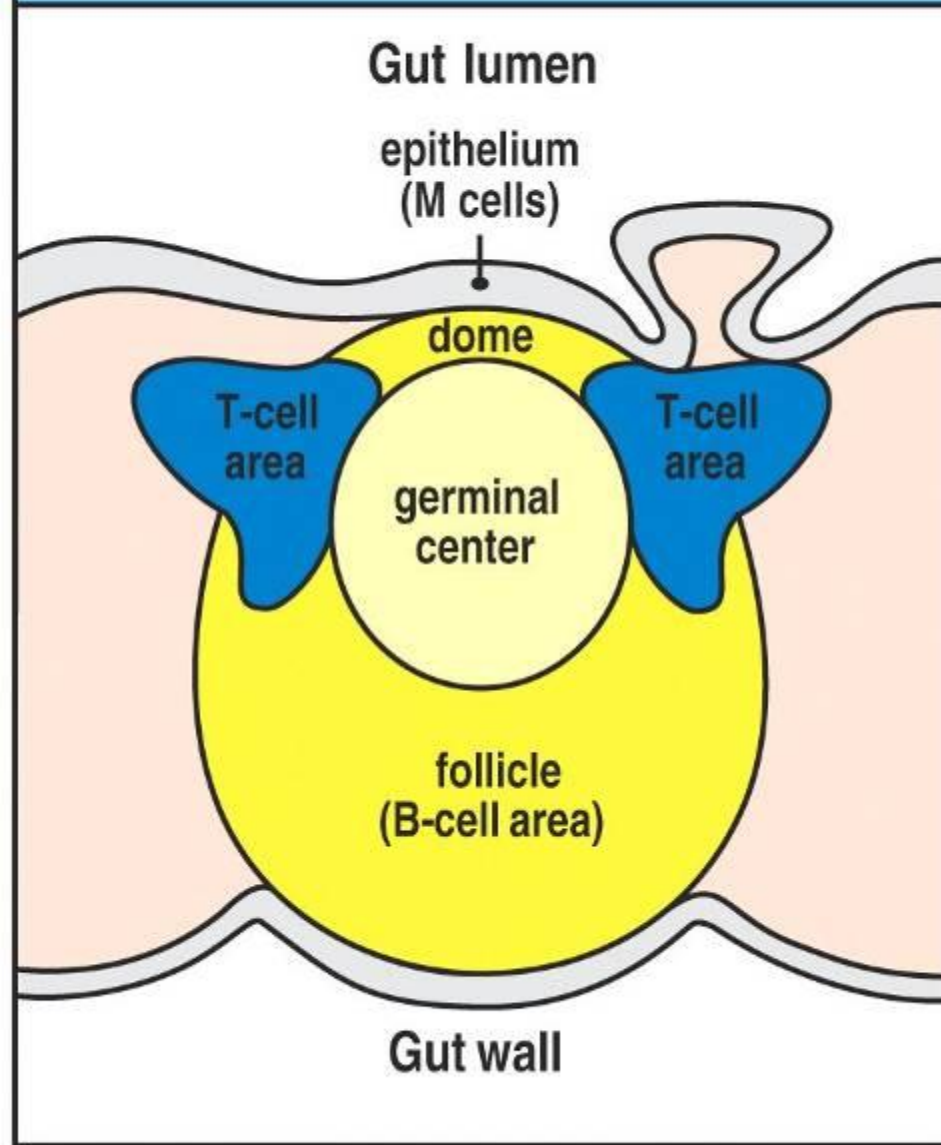
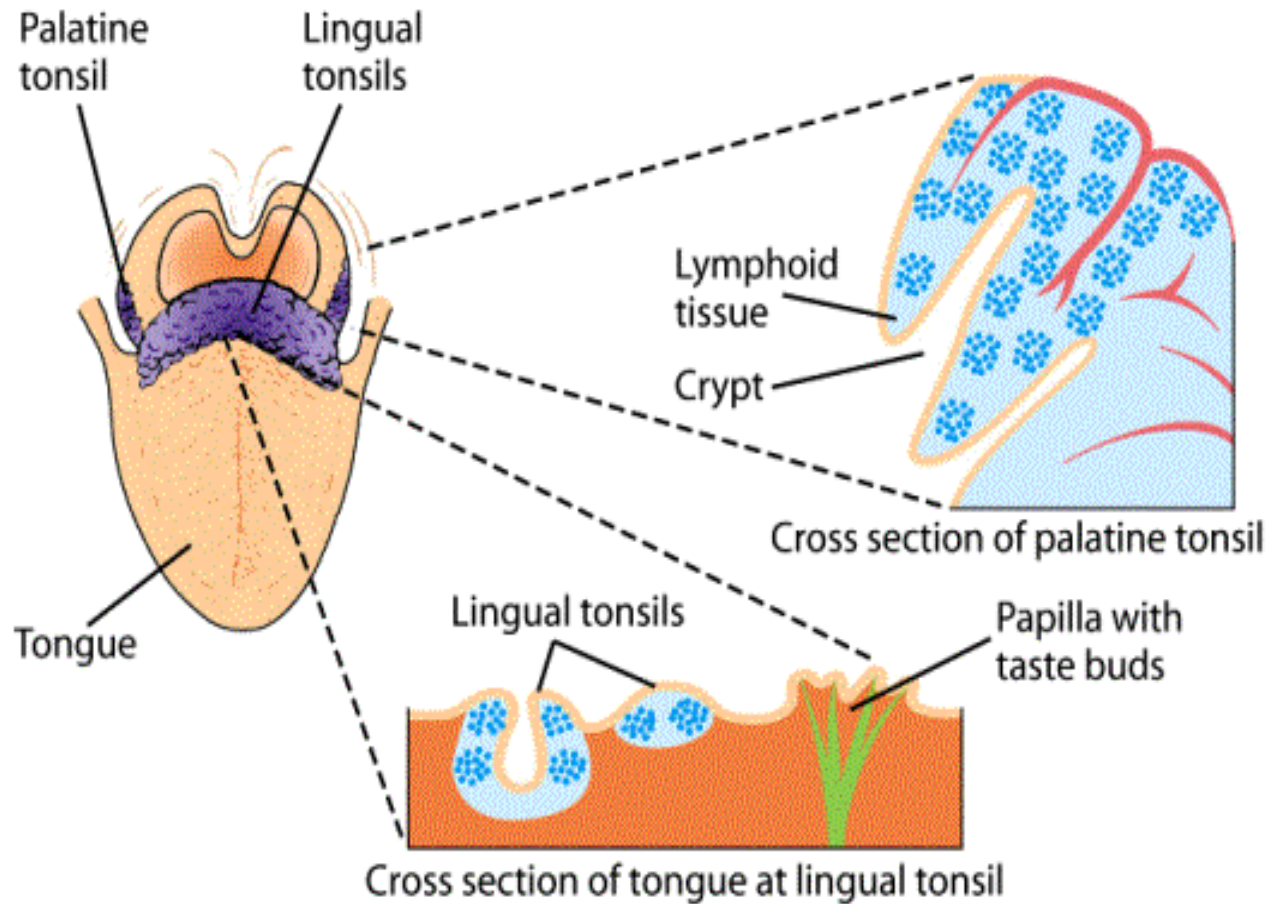
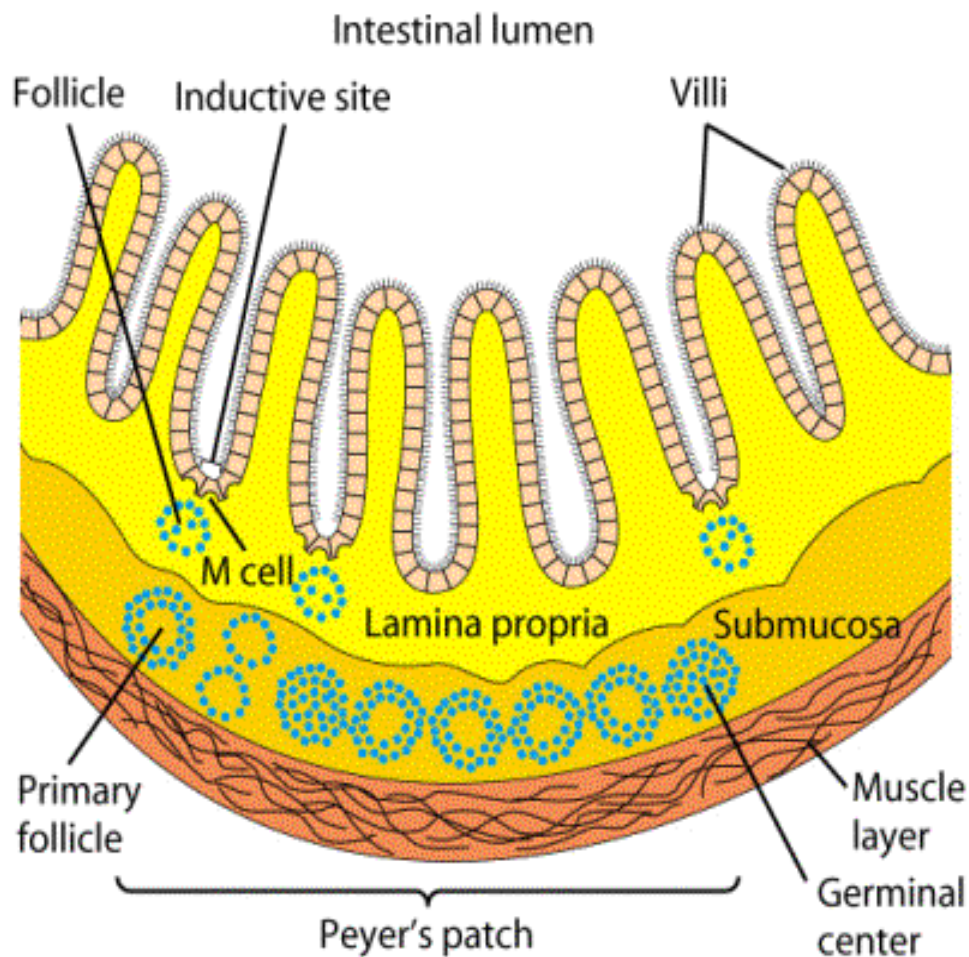


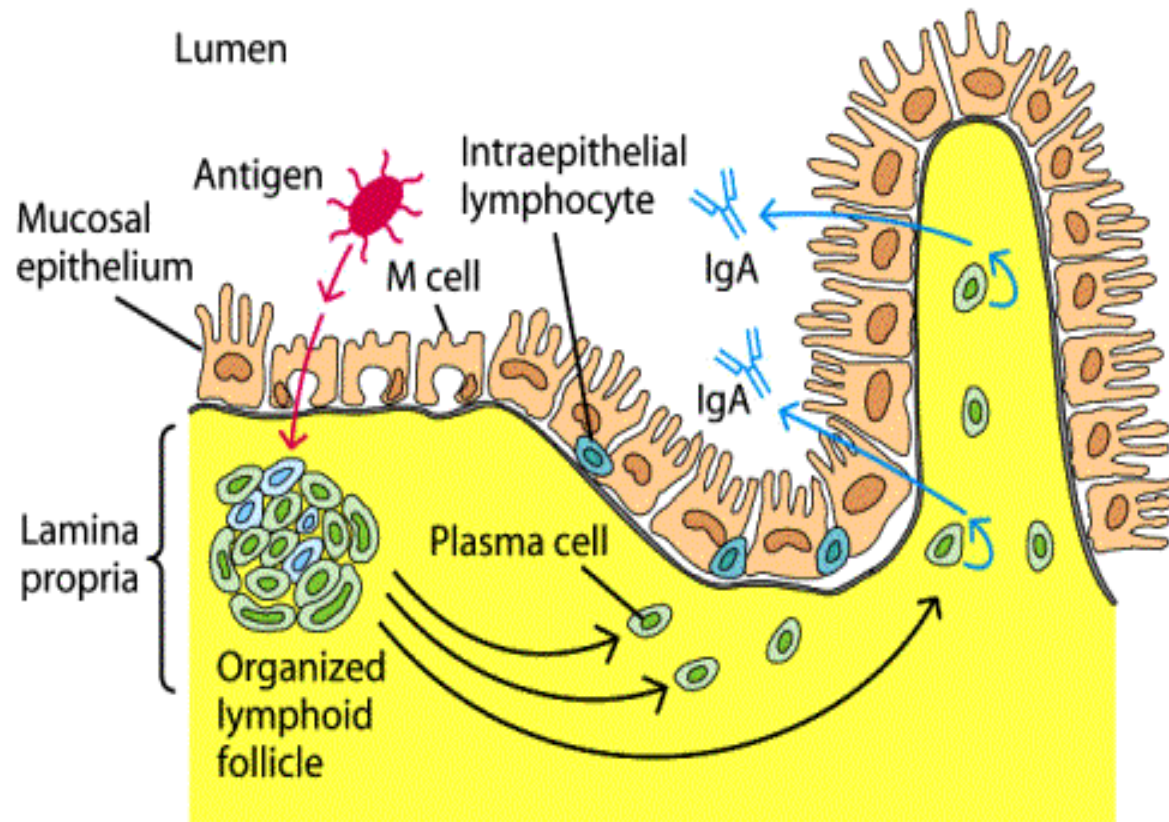
Figure 1-20 The Immune System, 