Immunology Lecture to Resume

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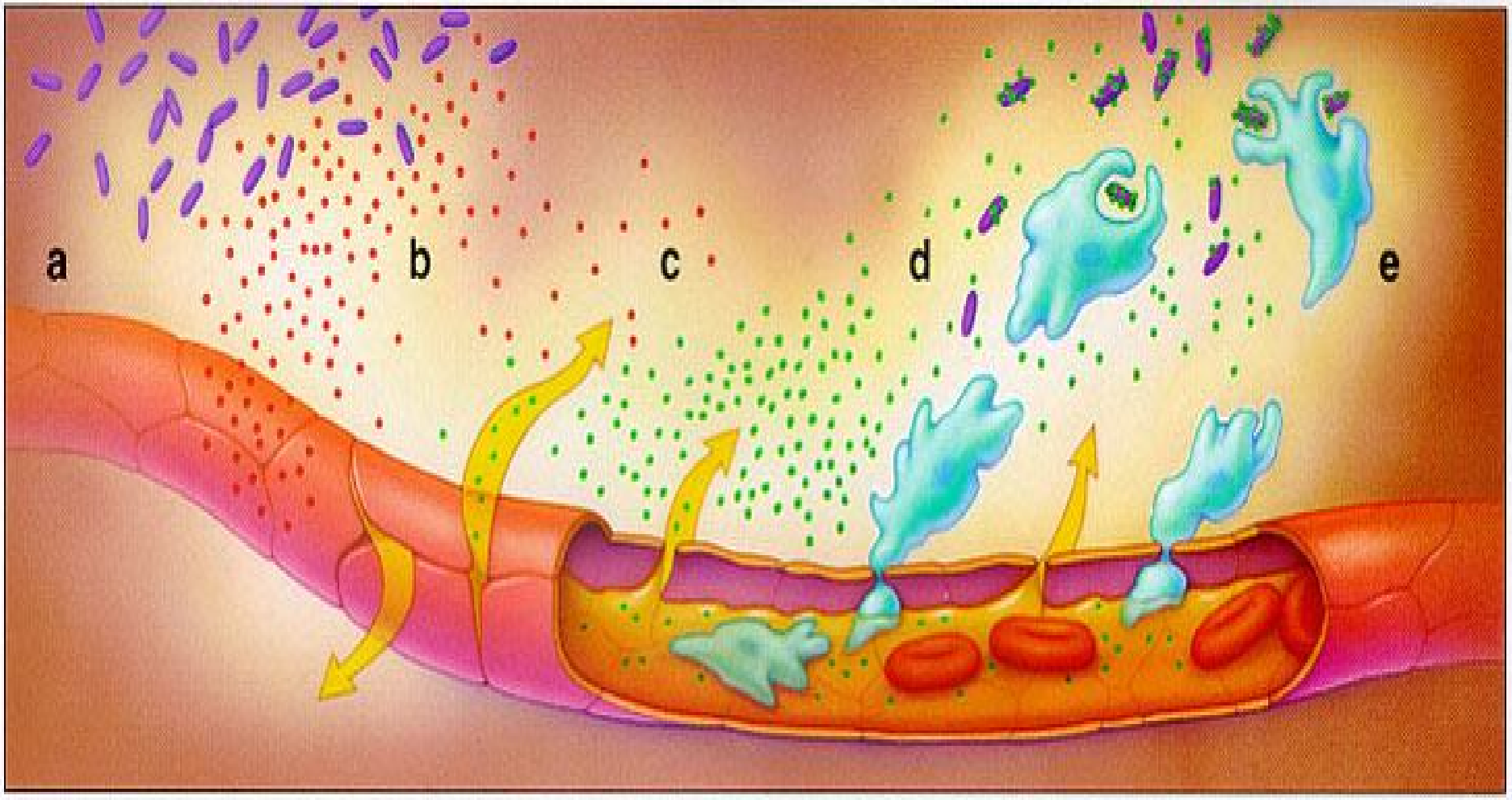
Part 1 :Generality



a Bacteria invade.

b Substances accumulate.

c The substances make plasma and proteins escape.

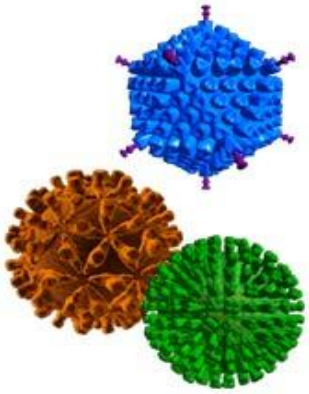
d Plasma proteins attack bacteria, phagocytes, or repair damage.

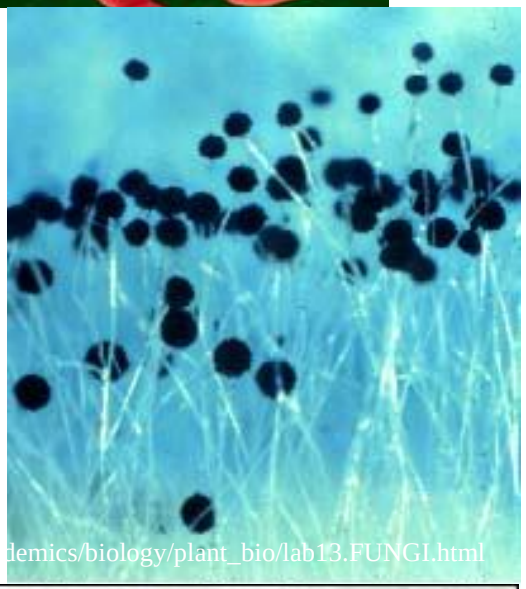
e Phagocytes engulf bacteria.

The Invaders . . .

- Bacteria
- Viruses
- parasites
  such as fungi,
  protista, & worms

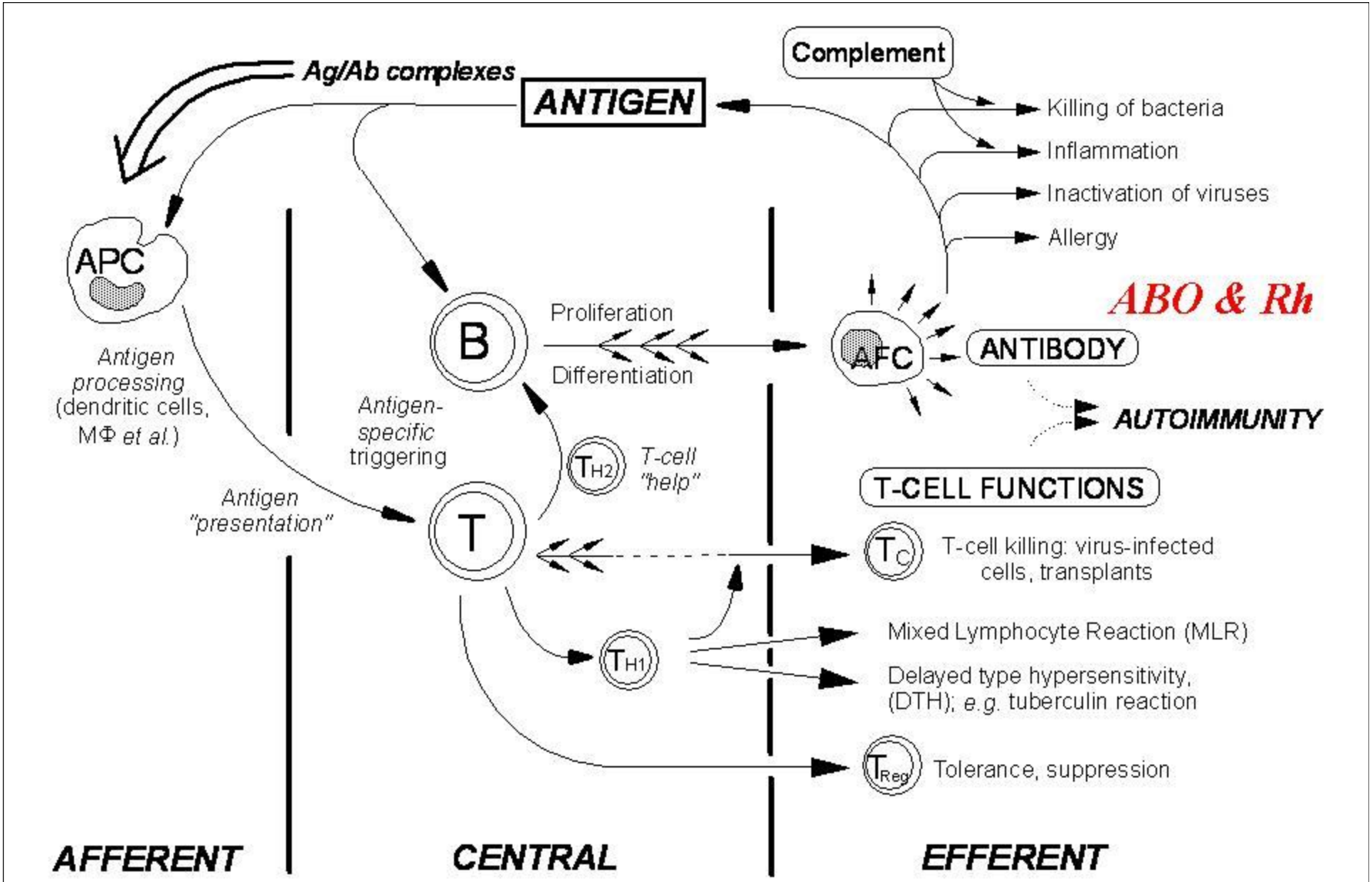

http://www.hhs.gov/asphep/presentation/images/bacteria.jpg




demics/biology/plant_bio/lab13.FUNGI.html


worm trichura.jpg

http://www.sdnhm.org/exhibits/epidemic/teachers/background.html



THREE "LIMBS" OF THE IMMUNE RESPONSE

Immunity: Two Intrinsic Defense Systems

- Innate (nonspecific) system responds quickly and consists of:[3 line of defense]
  - **First line of defense** – skin and mucosa prevent entry of microorganisms
  - **Second line of defense** – antimicrobial proteins, phagocytes, and other cells
    - Inhibit spread of invaders throughout the body
    - Inflammation is its most important mechanism

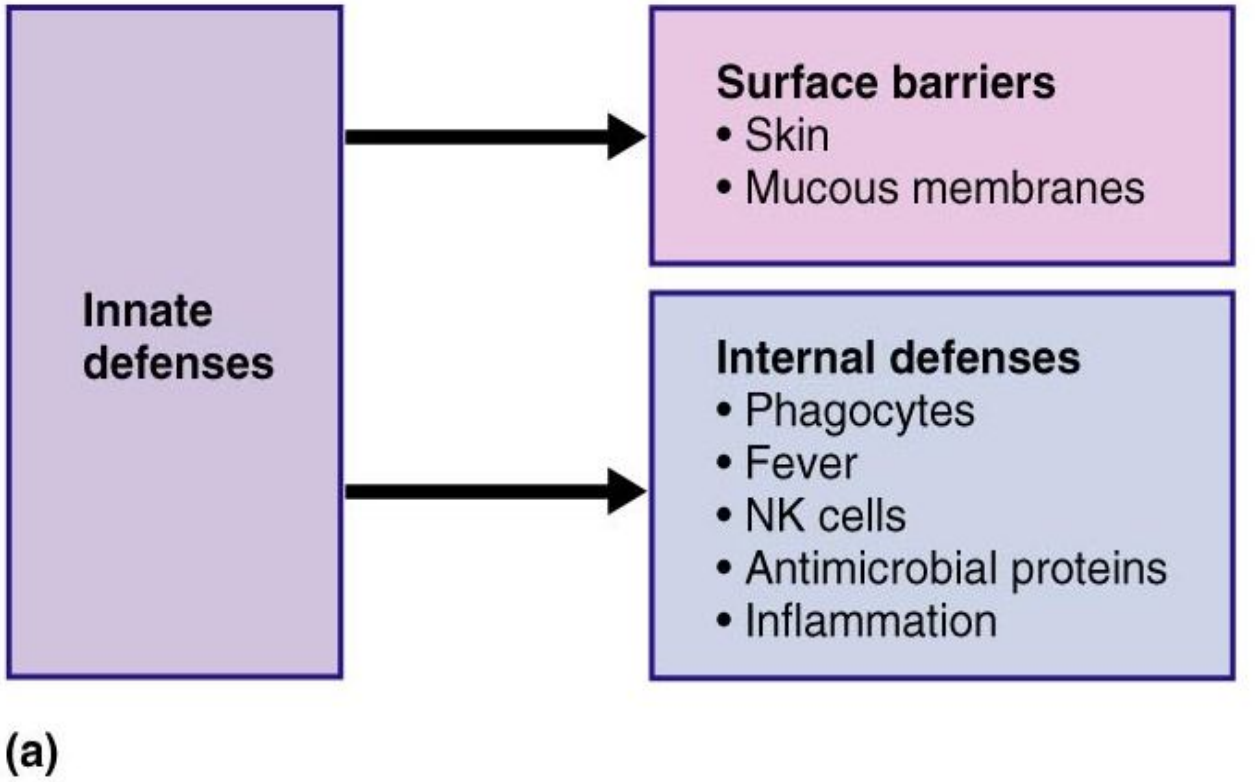
•Adaptive (specific) defense system

•**Third line of defense** – mounts attack against particular foreign substances

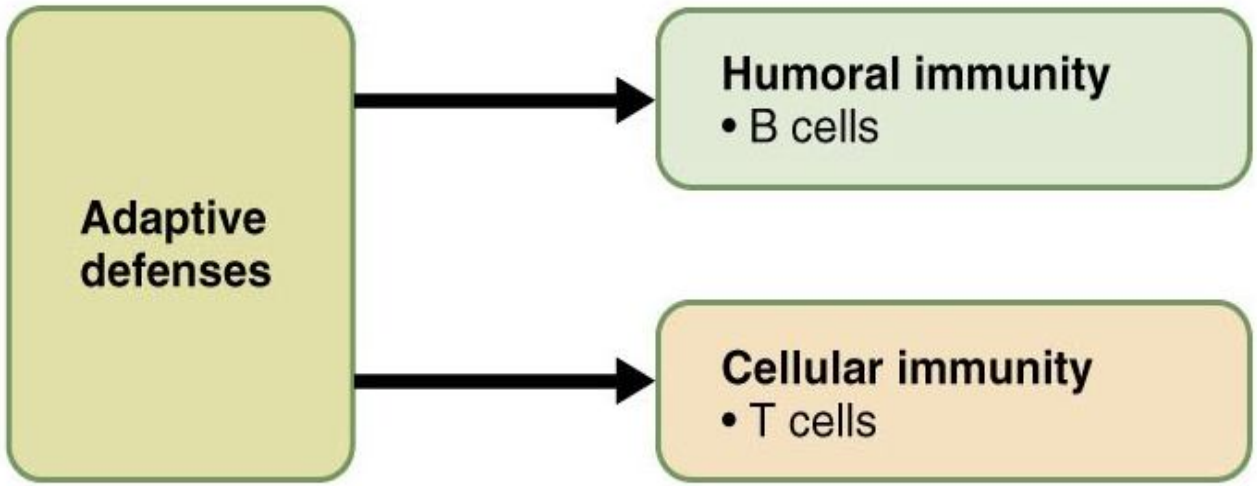
Takes longer to react than the innate system

Works in conjunction with the innate system

Innate and Adaptive Defenses



(a)



(b)

Outline of the Immune System

Innate Immunity	**1st** Line of Defense	Skin
		Mucus
		Secretions
		Phagocytic Cells
		Antimicrobial Proteins
	2nd Line of Defense	Other tissues which participate in inflammatory responses
Adaptive Immunity	**3rd** Line of Defense	Lymphocytes
		Antibodies
Acquired Immunity	Vaccines / Immunotherapies	Attenuated Viruses
		Killed Viruses
		Toxoid Vaccines
		Component Vaccines

Mechanical, Physical and Chemical Barriers

What are the examples of Physiologic and Chemical Barriers at the **skin and mucous membranes**?

Acid pH -- this also relates to the stomach

Hydrolytic enzymes Proteolytic enzymes

Interferon refers to a group of proteins that can help prevent the spread of viruses. There is one special one called gamma-interferon -- this one is a **cytokine** produced by **T_H cells**.
Complement is a term that refers to a group of serum proteins that are normally found "inactive" in the serum.

Antibody-antigen reactions and the cell walls of certain microorganisms can "activate" complement. When this happens the active components can destroy cells in the area of complement activation.

Mucous producing membrane together with cilia help eliminate organisms = **mucociliary escalator**

Surface Barriers

- Skin, mucous membranes, and their secretions make up the first line of defense

- Keratin in the skin:
  - **Presents a physical barrier to most microorganisms**
  - **Is resistant to weak acids and bases, bacterial enzymes, and toxins**

- Mucosae provide similar mechanical barriers

Skin -

- **Tough**, no bacteria can penetrate unaided.
- **Dry** (most skin infections take place in the wetter areas).
- **Acid** (approximately pH 5), Low temperature, Skin cells are constantly shedding, high salt content.
- **Lysozyme** in the pores.
- **Resident microflora**.
- Skin Associated Lymphoid Tissue

Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
  - **Skin acidity** (pH of 3 to 5) inhibits bacterial growth
  - **Sebum** contains chemicals toxic to bacteria
  - **Stomach mucosae** secrete concentrated HCl and protein-digesting enzymes
  - **Saliva and lacrimal fluid** contain lysozyme
  - **Mucus** traps microorganisms that enter the digestive and respiratory systems

Mucous Epithelia

- **GI**
- **Respiratory**
- **Urogenital**
- **Eyes**

- These areas are warm and wet. They are sites of **secretion** and/or **absorption** and therefore cannot be thick like the skin.

mucus - contains **polysaccharides** and **proteins** which trap organisms. Ciliated cells and parastalsis and cough reflex moves trapped organisms out. (ie.: Muco-ciliary escalator in the lungs.)
Lots of **lysozyme** and **lactoferrin** (an enzyme that binds iron and keeps it away from microorganisms).

Respiratory Tract Mucosae

- **Mucus-coated hairs in the nose** trap inhaled particles
- **Mucosa of the upper respiratory tract** is ciliated
  - Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages

Attributes of Selected areas

- **Mouth** - rich resident normal flora -- these help to keep the bad guys out.
- **Lungs** - sterile if not compromised Otherwise this is a vulnerable area. If organisms get down into the alveolar area they have easy access to the blood. Mucociliary escalator is very important
- **Stomach** - Low pH is an important barrier
- **Small Intestine** - Paneth cells in the crypts produce lysozyme and **defensins** (these are small proteins which inhibit bacterial growth).
- **Urethra** - flow of urine important.
- **Female Genitalia** - microflora very important. Mucus plug in the cervix important in preventing movement of microbes into the uterus.

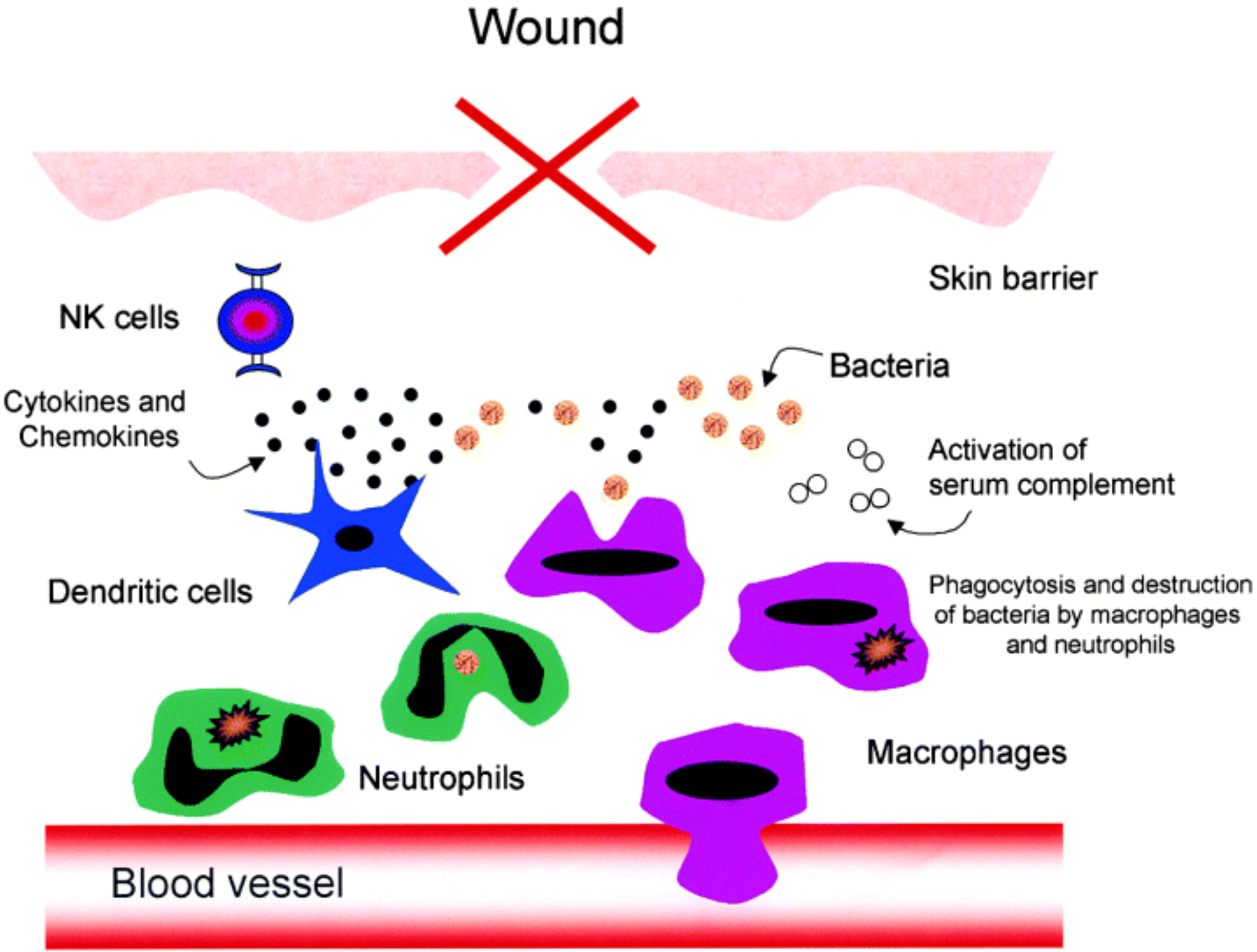
Complex Biological Responses of Innate Immunity

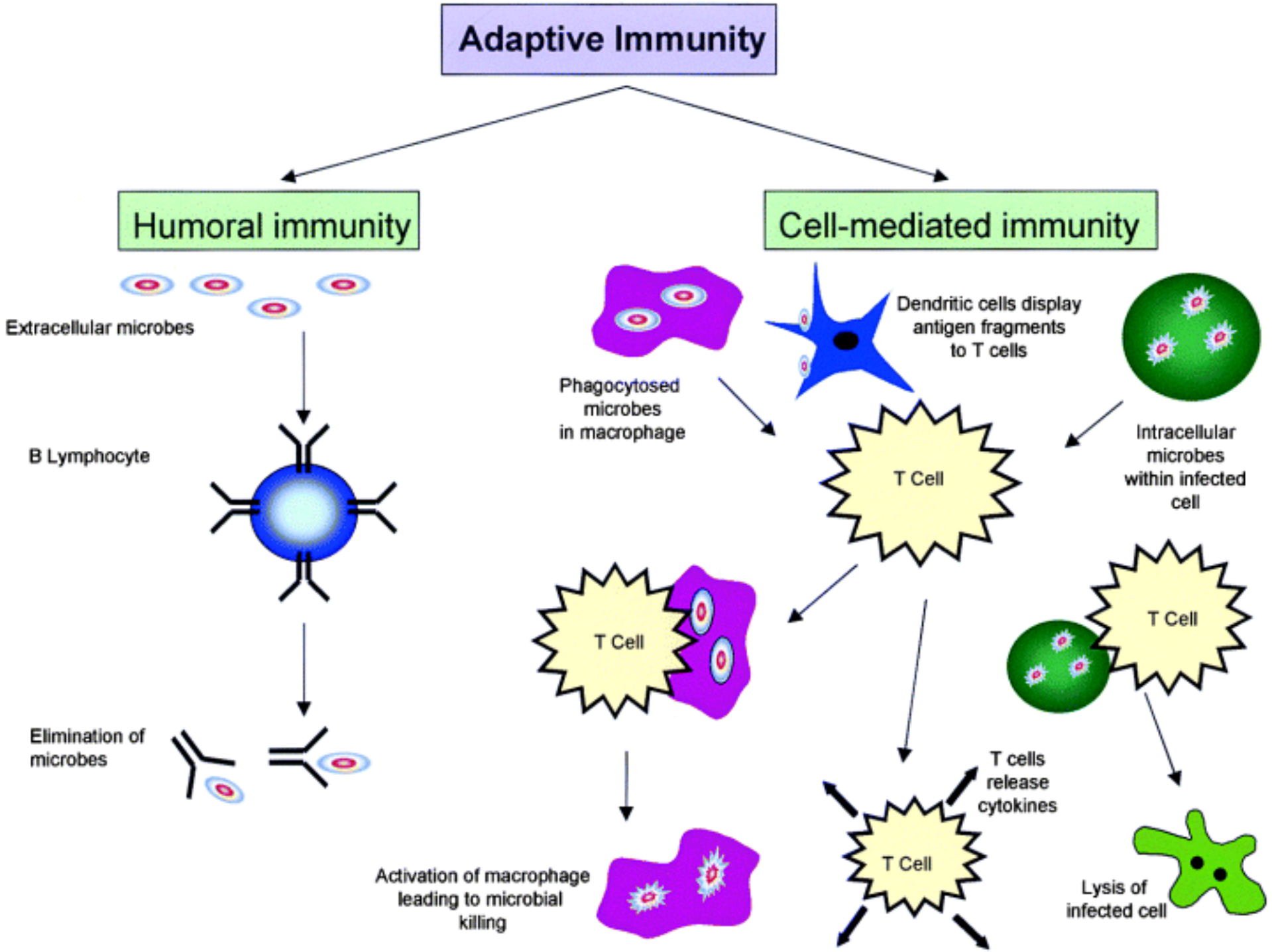
Complex biological responses include:

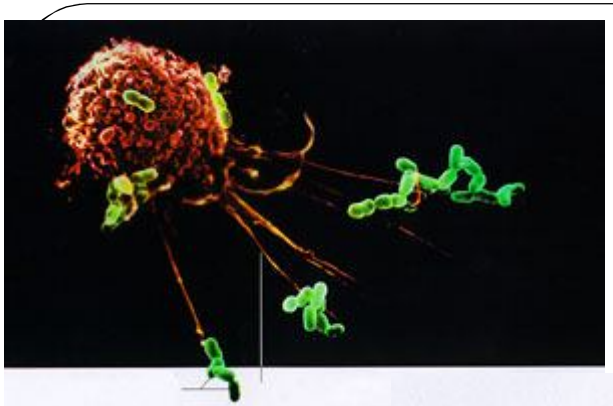
- **Phagocytosis**
- **Complement Activation**
- **Inflammation and Fever**
- **Interferon**

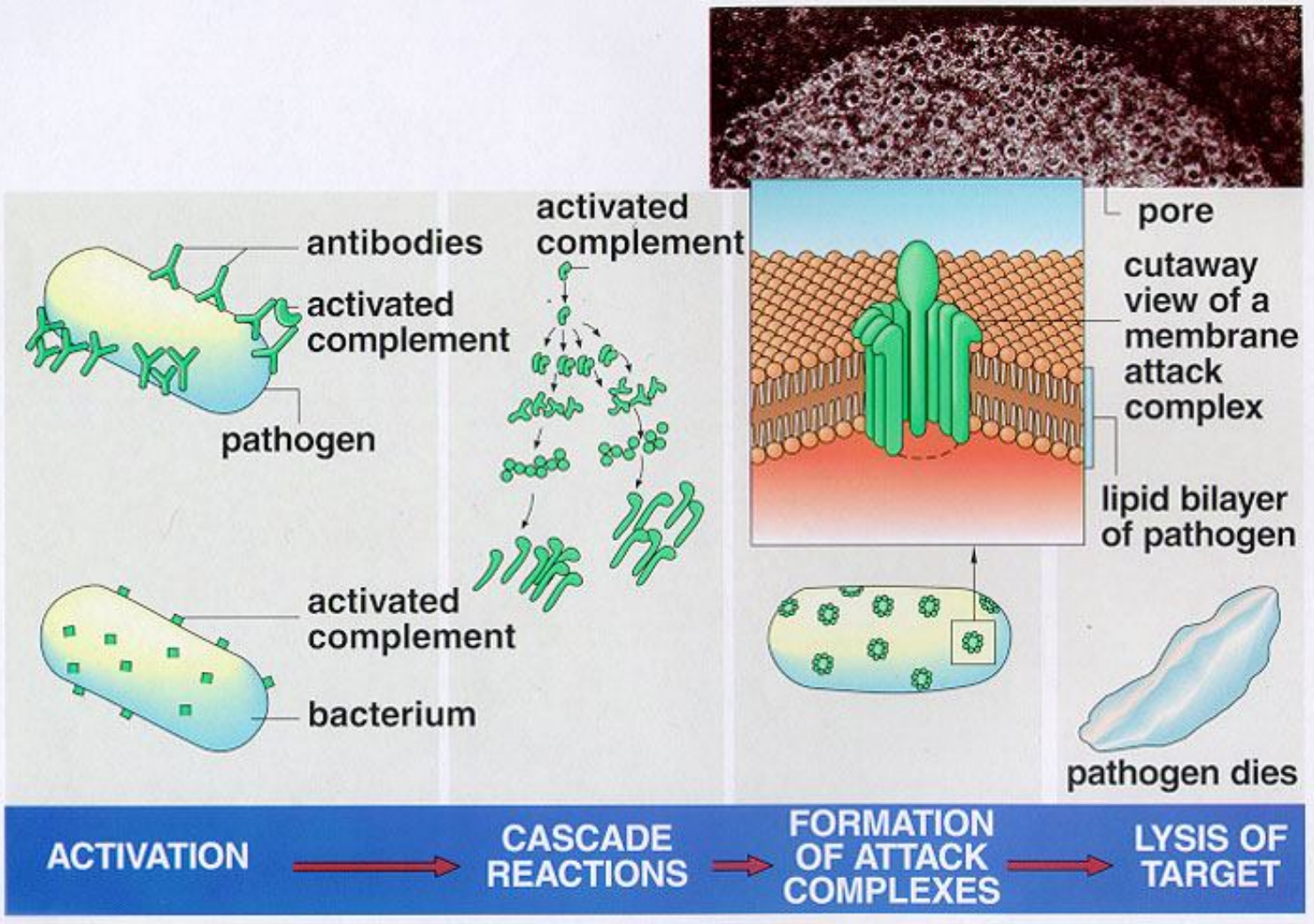
TABLE 21.2 Summary of Nonspecific Body Defenses

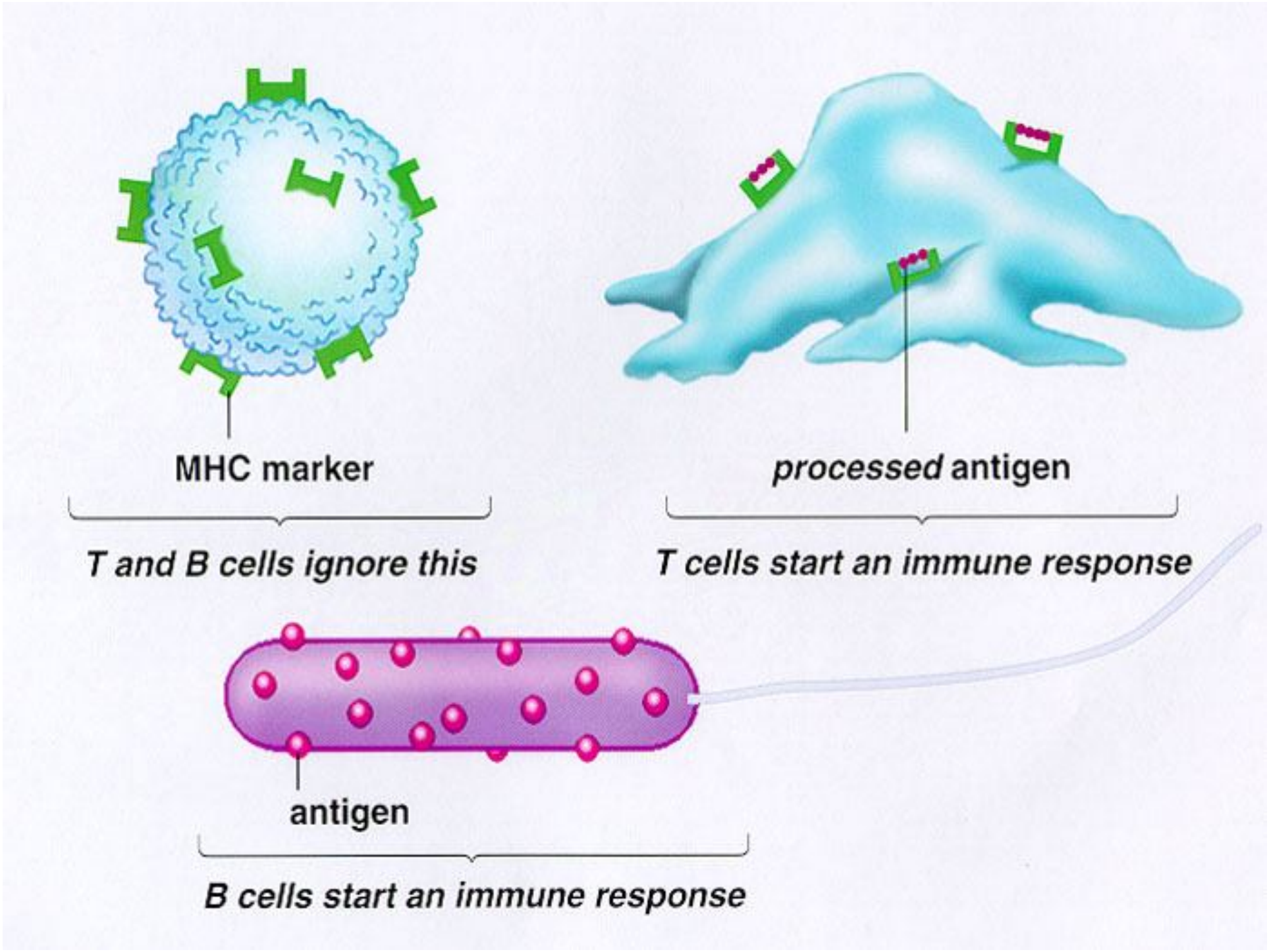
CATEGORY/ASSOCIATED ELEMENTS	PROTECTIVE MECHANISM
FIRST LINE OF DEFENSE: SURFACE MEMBRANE BARRIERS	
Intact skin epidermis	Forms mechanical barrier that prevents entry of pathogens and other harmful substances into body
▪ Acid mantle	Skin secretions (perspiration and sebum) make epidermal surface acidic, which inhibits bacterial growth; sebum also contains bactericidal chemicals
▪ Keratin	Provides resistance against acids, alkalis, and bacterial enzymes
Intact mucous membranes	Form mechanical barrier that prevents entry of pathogens
▪ Mucus	Traps microorganisms in respiratory and digestive tracts
▪ Nasal hairs	Filter and trap microorganisms in nasal passages
▪ Cilia	Propel debris-laden mucus away from lower respiratory passages
▪ Gastric juice	Contains concentrated hydrochloric acid and protein-digesting enzymes that destroy pathogens in stomach
▪ Acid mantle of vagina	Inhibits growth of most bacteria and fungi in female reproductive tract
▪ Lacrimal secretion (tears); saliva	Continuously lubricate and cleanse eyes (tears) and oral cavity (saliva); contain lysozyme, an enzyme that destroys microorganisms
▪ Urine	Normally acid pH inhibits bacterial growth; cleanses the lower urinary tract as it flushes from the body

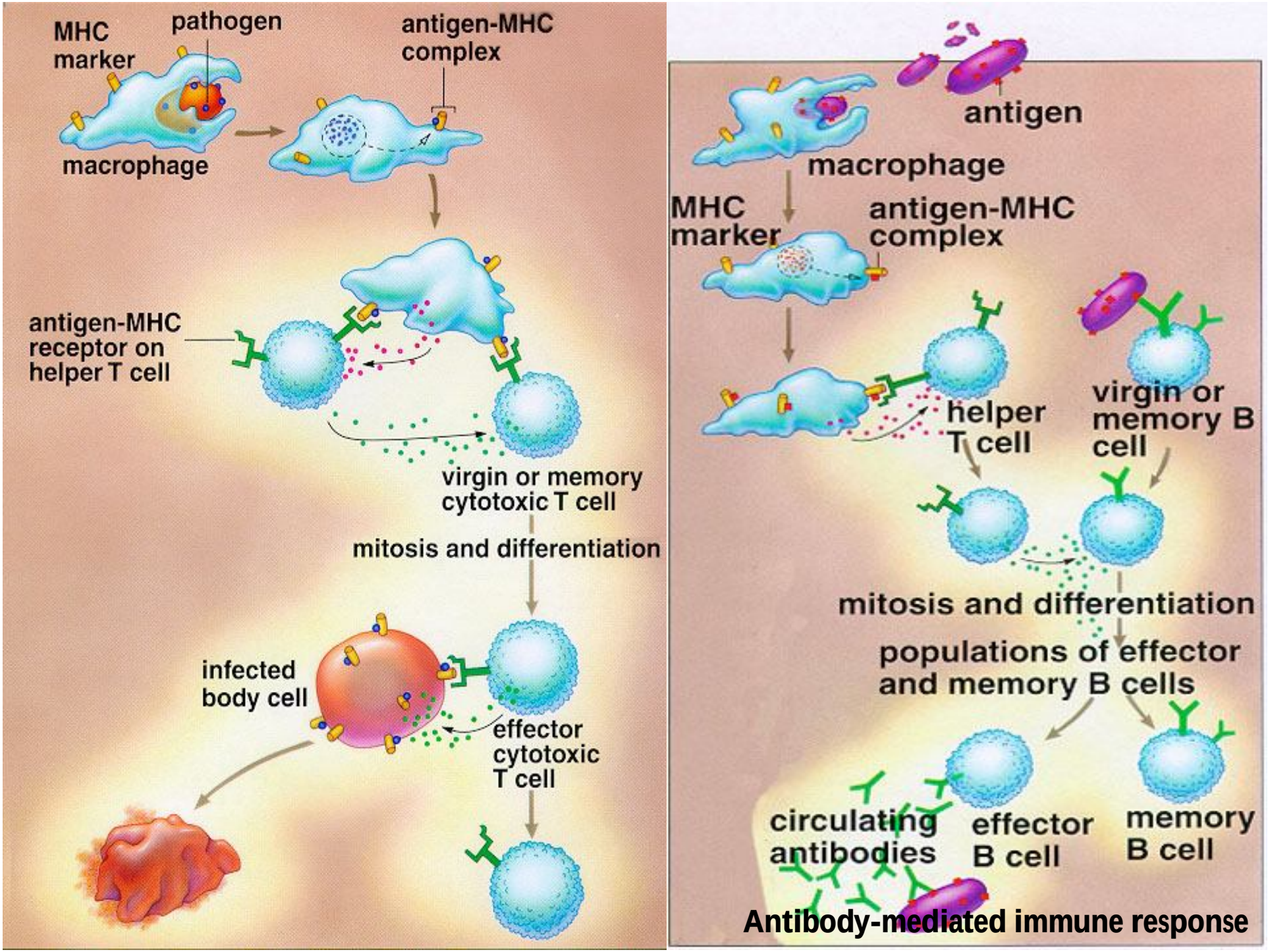

Wound
Skin barrier
NK cells
Bacteria
Cytokines and
Chemokines
Activation of
serum complement
Dendritic cells
Phagocytosis and destruction
of bacteria by macrophages
and neutrophils
Neutrophils
Macrophages
Blood vessel


Adaptive Immunity
Humoral immunity
Cell-mediated immunity
Extracellular microbes
B Lymphocyte
Elimination of microbes
Phagocytosed microbes in macrophage
Dendritic cells display antigen fragments to T cells
Intracellular microbes within infected cell
T Cell
T Cell
T Cell
T Cell
T cells release cytokines
Activation of macrophage leading to microbial killing
Lysis of infected cell




antibodies
activated complement
pathogen
activated complement
activated complement
bacterium
pore
cutaway view of a membrane attack complex
lipid bilayer of pathogen
pathogen dies
ACTIVATION
CASCADE REACTIONS
FORMATION OF ATTACK COMPLEXES
LYSIS OF TARGET


MHC marker
processed antigen
T and B cells ignore this
T cells start an immune response
antigen
B cells start an immune response