2/e (© Garland Science 2005)



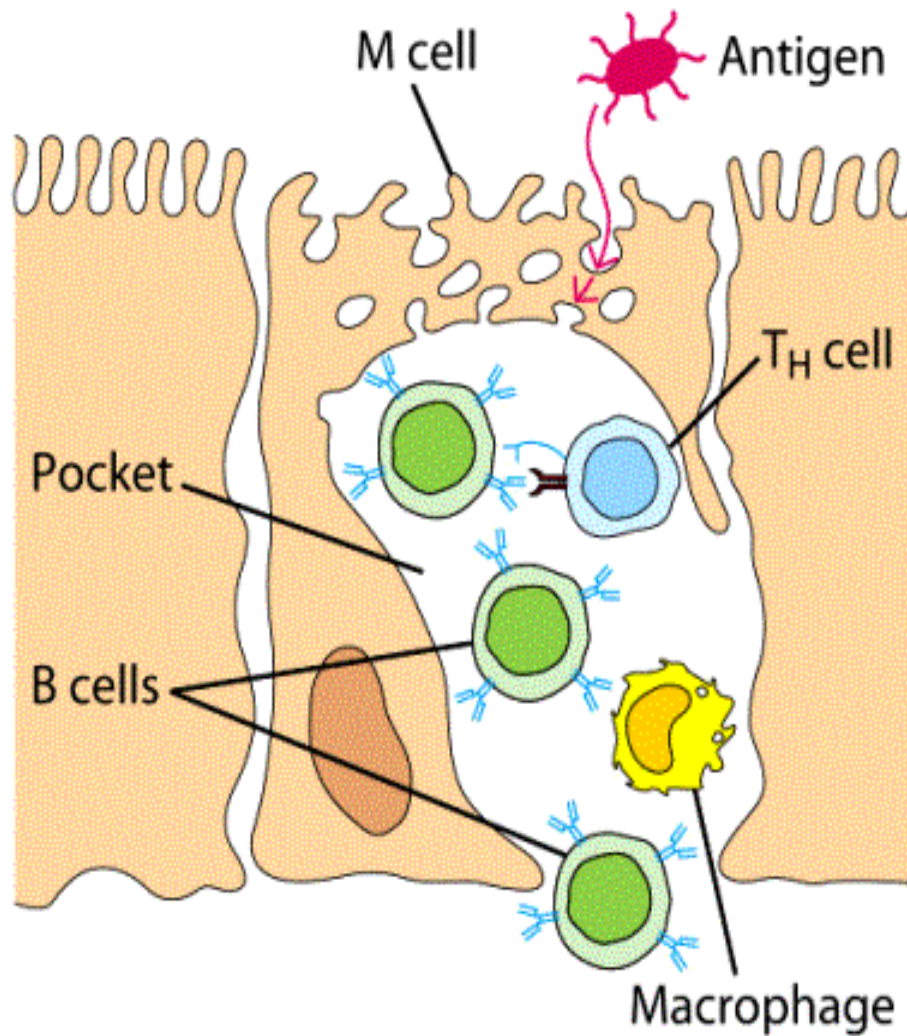
- Mucosal-Associated Lymphoid Tissue (MALT)
 - Tonsils
 - Three locations
 - Structure and function



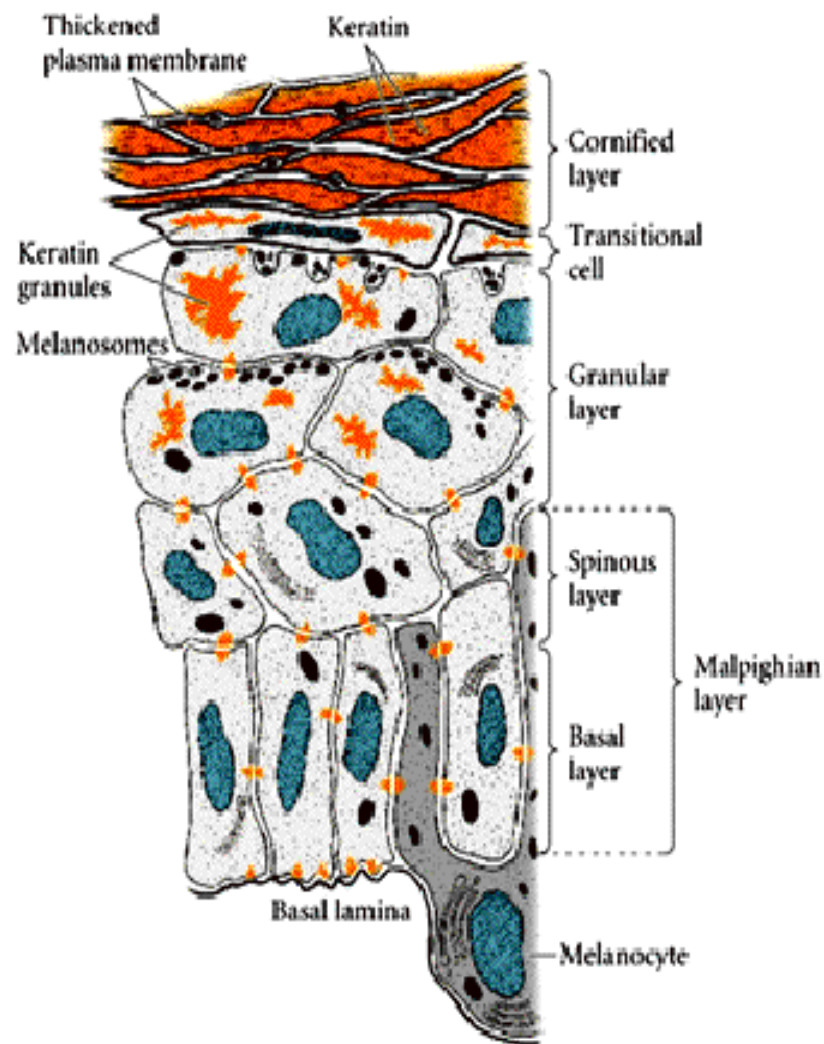
- Mucosal membrane of GI tract and its MALT defenses
- General defense mechanism
- Anatomical Structure and function



- Anatomical structure and function
 - Outer layer
 - Intraepithelial cells, epithelial cells, M cells
 - Lamina propria
 - Submucosal layer



- M cells in detail
 - Structure
 - Location
 - Function
 - Accessibility and vulnerability



- Cutaneous-Associated Lymphoid Tissue
 - Skin
 - Anatomical structure and function
 - Epidermal outer layer
 - Function of keratinocytes, sweat and sebaceous secretions and low pH, Langerhan cells
 - Dermal inner layer