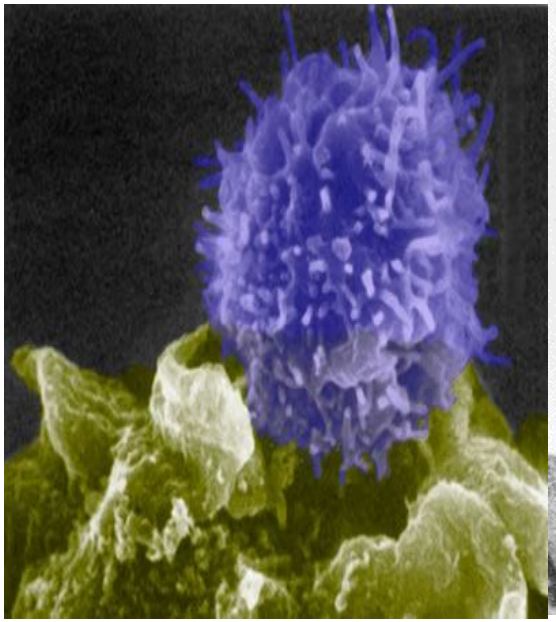


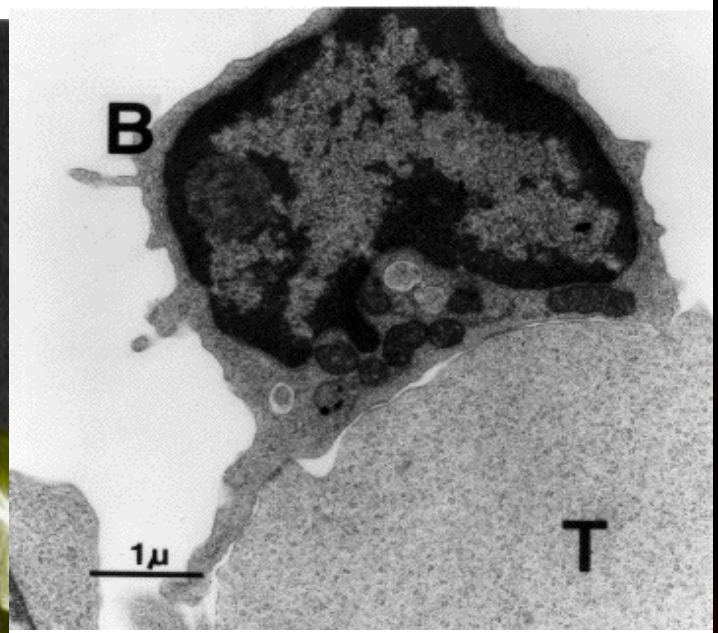
Antibody-mediated immune response

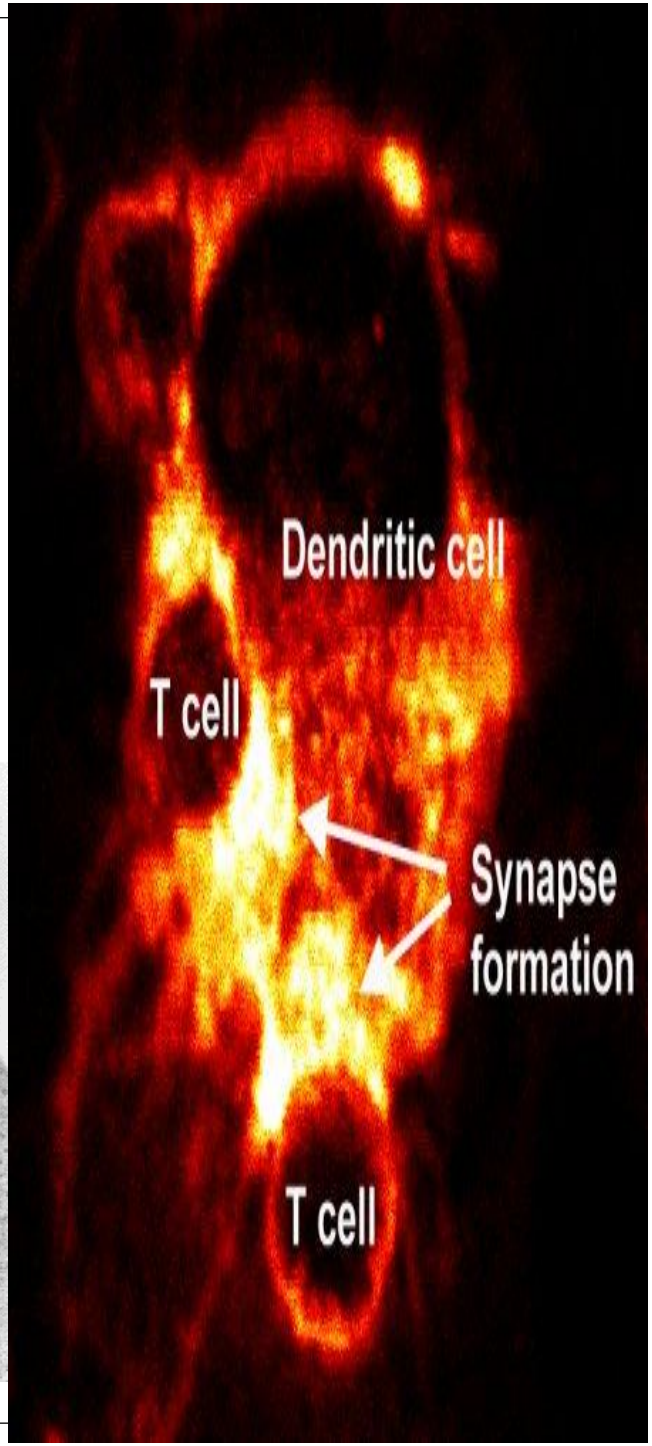
PART 2 : Cells and Chemicals

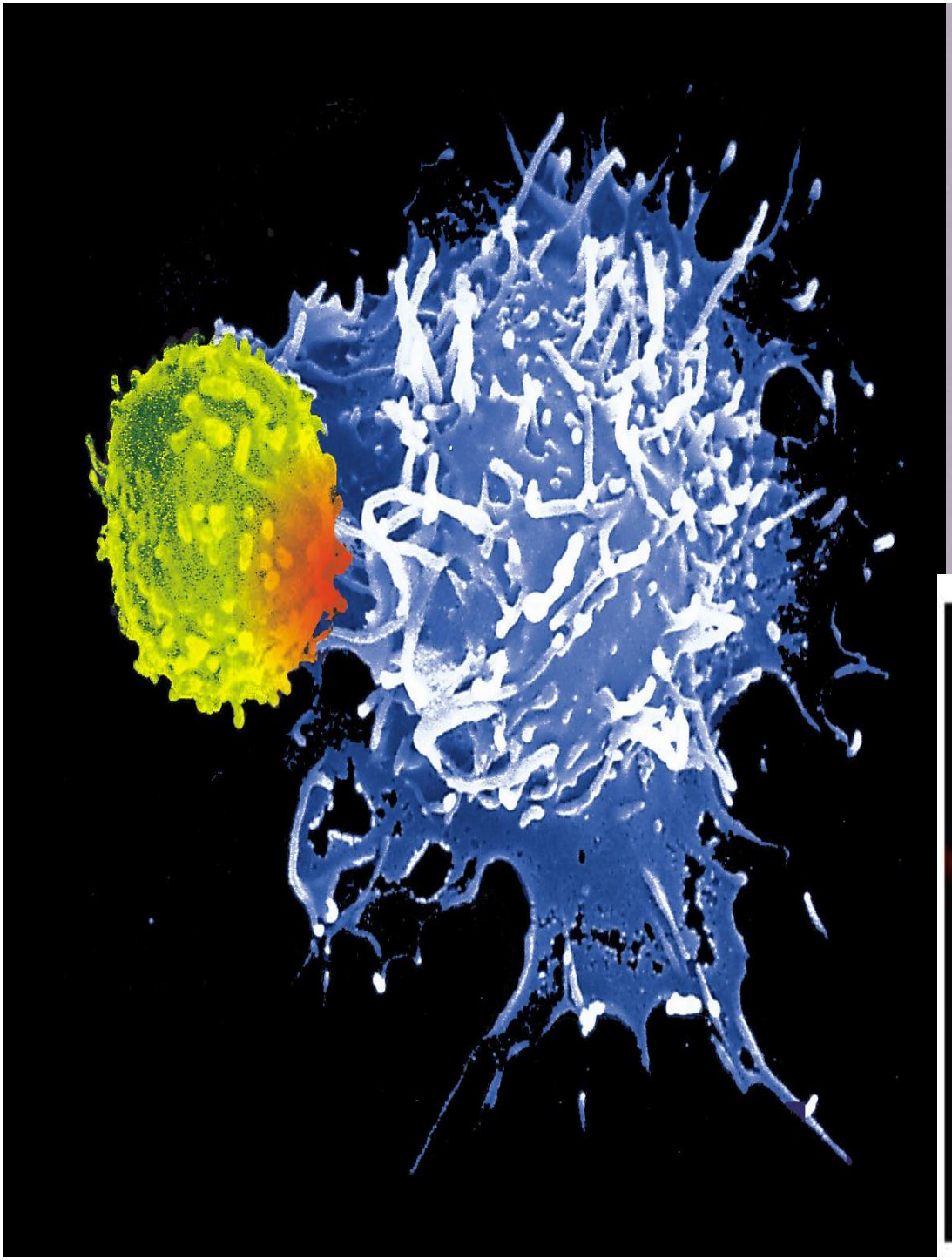
Immunological Synapse

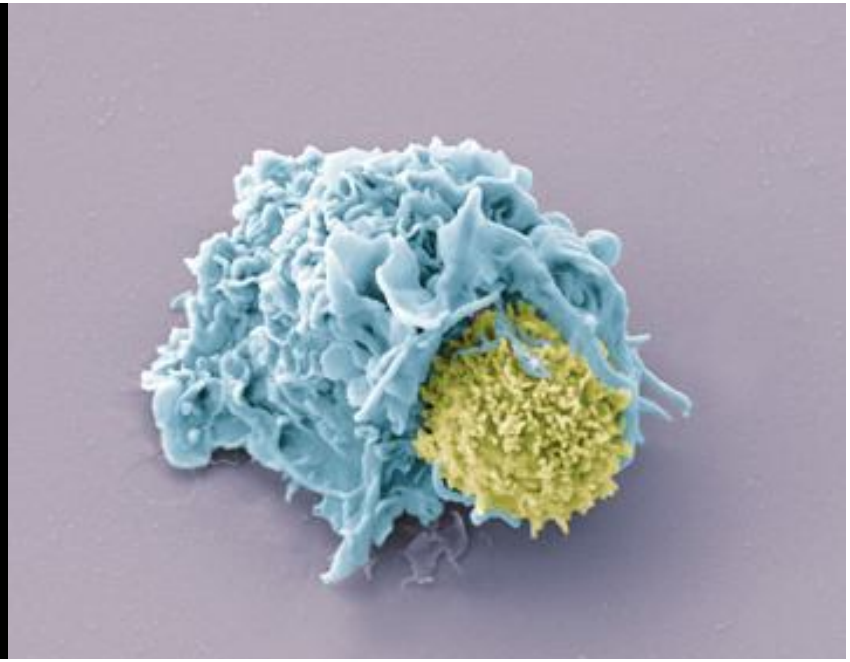
Is the interface between an antigen-presenting cell and a lymphocyte

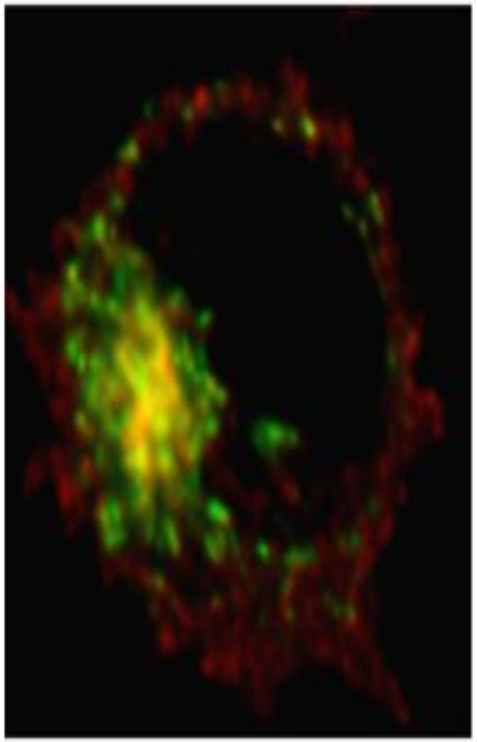




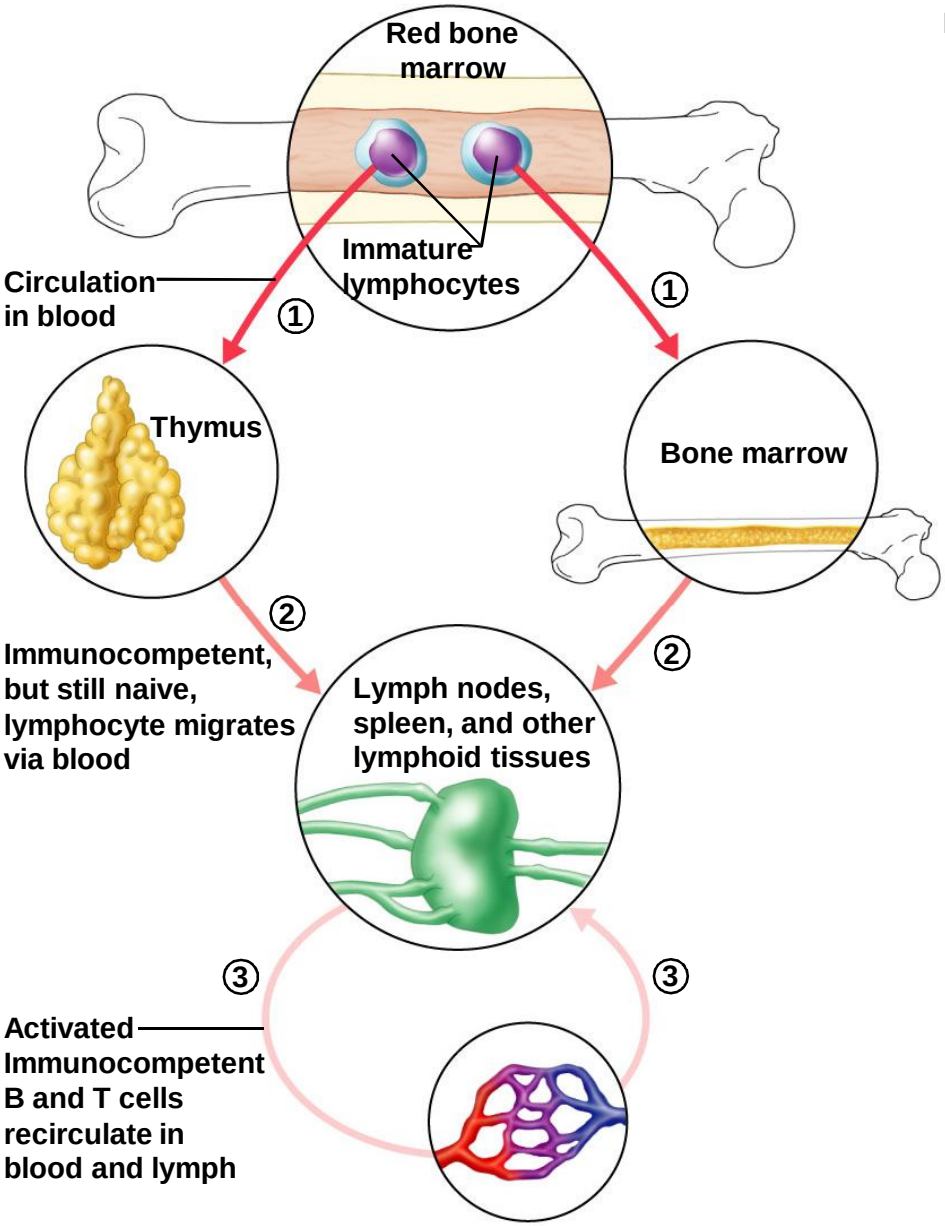








HIV-1-infected T cell displaying Lck (red) retained in recycling endosomes (marked by the transferrin receptor, green). Yellow color indicates the co-localization of both proteins



Key:
= Site of lymphocyte origin
= Site of development of immunocompetence as B or T cells; primary lymphoid organs
= Site of antigen challenge, activation, and final diff erentiation of B and T cells

① Lymphocytes destined to become T cells migrate to the thymus and develop immunocompetence there. B cells develop immunocompetence in red bone marrow.

② After leaving the thymus or bone marrow as naïve immunocompetent cells, lymphocytes “seed” the lymph nodes, spleen, and other lymphoid tissues where the antigen challenge occurs.

③ Antigen-activated immunocompetent lymphocytes circulate continuously in the bloodstream and lymph and throughout the lymphoid organs of the body.

Figure 21.8

TABLE 21.1 Inflammatory Chemicals

CHEMICAL	SOURCE	PHYSIOLOGICAL EFFECTS
Histamine	Granules of basophils and mast cells; released in response to mechanical injury, presence of certain microorganisms, and chemicals released by neutrophils	Promotes vasodilation of local arterioles; increases permeability of local capillaries, promoting exudate formation
Kinins (bradykinin and others)	A plasma protein, kininogen, is cleaved by the enzyme kallikrein found in plasma, urine, saliva, and in lysosomes of neutrophils and other types of cells; cleavage releases active kinin peptides	Same as for histamine; also induce chemotaxis of leukocytes and prompt neutrophils to release lysosomal enzymes, thereby enhancing generation of more kinins; induce pain
Prostaglandins	Fatty acid molecules produced from arachidonic acid—found in all cell membranes; generated by enzymes of neutrophils, basophils, mast cells, and others	Sensitize blood vessels to effects of other inflammatory mediators; one of the intermediate steps of prostaglandin generation produces free radicals, which themselves can cause inflammation; induce pain
Platelet-derived growth factor (PDGF)	Secreted by platelets and endothelial cells	Stimulates fibroblast activity and repair of damaged tissues
Complement	See Table 21.2 (p. 796)	
Cytokines	See Table 21.4 (pp. 817–818)	

Internal Defenses: Cells and Chemicals

- **The body uses nonspecific cellular and chemical devices to protect itself**
  - **Phagocytes and natural killer (NK) cells**
  - **Antimicrobial proteins in blood and tissue fluid**
  - **Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals**
- **Harmful substances are identified by surface carbohydrates unique to infectious organisms**

Cells of the Adaptive Immune System

- Two types of lymphocytes
  - B lymphocytes – oversee humoral immunity
  - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
- Antigen-presenting cells (APCs):
  - **Do not respond to specific antigens**
  - **Play essential auxiliary roles in immunity**

Lymphocytes [see the specific in blood slides

- Immature lymphocytes released from bone marrow are essentially identical
- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
  - B cells mature in the bone marrow
  - T cells mature in the thymus

The Cells of the Immune Response

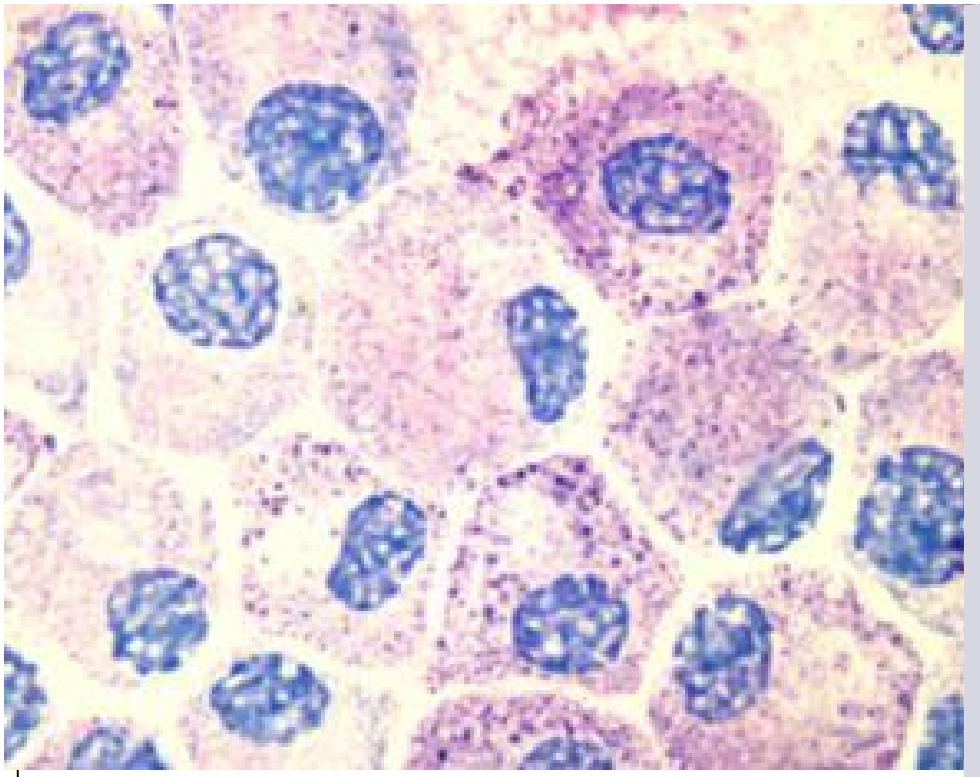
T cells: Lymphocytes that regulate response

- *Cytotoxic T cells*: destroy specific targeted cells
- *Helper T cells*: stimulate immune responses
- *Suppressor T cells*: stop immune response
- *Memory T cells*: provide future immunity

Table 24.1	Types of Lymphocytes	
Cell Type	**Function**	**Type of Antigen Response**
T-LYMPHOCYTE		
Helper T-lymphocyte	Initiates and oversees the immune response	Responds to a single antigen
Cytotoxic T-lymphocyte	Directly kills foreign cells; must be activated by a helper T-lymphocyte first	Responds to a single antigen
Memory T-lymphocyte	A type of cytotoxic T-lymphocyte that has already killed; patrols the body looking for the same antigen again	Responds to a single antigen
Suppressor T-lymphocyte	Helps "turn off" the immune response once it has been activated	Responds to a single antigen
B-LYMPHOCYTE		
Plasma cell	Produces and secretes antibodies	Responds to a single antigen
Memory B-lymphocyte	Remembers an initial antigen attack and mounts a faster, more efficient response should the same antigen type attack again	Responds to a single antigen
NK (NATURAL KILLER) CELL		
NK (natural killer) cell	Kills a wide variety of infected and cancerous cells	Responds to multiple antigens

TABLE 21.2 Summary of Nonspecific Body Defenses (*continued*)

CATEGORY/ASSOCIATED ELEMENTS	PROTECTIVE MECHANISM
SECOND LINE OF DEFENSE: INNATE, CELLULAR AND CHEMICAL DEFENSES	
Phagocytes	Engulf and destroy pathogens that breach surface membrane barriers; macrophages also contribute to immune response
Natural killer (NK) cells	Promote apoptosis (cell suicide) by direct cell attack against virus-infected or cancerous body cells; do not require specific antigen recognition; do not exhibit a memory response
Inflammatory response	Prevents spread of injurious agents to adjacent tissues, disposes of pathogens and dead tissue cells, and promotes tissue repair; chemical mediators released attract phagocytes (and immunocompetent cells) to the area
Antimicrobial proteins	
▪ Interferons (α, β, γ)	Proteins released by virus-infected cells and certain lymphocytes that protect uninfected tissue cells from viral takeover; mobilize immune system
▪ Complement	Lyses microorganisms, enhances phagocytosis by opsonization, and intensifies inflammatory and immune responses
Fever	Systemic response initiated by pyrogens; high body temperature inhibits microbial multiplication and enhances body repair processes



Mast cells can be stimulated to degranulate by direct injury (e.g. physical or chemical), cross-linking of Immunoglobulin E (IgE) receptors, or by activated complement proteins

A **mast cell** (or *mastocyte*) is a resident cell of several types of tissues and contains many granules rich in histamine and heparin.

Although best known for their role in **allergy and anaphylaxis**,

mast cells play an important protective role as well,being intimately involved in **wound healing and defense against pathogens**

Prominent near the boundaries between the outside world and the internal milieu, such as the **skin, mucosa of the lungs and digestive tract, as well as in the mouth, conjunctiva and nose**

Basophils / Mast Cells

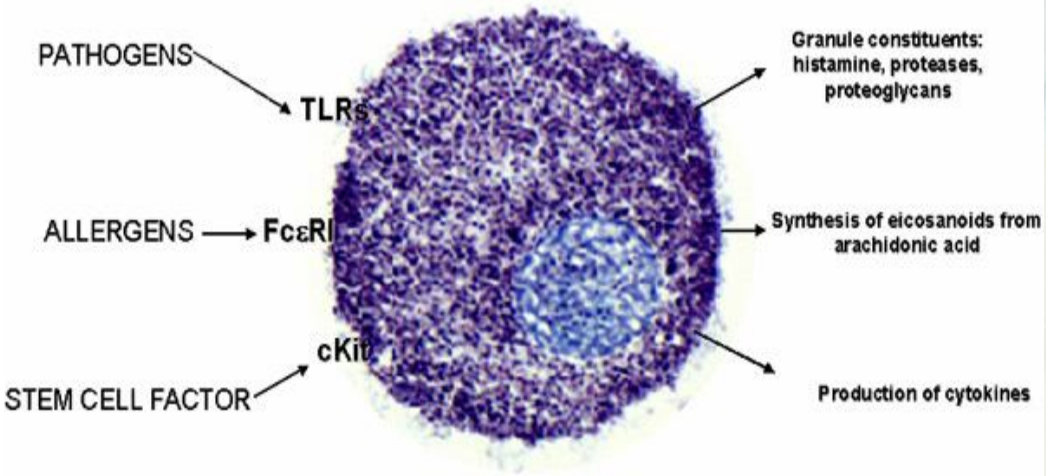
These cells are filled with mediators of inflammation:

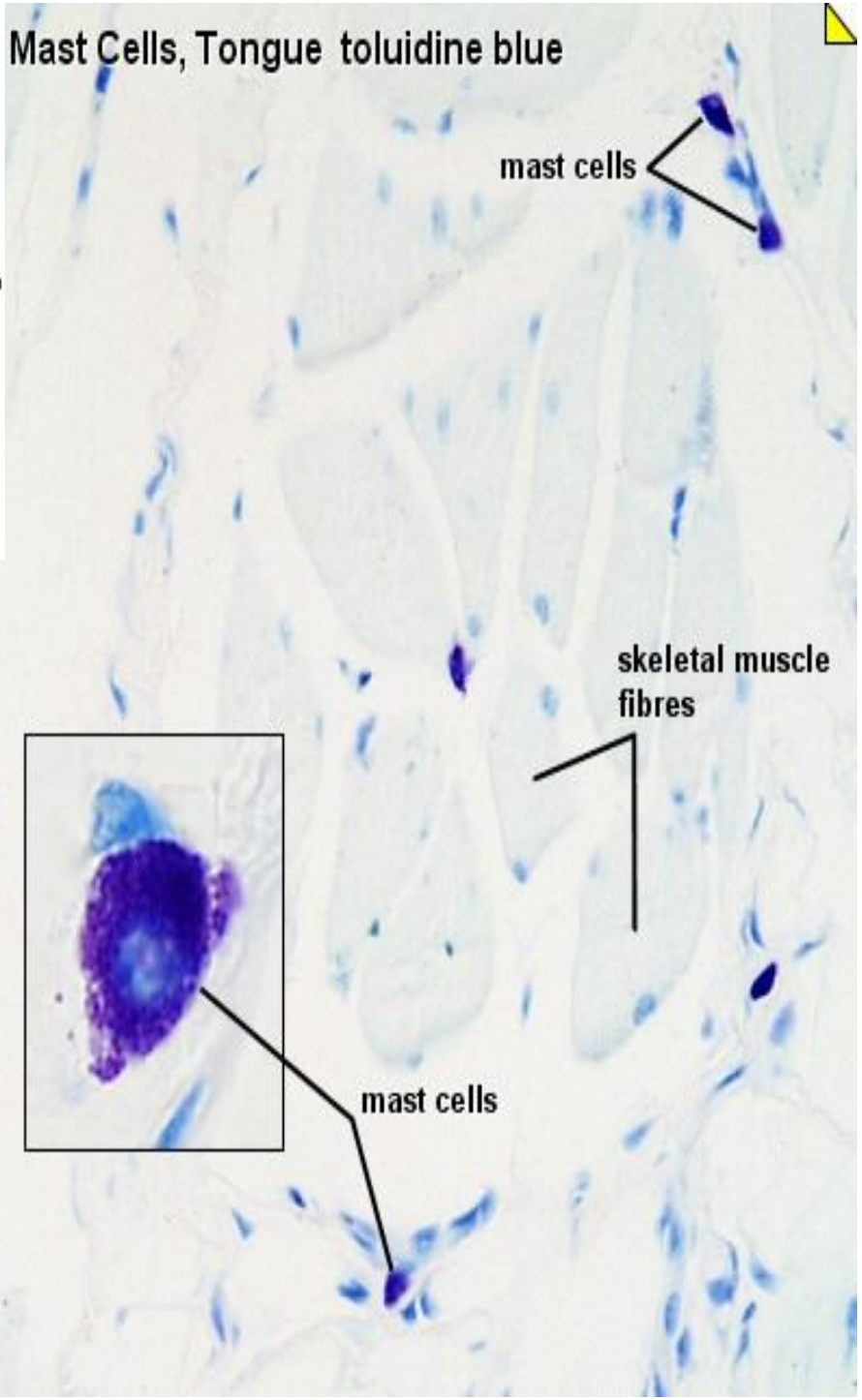
- **histamine** - causes vasodilation (blood vessels dialate) and bronchoconstriction (because it causes smooth muscles to constrict)

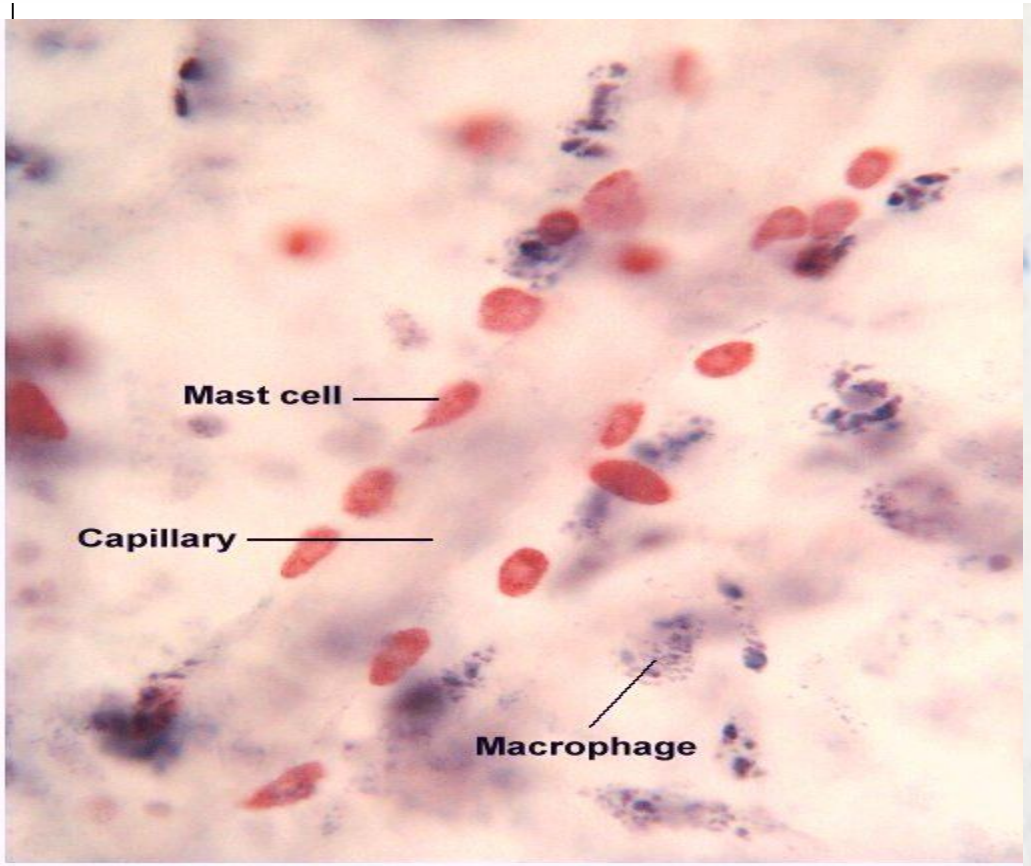
  heparin - inhibits blood coagulation

  leukotrienes - prolonged constriction of smooth muscles, pain

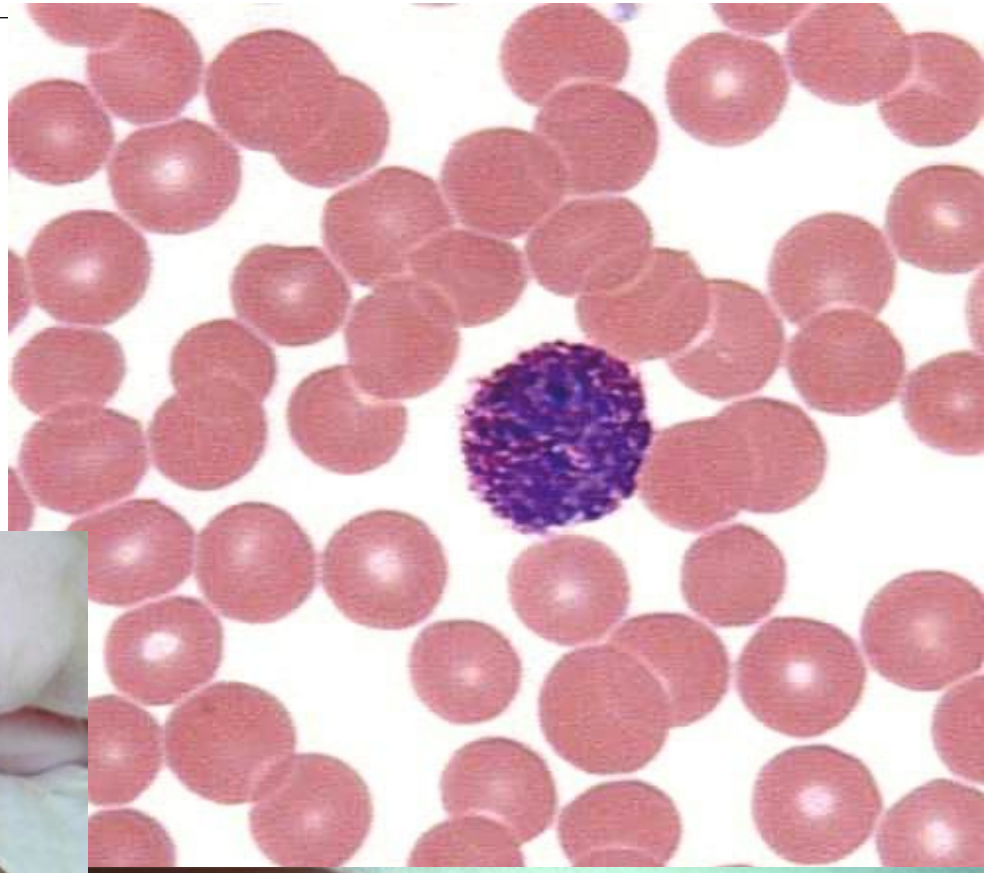
  prostaglandins - smooth muscle constriction and vasodilation, pain

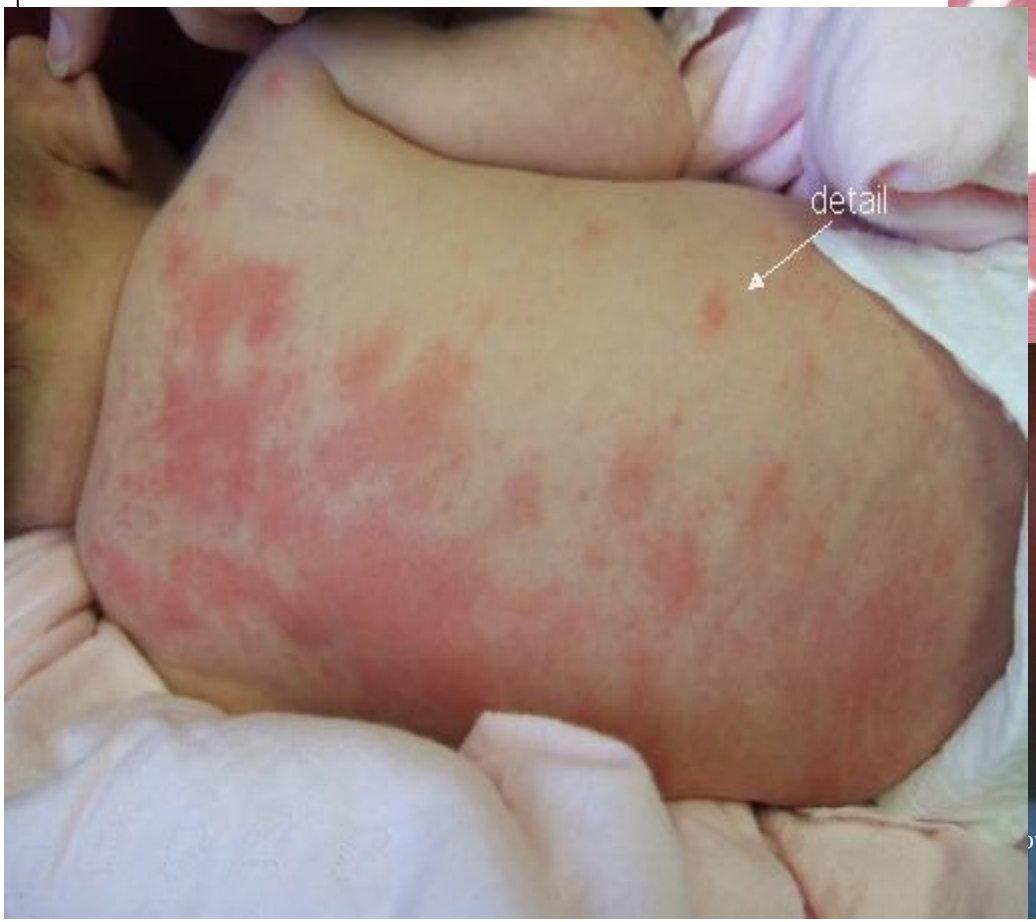

PATHOGENS
TLRs
ALLERGENS
FcεRI
cKit
STEM CELL FACTOR
Granule constituents: histamine, proteases, proteoglycans
Synthesis of eicosanoids from arachidonic acid
Production of cytokines

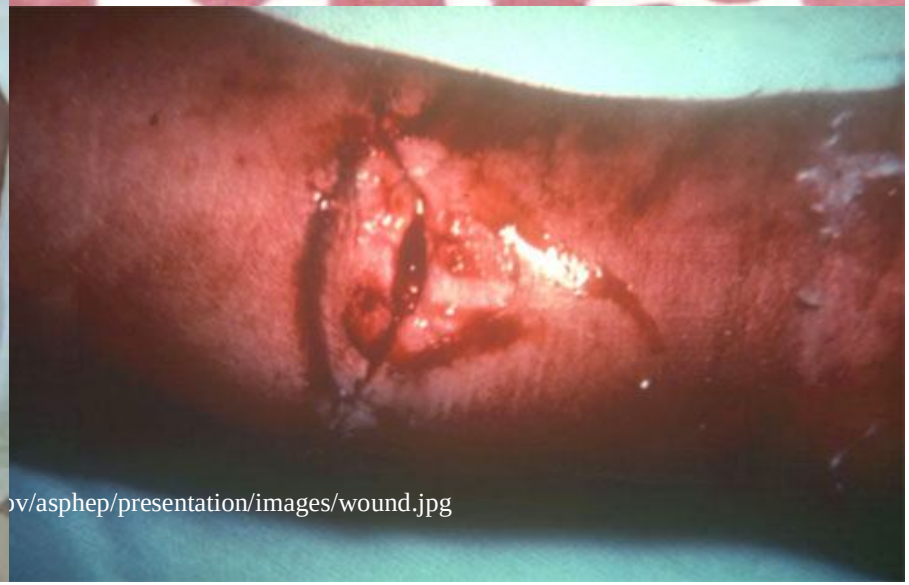

Mast Cells, Tongue toluidine blue
mast cells
skeletal muscle fibres
mast cells

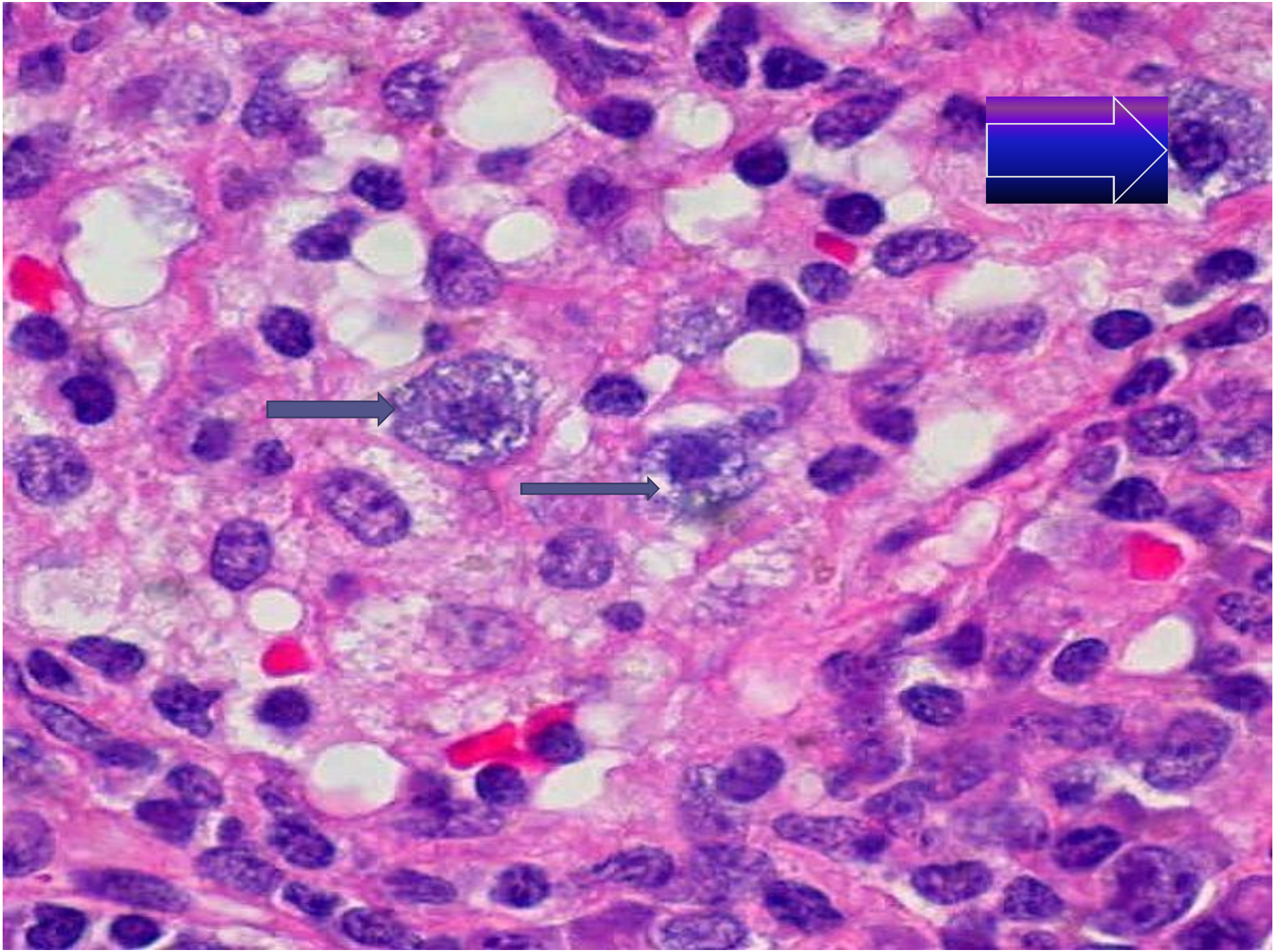

Mast cell
Capillary
Macrophage

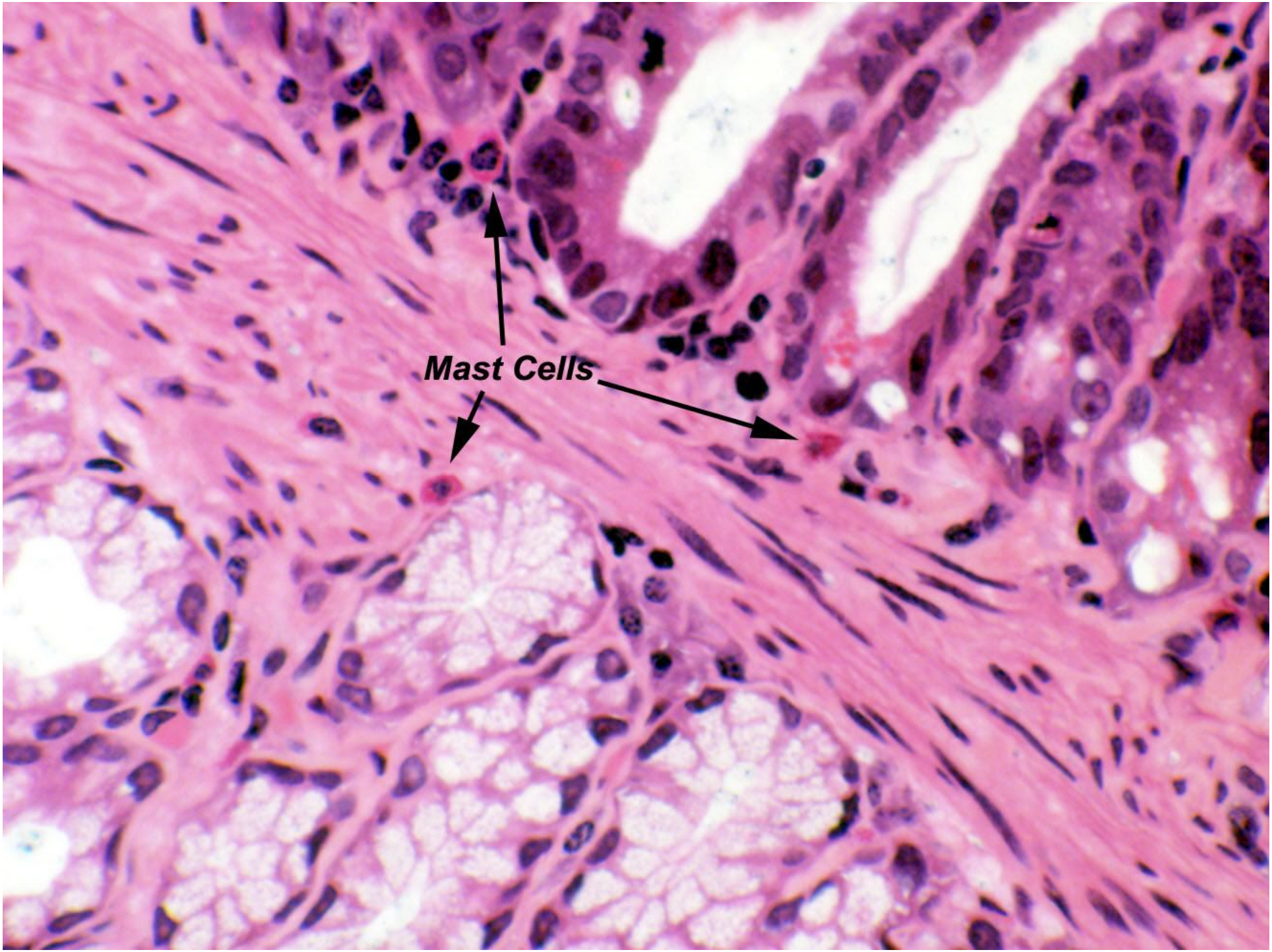
- Mast cells /basophils
  - release histamine that dilates blood vessels
  - causes redness [erythema], swelling [edema], and heat

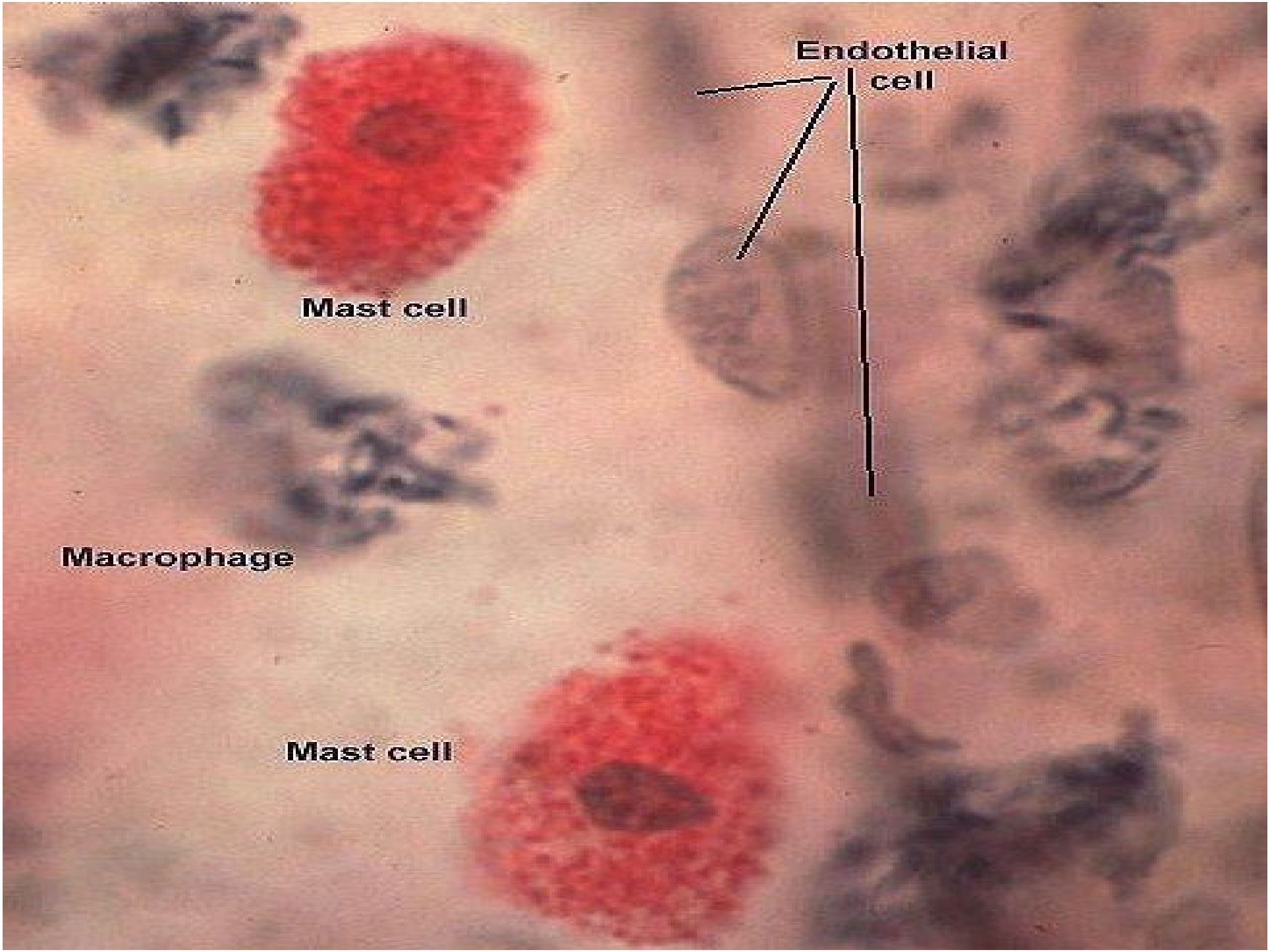









Mast Cells


Endothelial cell
Mast cell
Macrophage
Mast cell

Cells of Immune Response

Non hematopoietic cells:

- Dentritic cells
- Astrocytes and
- Endothelial cells

Function : antigen presentation

Self-Antigens: MHC Proteins

Are coded for by genes of the major histocompatibility complex (MHC) and are unique to an individual

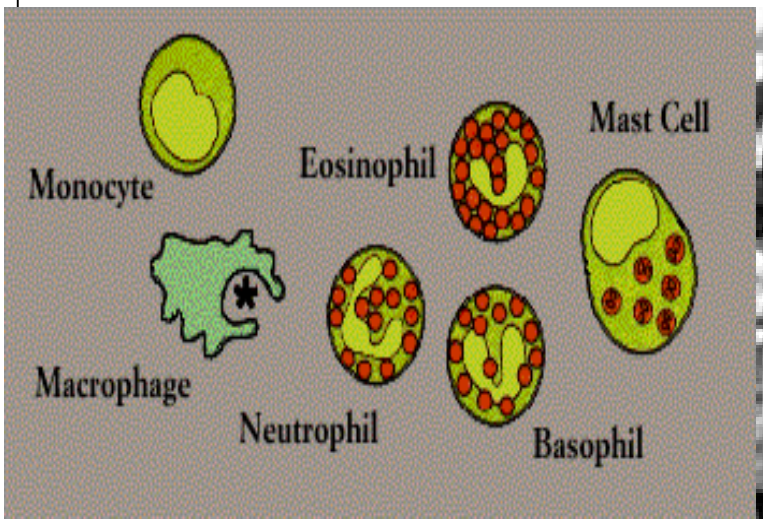
- Our cells are dotted with protein molecules (self-antigens) that are not antigenic to us but are strongly antigenic to others
- One type, MHC proteins, mark a cell as self
- The two classes of MHC proteins are:
  - **Class I MHC proteins – found on virtually all body cells**
  - **Class II MHC proteins – found on certain cells in the immune response**

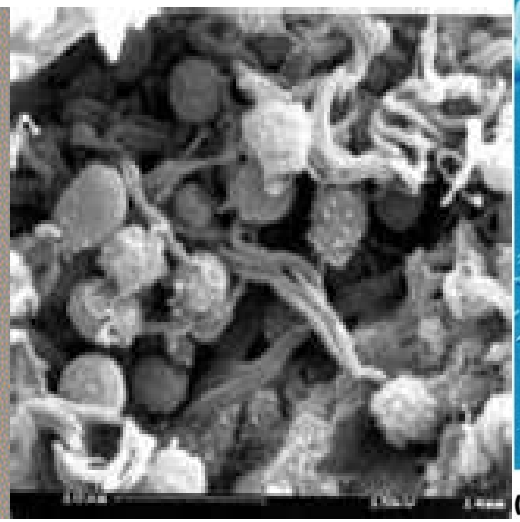
Part 3 : Mechanisms

Phagocytes

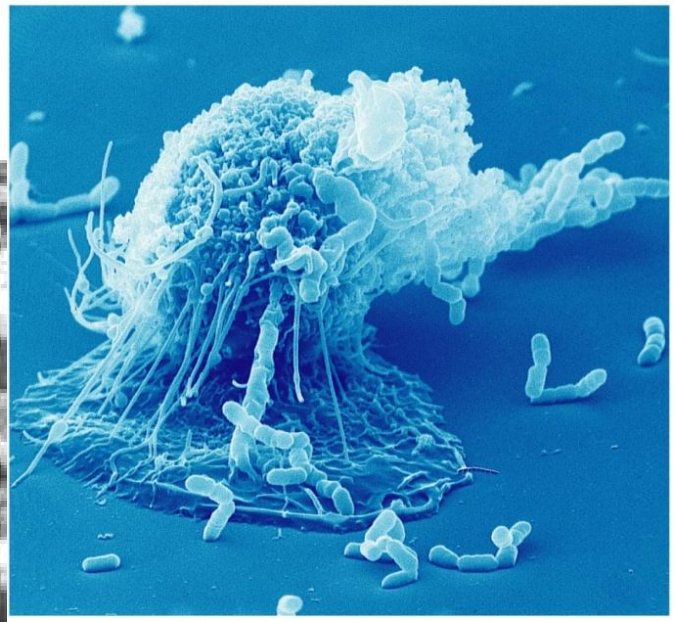
- **Macrophages are the chief phagocytic cells**
- Free macrophages wander throughout a region in search of cellular debris
- Kupffer cells (liver) and microglia

(brain) are fixed macrophages





Innate defenses → Internal defenses



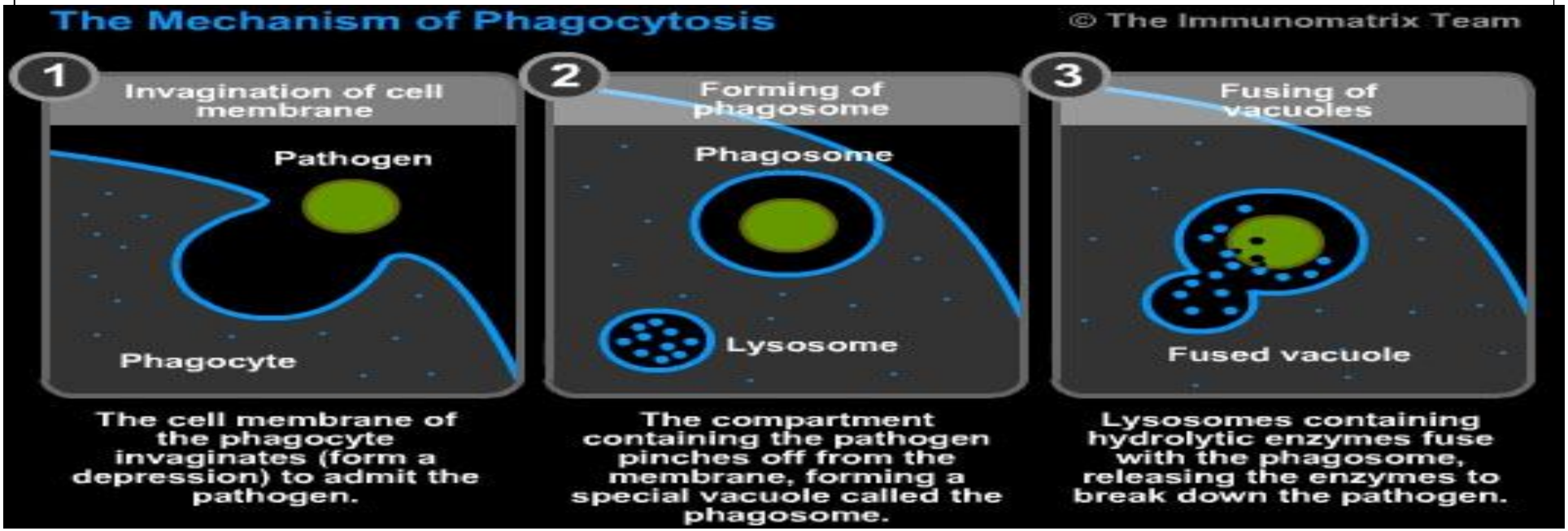
(a)

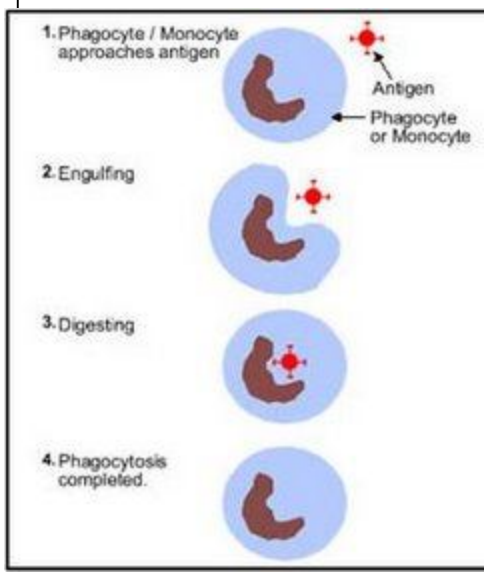
Phagocytes

- **Neutrophils** become phagocytic when encountering infectious material
- **Eosinophils** are weakly phagocytic against parasitic worms
- **Mast cells** bind and ingest a wide range of bacteria

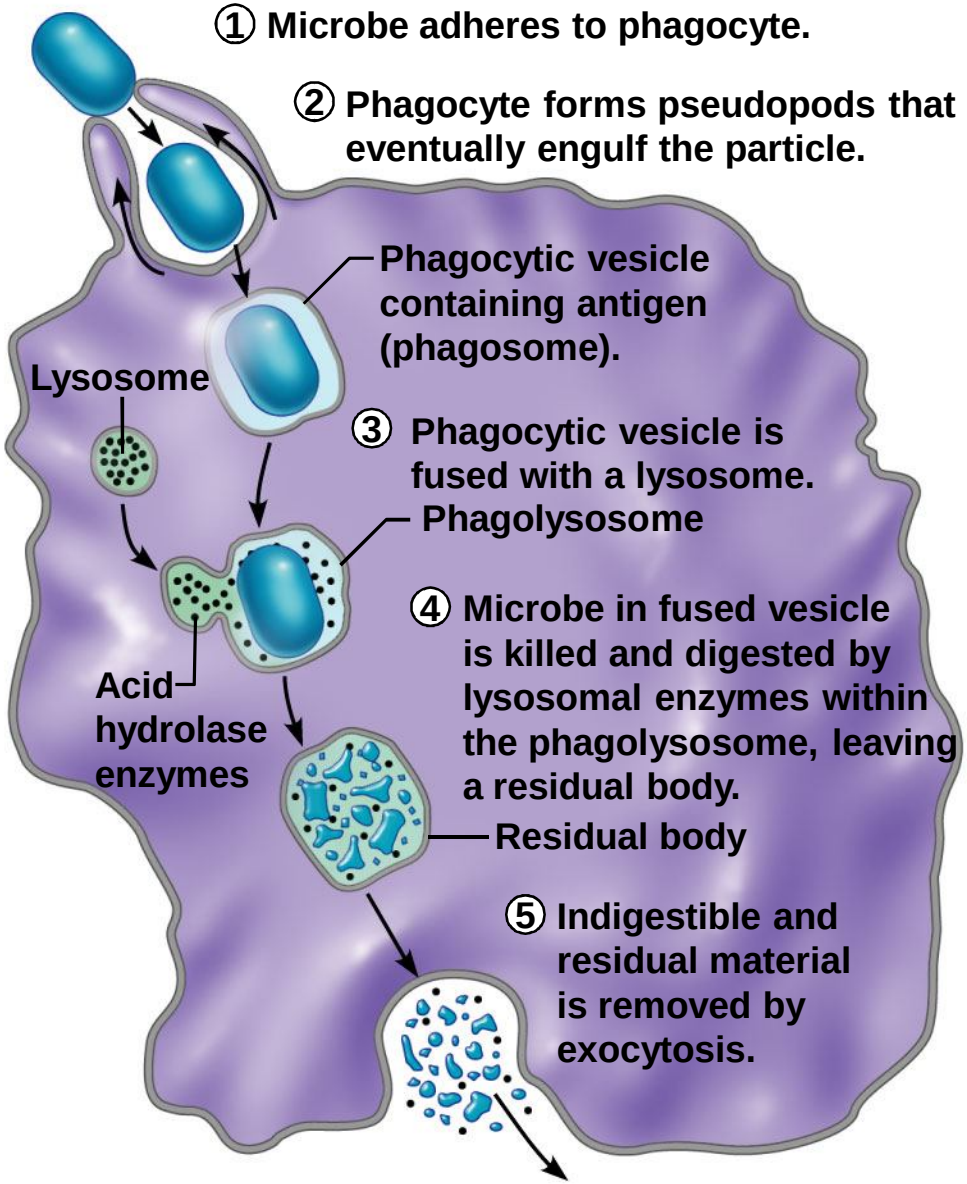
Mechanism of Phagocytosis

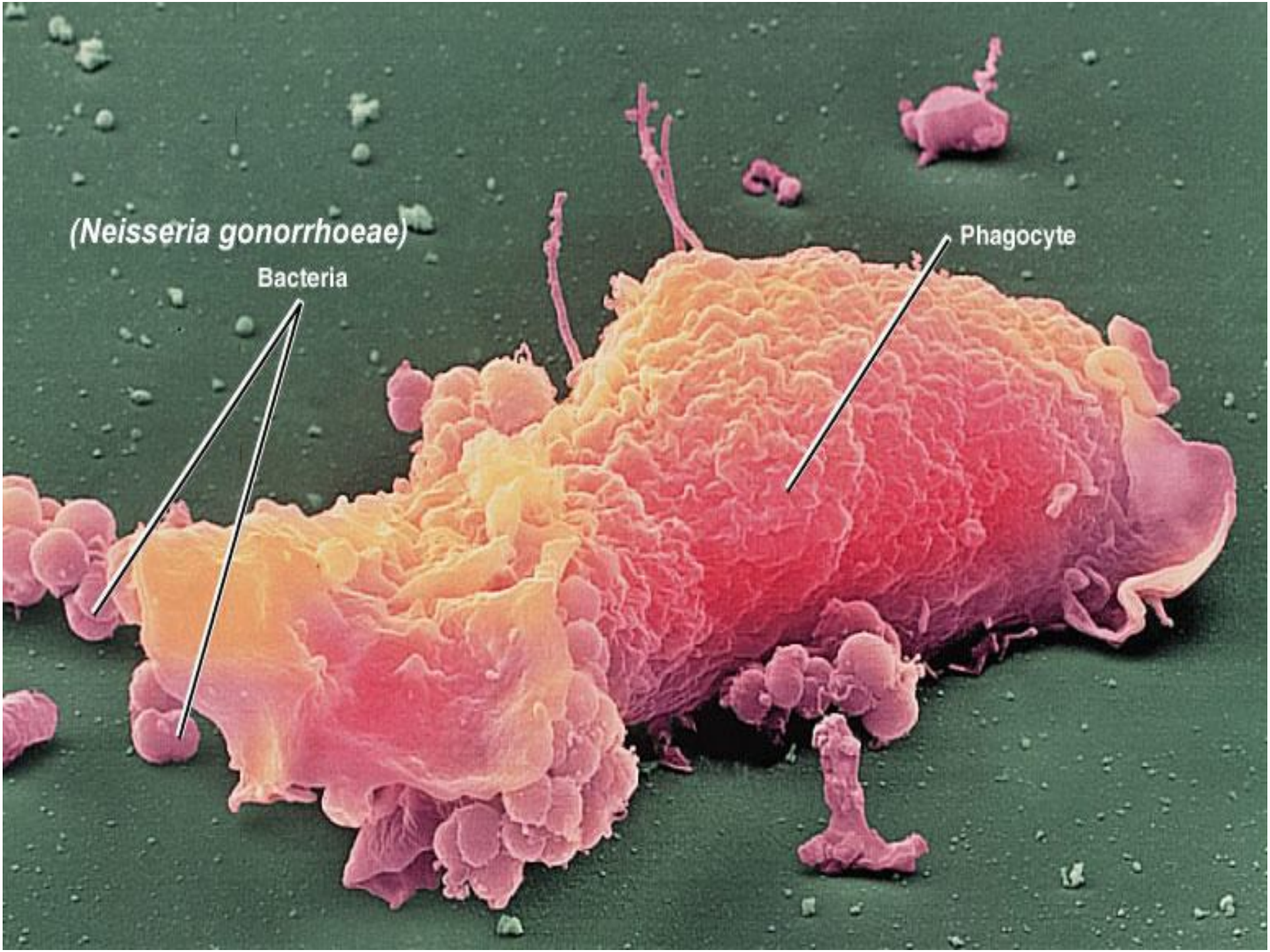
- 1/ Microbes **adhere** to the phagocyte
- **2/Pseudopods engulf** the particle (antigen) into a phagosome
- **3/Phagosomes fuse with a lysosome to form a phagolysosome**
- 4/Invaders in the phagolysosome are **digested by proteolytic enzymes**
- 5/Indigestible and residual material is removed by exocytosis

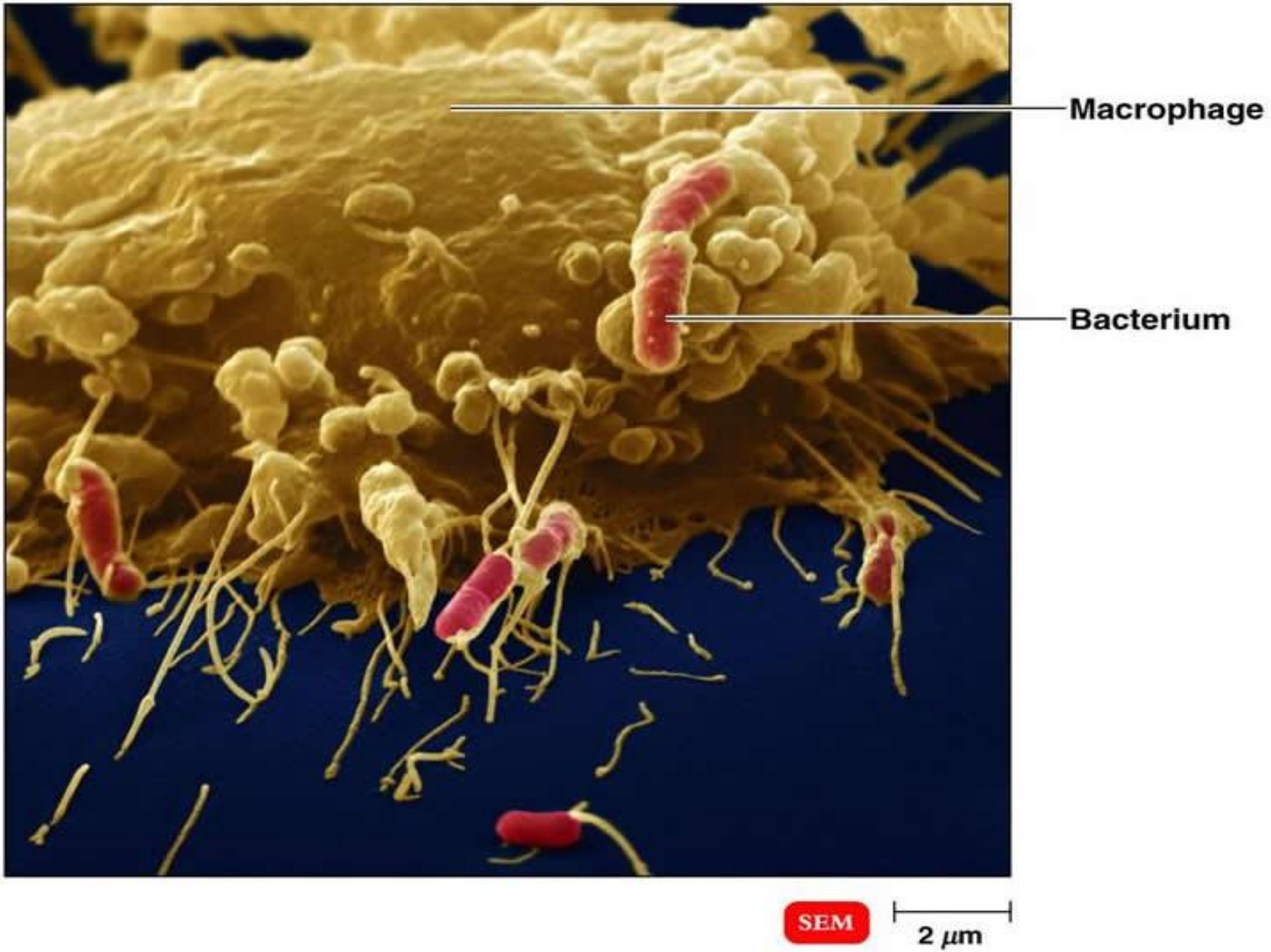


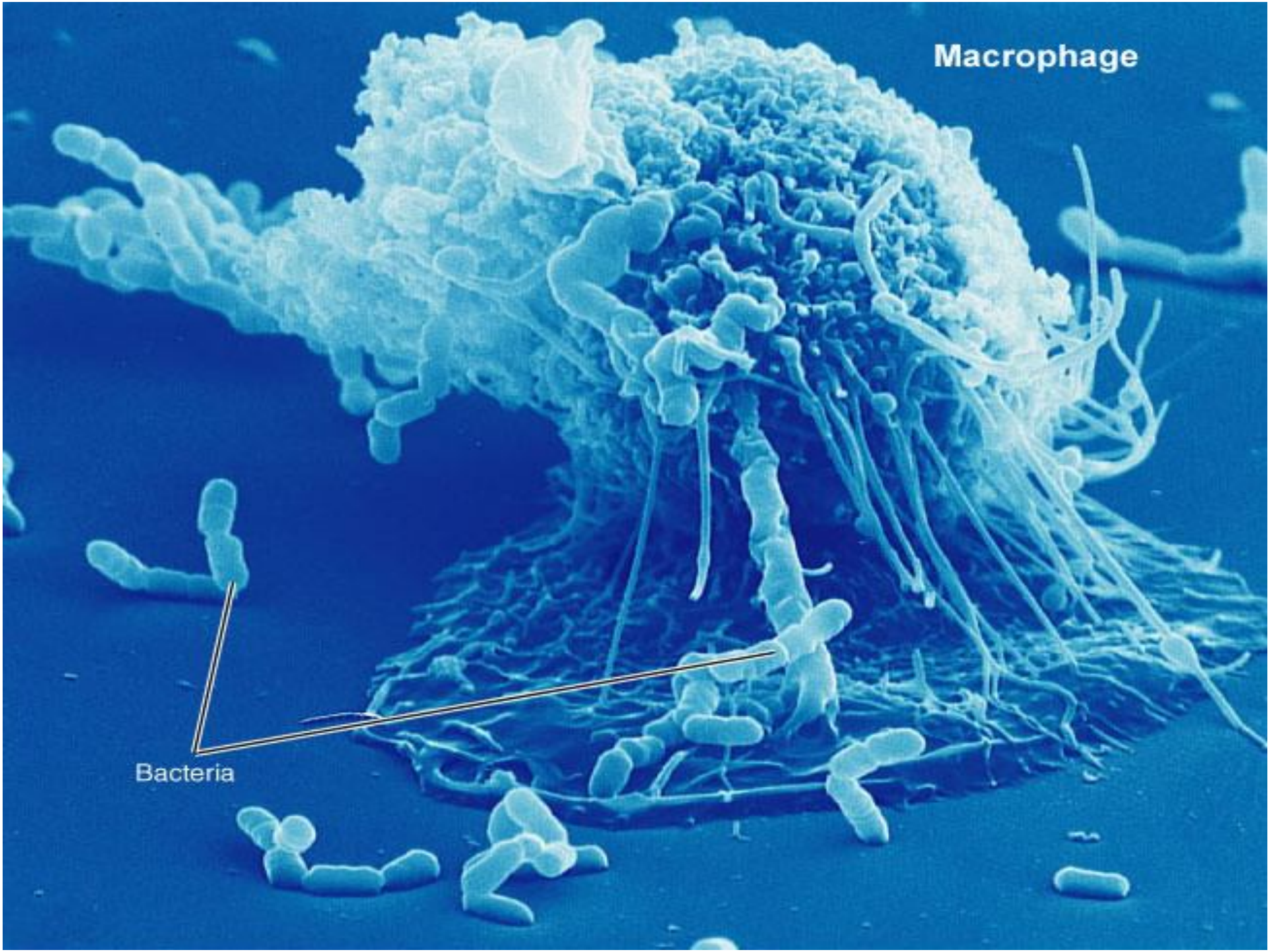

1. Phagocyte / Monocyte approaches antigen
Antigen
Phagocyte or Monocyte
2. Engulfing
3. Digesting
4. Phagocytosis completed.

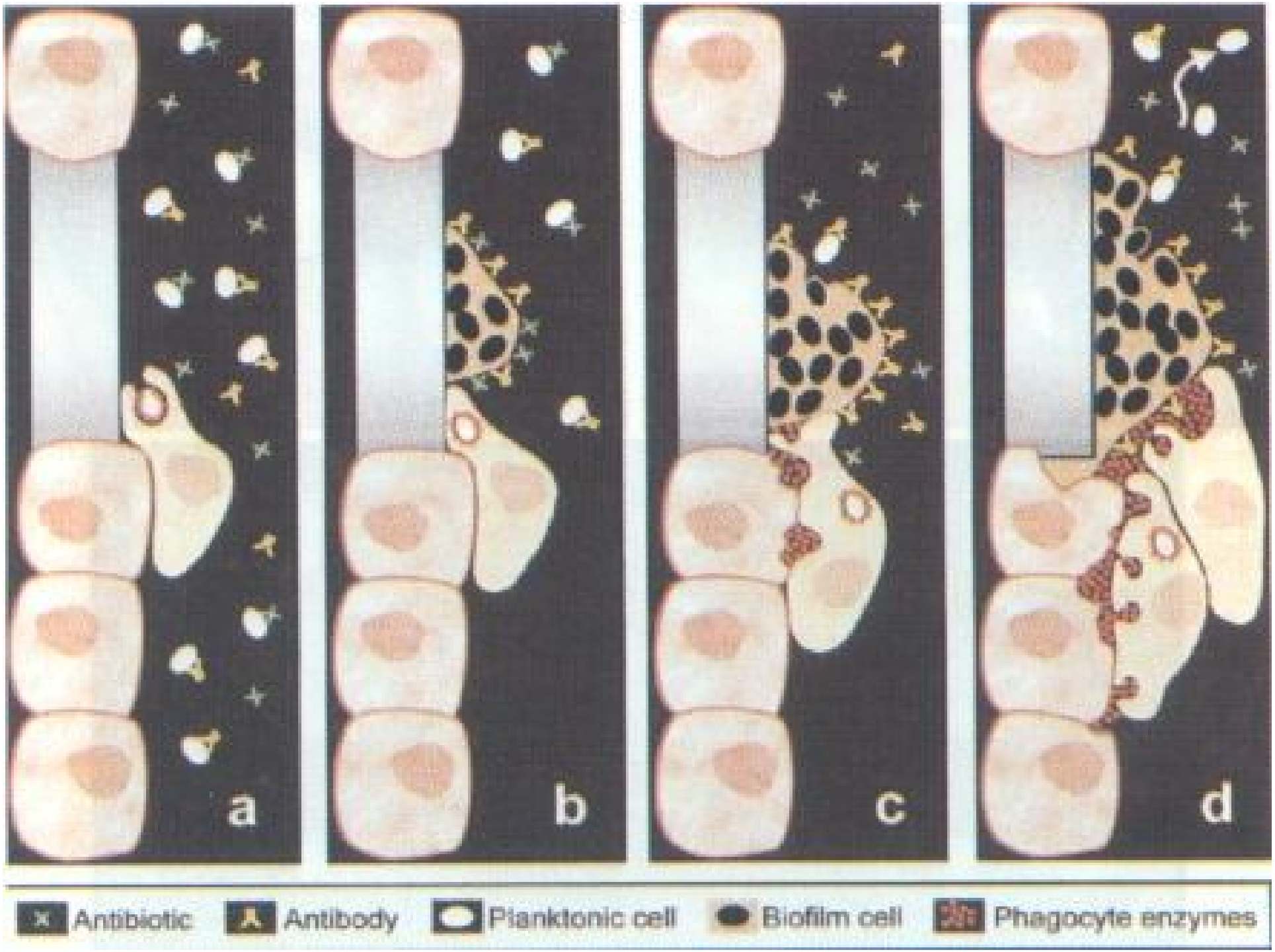
(b)

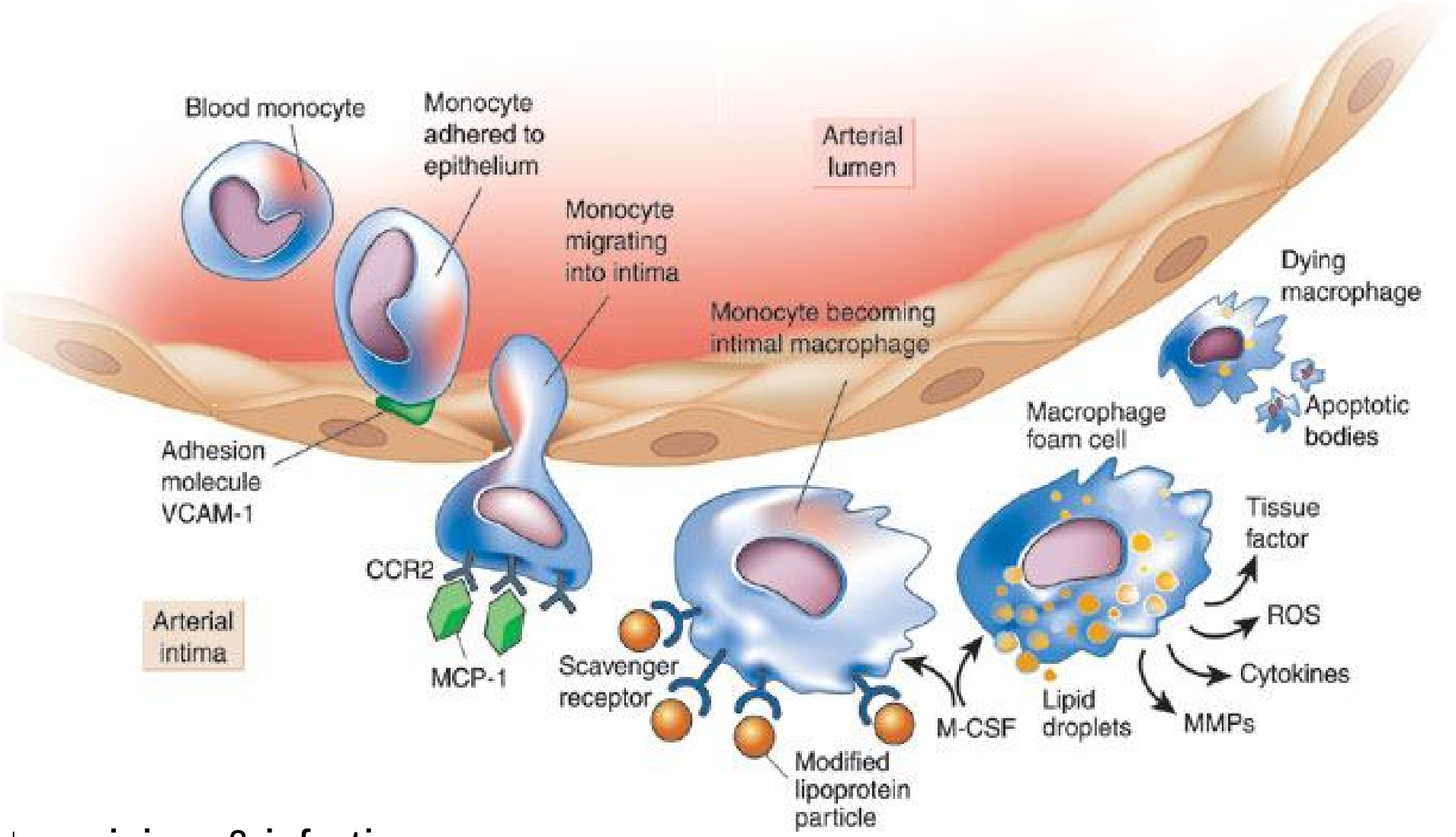

① Microbe adheres to phagocyte.
② Phagocyte forms pseudopods that eventually engulf the particle.
Phagocytic vesicle containing antigen (phagosome).
Lysosome
③ Phagocytic vesicle is fused with a lysosome.
Phagolysosome
④ Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body.
Acid hydrolase enzymes
Residual body
⑤ Indigestible and residual material is removed by exocytosis.


(Neisseria gonorrhoeae)
Bacteria
Phagocyte


Macrophage
Bacterium
SEM
2 μm


Macrophage
Bacteria


a
b
c
d
Antibiotic
Antibody
Planktonic cell
Biofilm cell
Phagocyte enzymes



- injury & infection
- macrophages slip between cells [extravasation] to arrive
- cytokine chemicals attract other "troops" [chemotaxis]
- histamine chemicals dilate blood vessels for easier access to injury [vasodilation]

Receptor Type	Present On	Interacts With
CD4	Lymphocytes	MHC II
CD8	Lymphocytes	MHC I
MHC I	General Body Cells	CD8
MHC II	Phagocytes	CD4

The **major histocompatibility complex** =**MHC**

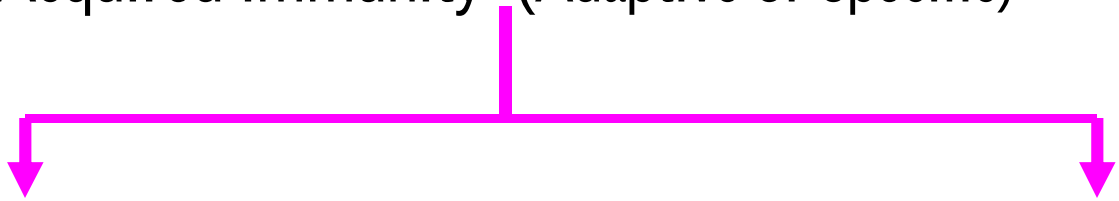
HIV infects primarily vital cells in the human immune system such as helper T cells (to be specific, $CD4^+$ T cells), macrophages, and dendritic cells

Acquired (Adaptive) Immunity

Defensive mechanisms include :

1) Innate immunity (Natural or Non specific)

2) Acquired immunity (Adaptive or Specific)



Cell-mediated immunity **Humoral immunity**

Aquired (specific) immunity

Two mechanisms

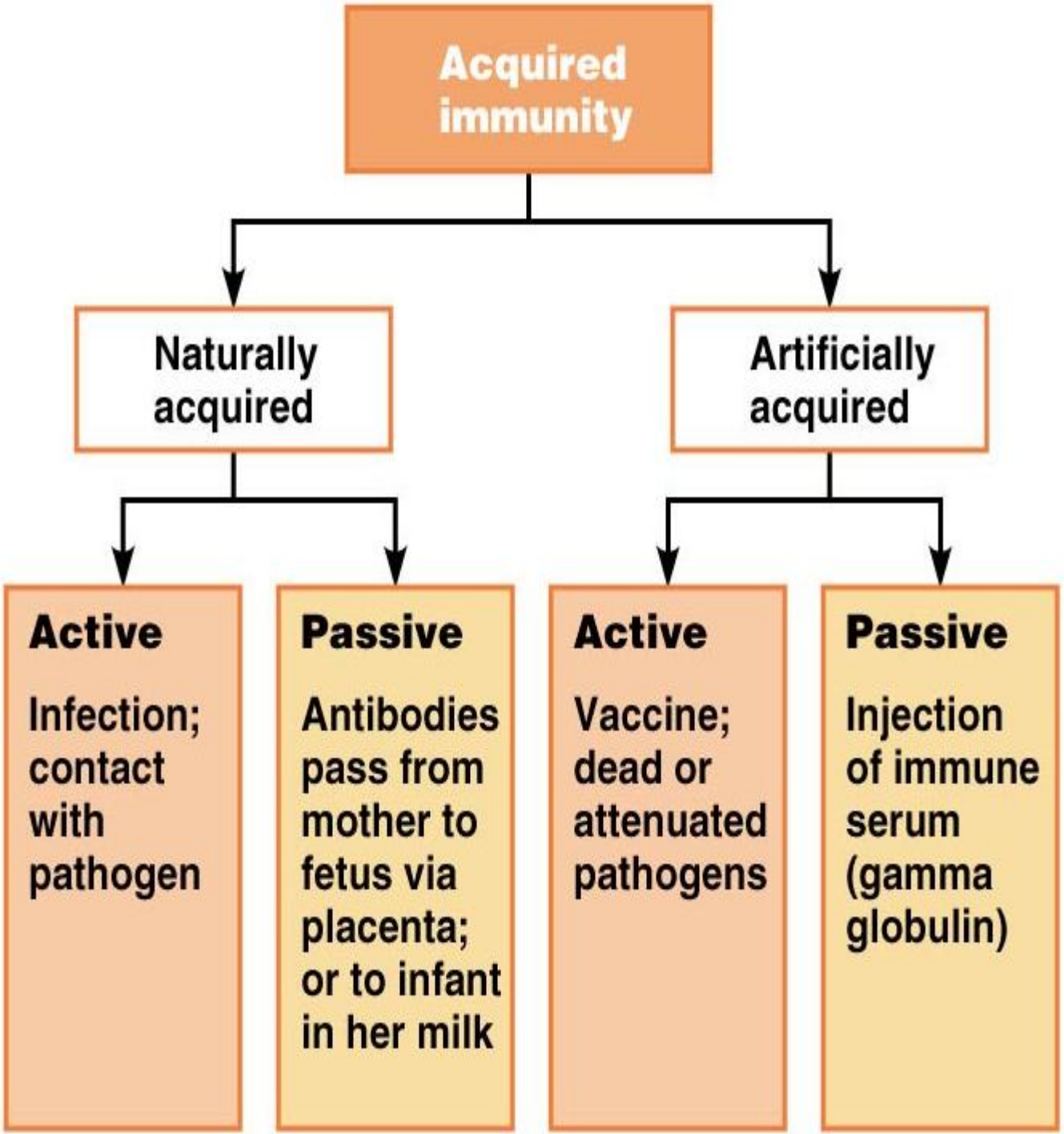
1) **Humoral immune response**:

- Antibodies are produced by B-lymphocytes
- These have the ability to recognize and bind specifically to antigen that induced their formation

2) **The cell mediated immune response (CMI)**

- It is mediated by certain types of **T-lymphocytes**
- T-lymphocytes recognize foreign material by means of surface receptors
- T-lymphocytes attack and destroy foreign material directly or through release of soluble mediators i.e. cytokines

Types of Acquired Immunity



Adaptive defenses → Cellular immunity

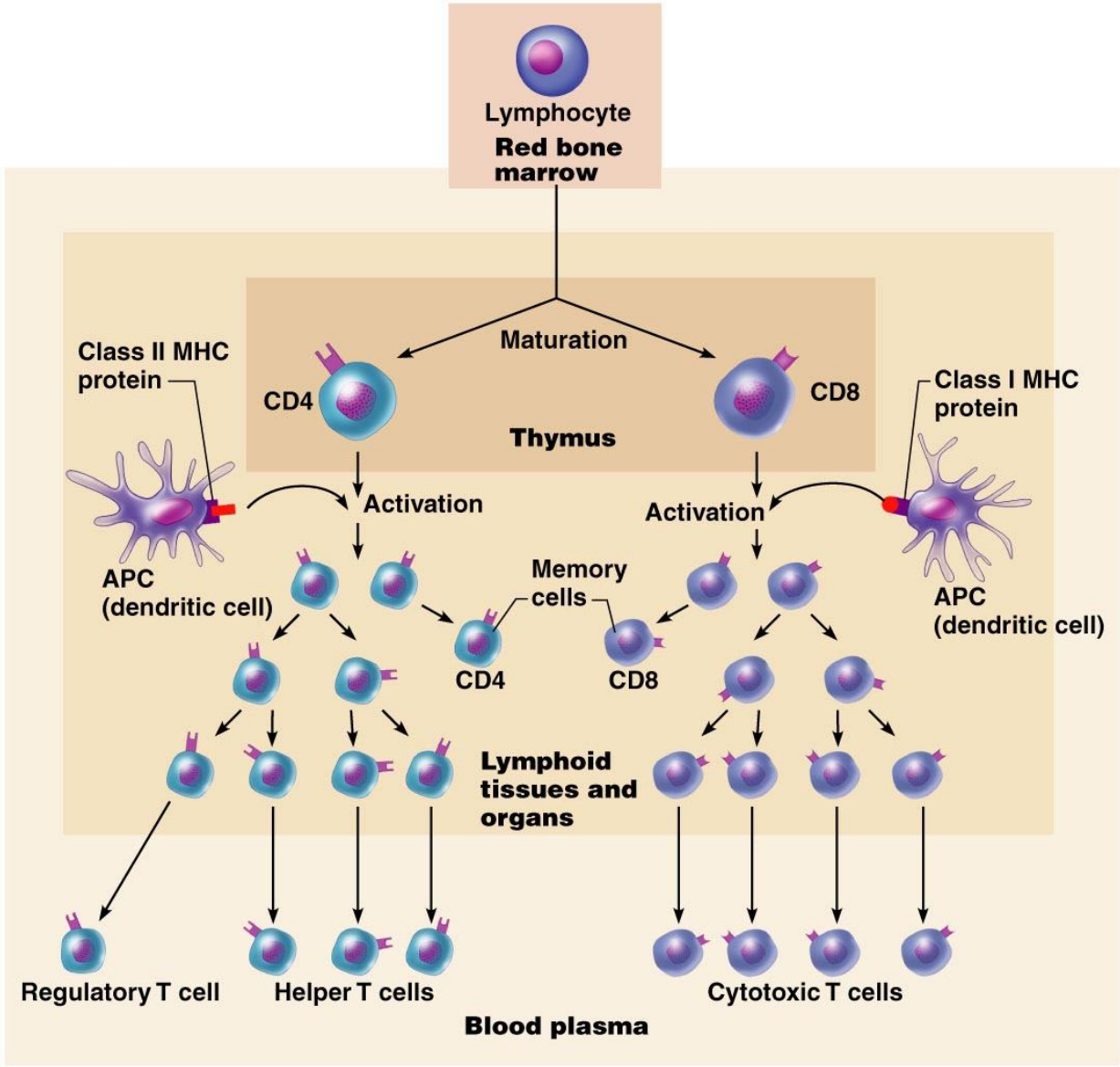


Figure 21.15

Acquired Or Adaptive Immunity

I- Passive acquired immunity

a-Naturally passive acquired immunity

Antibodies are passed through placenta to the fetus

b- Artificially passive acquired immunity

The injection of alredy prepared antibodies, such as gamma globulin (short-term immunization)

II- Active acquired immunity

a-Natural active acquired immunity :

- Following clinical or subclinical infections

- measles or mumps, in which immunity is long lasting

b- Artificial active acquired immunity :

- Following vaccination with live or killed infectious agents or their products

Mechanism of Humoral immunity

* Antibodies induce resistance through:

1) Antitoxin neutralize bacterial toxins (diphtheria,tetanus)

Antitoxin are developed actively as a result of:

a- Previous infection

b- Artificial immunization

c- Transferred passively as antiserum

*** Neutralization of toxin with antitoxin prevents a combination with tissue cells**

Mechanism of Humoral immunity

2) Antibodies attach to the surface of bacteria and

a- act as opsonins and enhance phagocytosisd

b- prevent the adherence of microorganisms to their target cells, e.g. IgA in the gut

c- Activate the complement and lead to bacterial lysis

d- Clump bacteria (agglutination) leading to phagocytosis

Cell Mediated Immunity

* Host defenses against extracellular infection are mediated by:
  - Antibody
  - Complement
  - Macrophages

* Intercellular infections are mediates by CMI

* CMI are responsible for:
  - Resistance to intracellular pathogens
  - Resistance to fungal and protozoal infections
  - Resistance to tumors

Cell Mediated Immunity

* CMI may play a role in some harmful conditions:
  - Hypersensitivity reactions type IV (contact dermatitis)
  - Graft rejection
  - Autoimmune diseases

* Cell mediated cytotoxicity mediated by:
  - T-cytotoxic cells cells
  - Natural killer cells
  - Activated macrophages

T-lymphocytes:

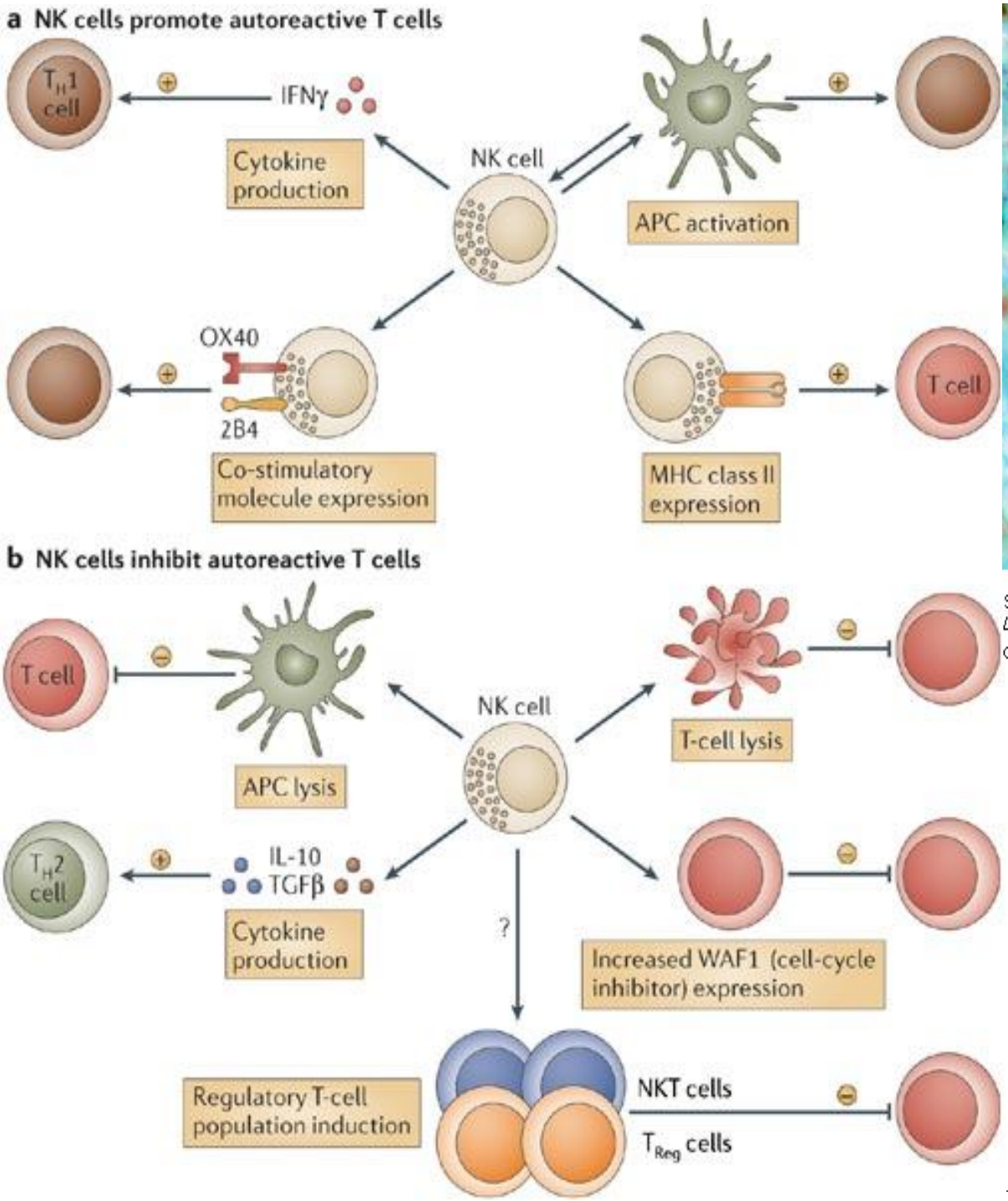
- Antigen specific cells carrying CD_3 complex, CD_4, CD_8
- Dominant blood lymphocytes (70%)
- Produce cytokines
- **Activation of other cells (Th CD4)**
- **Suppressors for others (Ts CD8)**

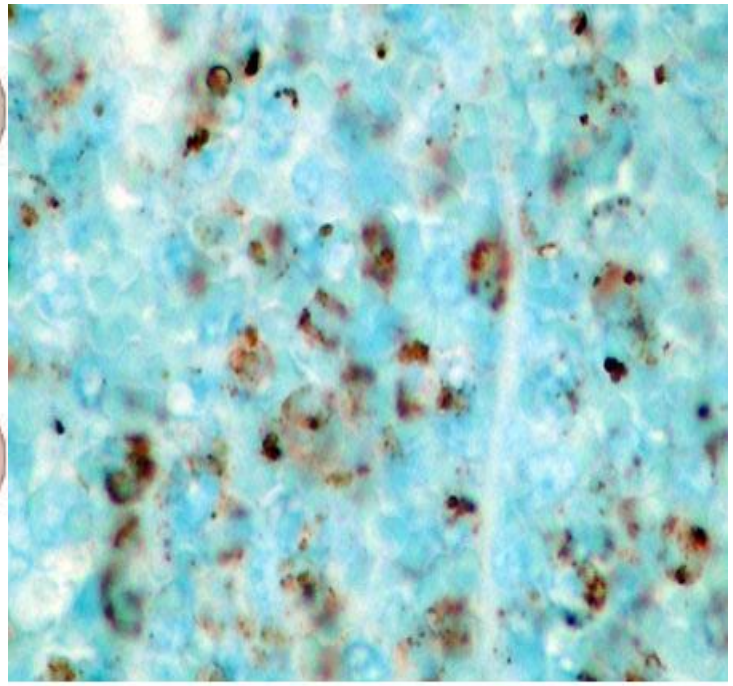
B-lymphocytes:

- Antigen specific cells with surface receptor
- Less common lymphocytes (20%)
- Responsible for antibody production

* NK, K cells:

- Not antigen specific
- Carry Fc receptors , NK-target cell receptor





Natural Killer (NK) Cells

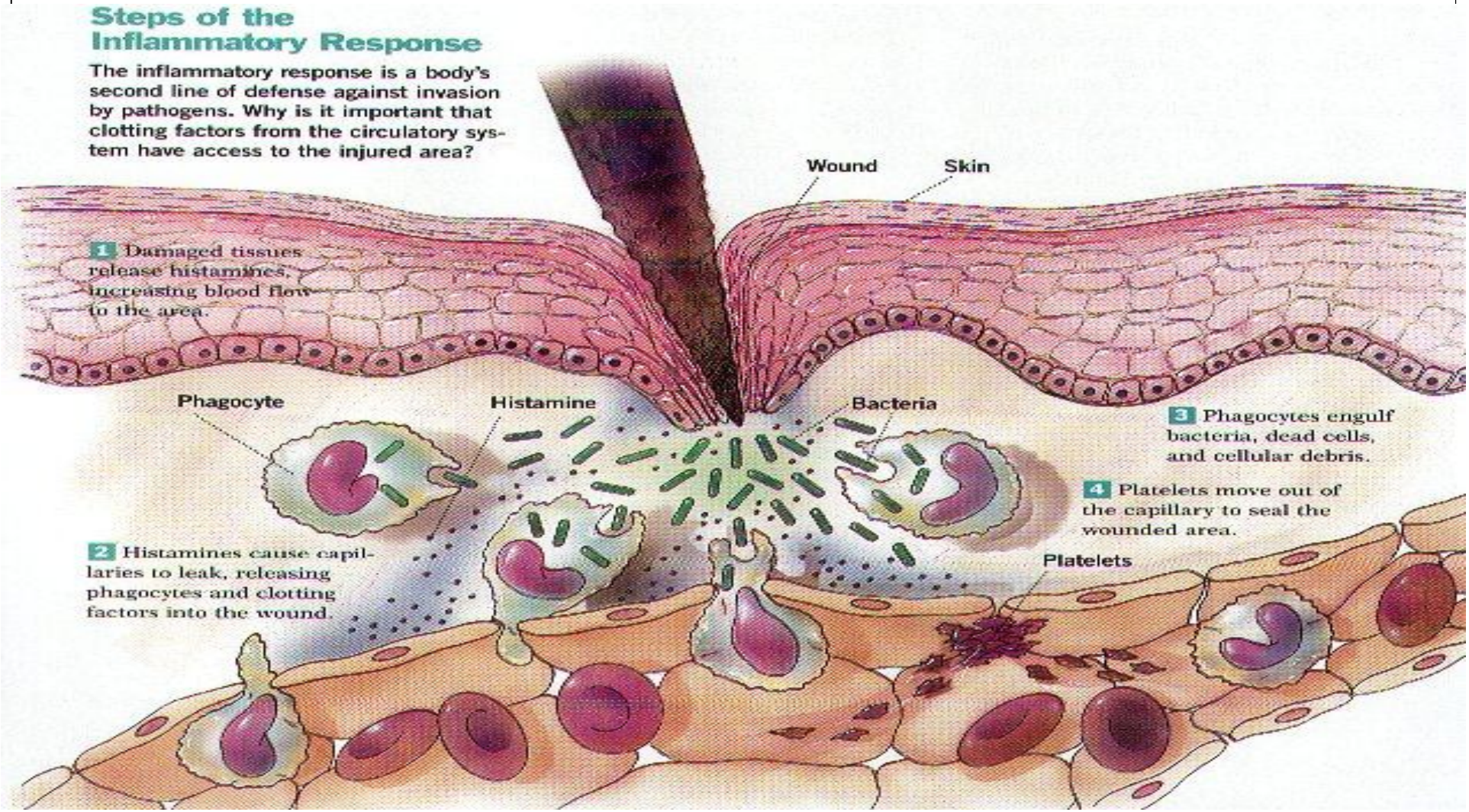
- Can **lyse and kill cancer cells and virus-infected cells**
- Are a small, distinct group of large granular lymphocytes
- React nonspecifically and eliminate cancerous and virus-infected cells
- Kill their target cells by releasing perforins and other cytolytic chemicals
- Secrete potent chemicals that enhance the inflammatory response

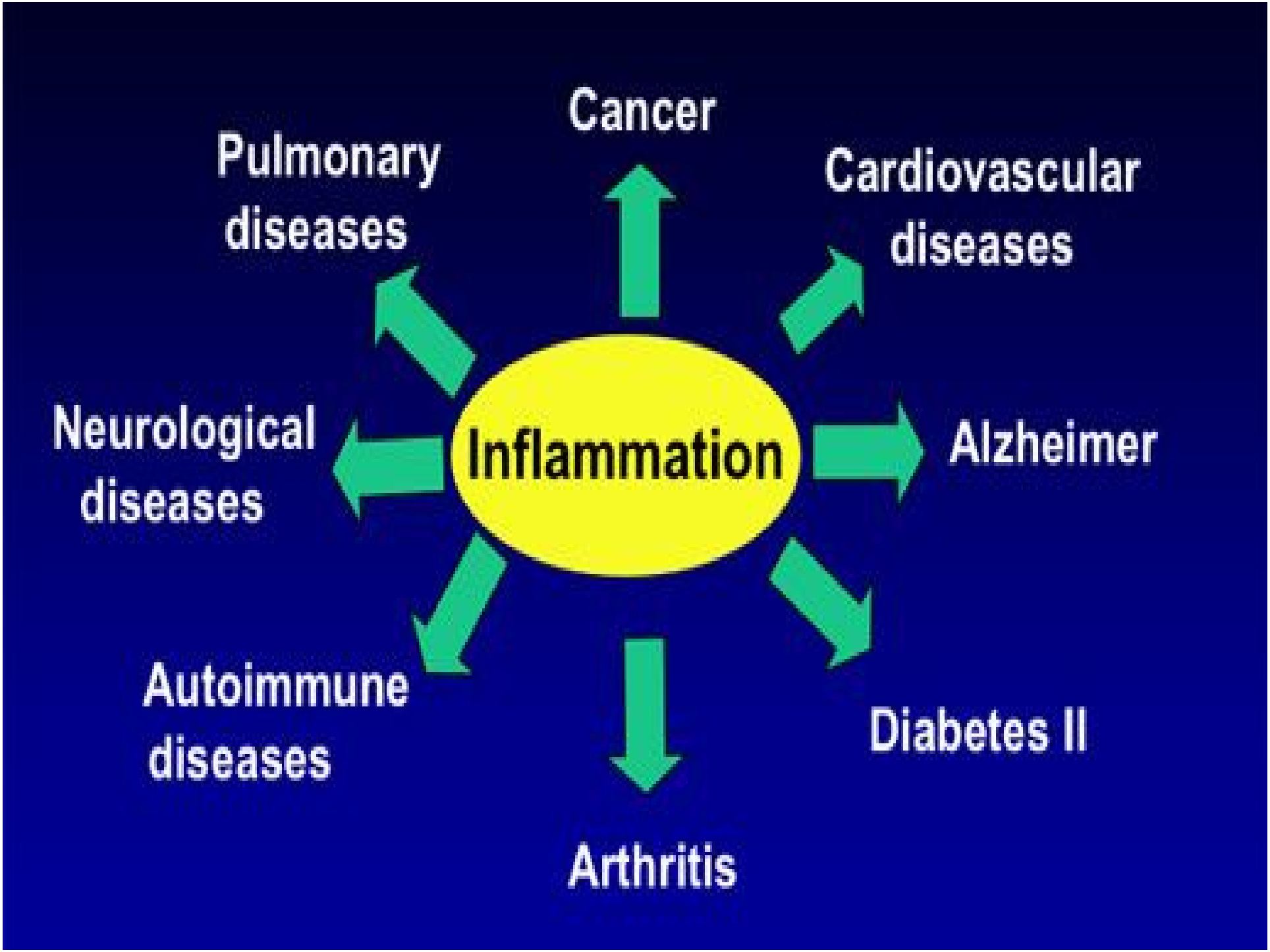
TABLE 21.4 Cells and Molecules of the Adaptive Immune Response

ELEMENT	FUNCTION IN IMMUNE RESPONSE
CELLS	
B cell	Lymphocyte that matures in bone marrow. Induced to replicate by antigen binding, usually followed by helper T cell interactions in lymphoid tissues. Its progeny (clone members) form memory cells and plasma cells
Plasma cell	Antibody-producing "machine"; produces huge numbers of antibodies (immunoglobulins) with the same antigen specificity. Specialized B cell clone descendant
Helper T cell (T_H)	A CD4 T cell that is central to both humoral and cellular immunity. After binding with a specific antigen presented by an APC, it stimulates production of cytotoxic T cells and B cells to help fight invader, activates macrophages, and acts both directly and indirectly by releasing cytokines
Cytotoxic T cell (T_C)	A CD8 cell; also called a cytolytic (CTL) T cell. Activated by antigen presented by an antigen-presenting cell, often with helper T cell involvement. Its specialty is killing virus-invaded body cells and cancer cells; also involved in rejection of foreign tissue grafts
Regulatory T cell (T_{Reg})	Formerly called suppressor T cell; slows or stops activity of immune system. Thought to be important in controlling autoimmune diseases; likely several different populations exist
Memory cell	Descendant of activated B cell or any class of T cell; generated during initial immune response (primary response); may exist in body for years after, enabling it to respond quickly and efficiently to subsequent infections or meetings with same antigen
Antigen-presenting cell (APC)	Any of several cell types (dendritic cell, macrophage, B cell) that engulfs and digests antigens that it encounters, presenting parts of them on its plasma membrane (bound to an MHC protein) for recognition by T cells bearing receptors for same antigen. This function, antigen presentation, is essential for normal cell-mediated responses. Macrophages also release chemicals (cytokines) that activate T cells

Part IV : Inflammation

Inflammation




Cancer
Pulmonary diseases
Cardiovascular diseases
Neurological diseases
Inflammation
Alzheimer
Autoimmune diseases
Diabetes II
Arthritis

Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are injured
  - **Prevents the spread of damaging agents to nearby tissues**
  - **Disposes of cell debris and pathogens**
  - **Sets the stage for repair processes**
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain

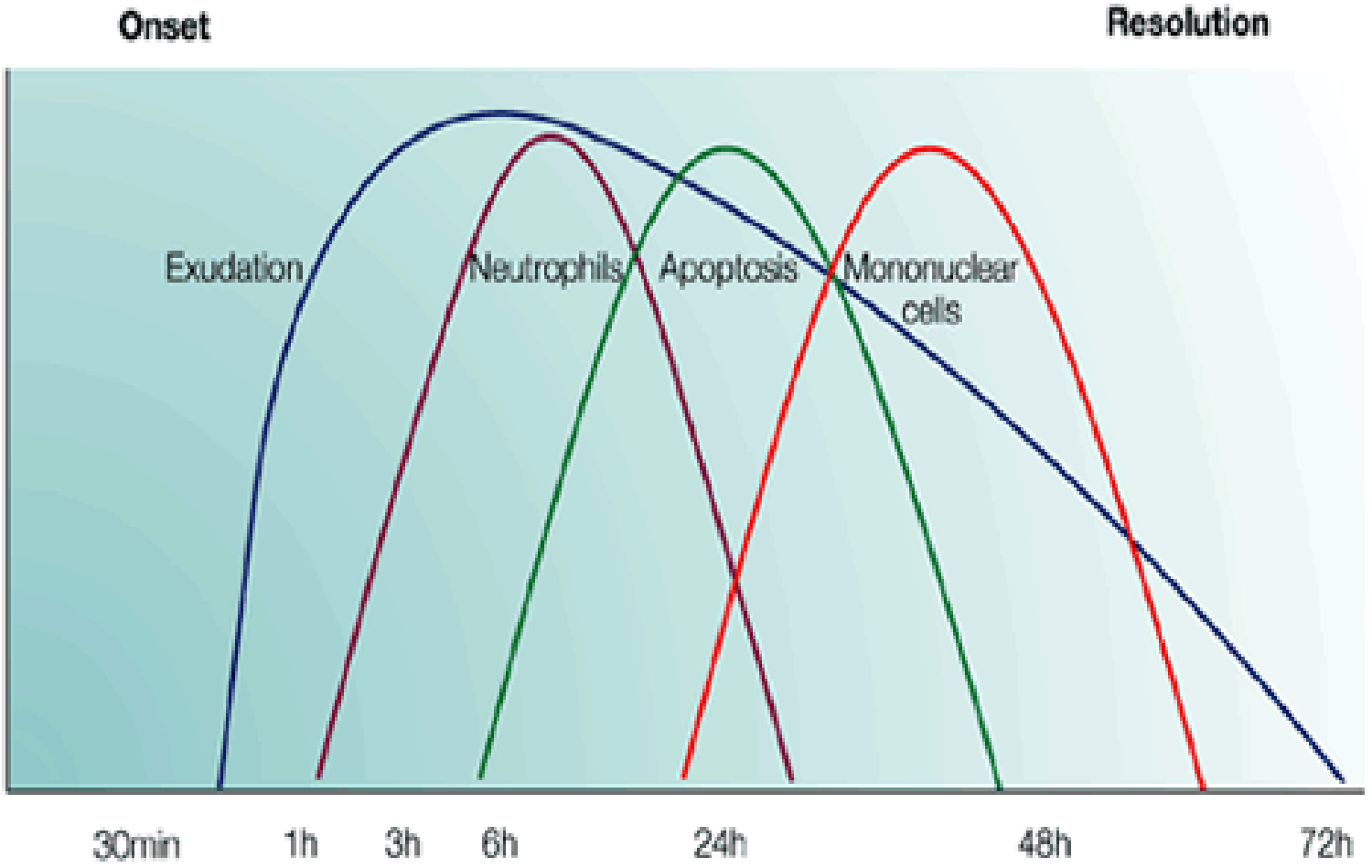
Plasma cascade systems

- **The complement system**, when activated, results in the increased removal of pathogens via opsonisation and phagocytosis.

- **The kinin system** generates proteins capable of sustaining vasodilation and other physical inflammatory effects.

- **The coagulation system or *clotting cascade*** which forms a protective protein mesh over sites of injury.

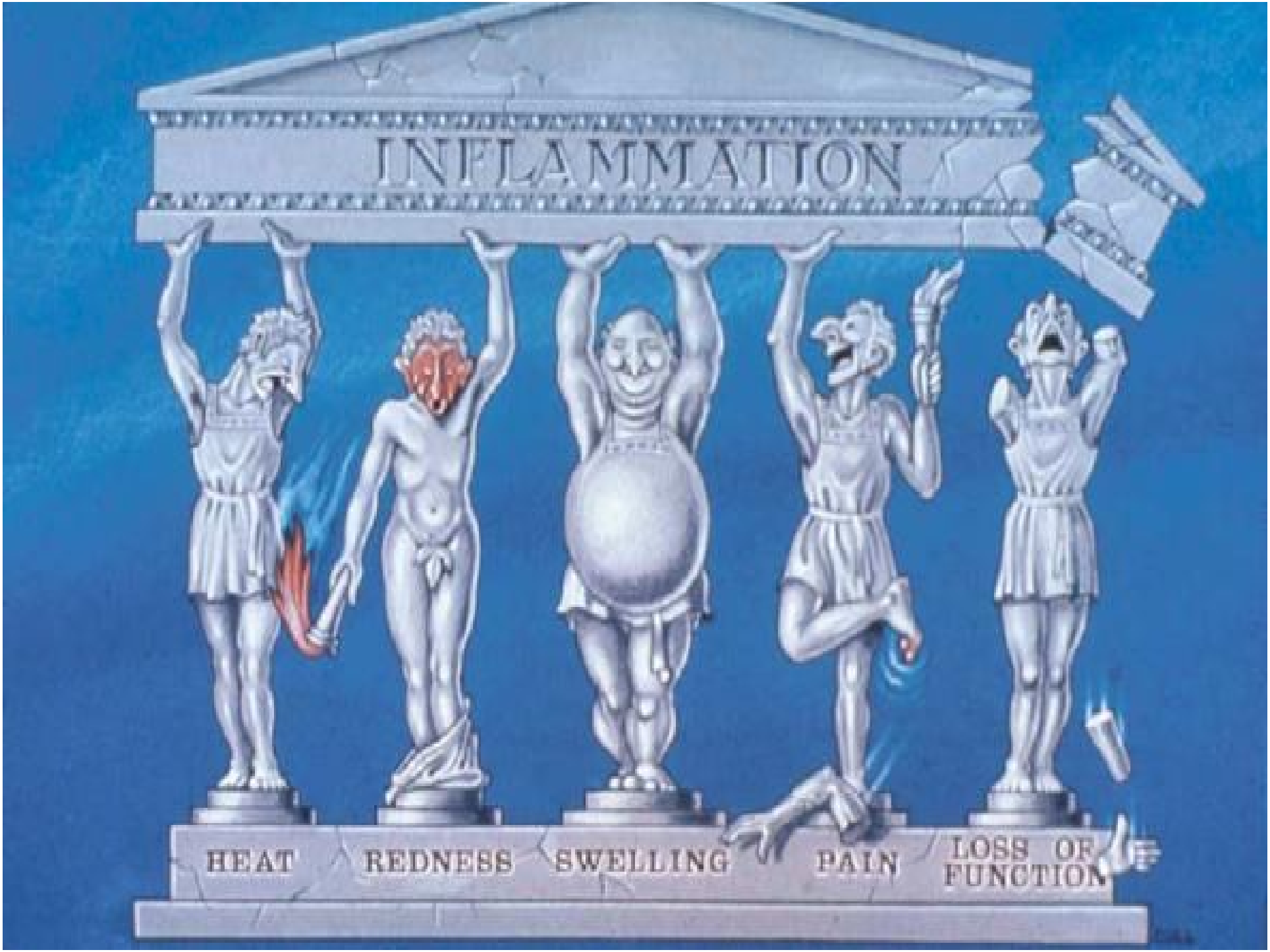
- **The fibrinolysis system**, which acts in opposition to the *coagulation system*, to counterbalance clotting and generate several other inflammatory mediators.



Histamine	Substance P	TNF	MCP1	cyPGs
Serotonin	PAF	IL-1β	IL-6	BAX
Bradykinin	PGs	IL-8/KC		p53
Complement	LTs	LXs		TGF-β1

Comparison between acute and chronic inflammation:

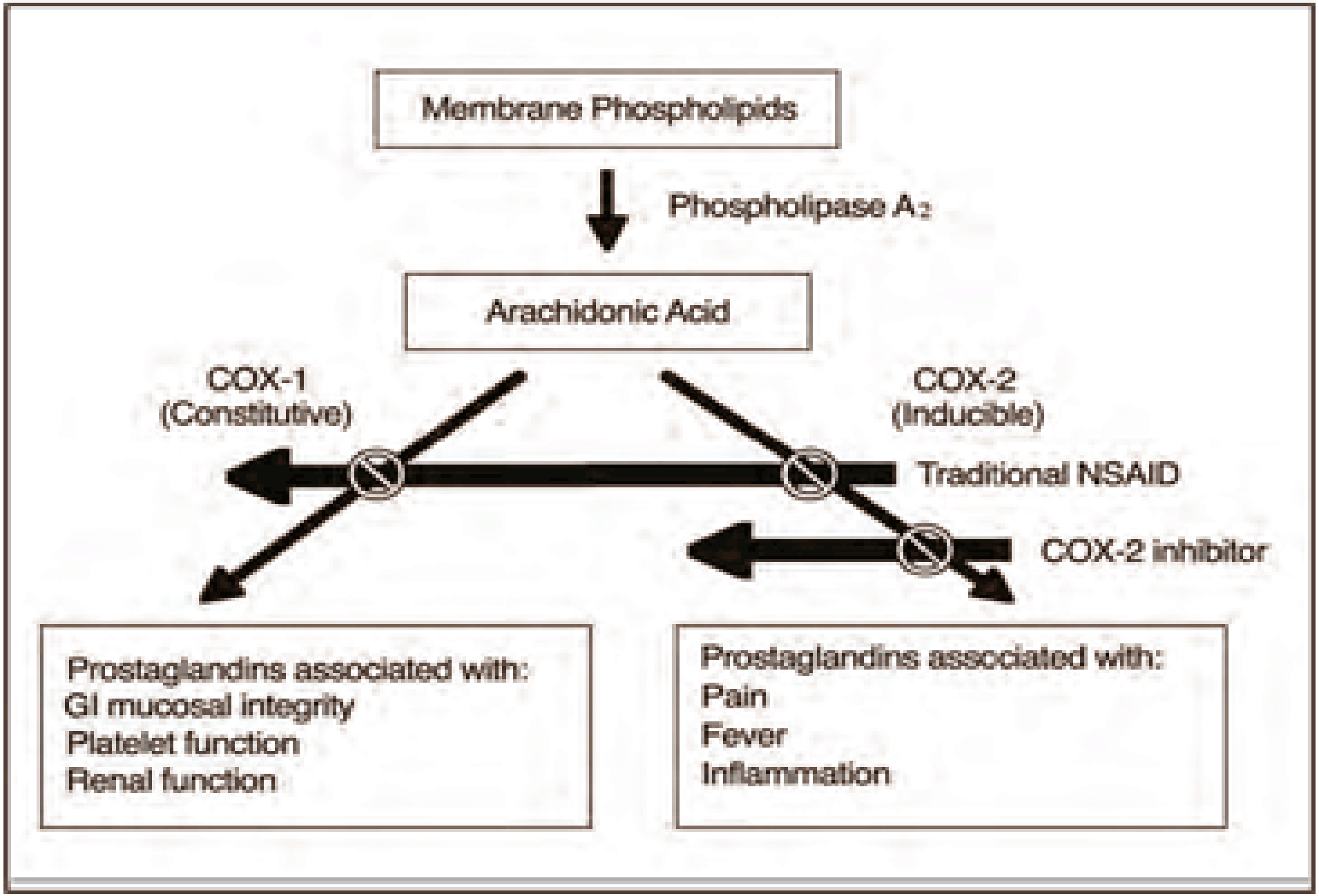
	Acute	Chronic
Causative agent	Pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
Major cells involved	Neutrophils, mononuclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed
Duration	Few days	Up to many months, or years
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis


INFLAMMATION
HEAT
REDNESS
SWELLING
PAIN
LOSS OF FUNCTION

The classic signs and symptoms of acute inflammation:

Redness	*Rubor*
Swelling	*Tumor / Turgor*
Heat	*Calor*
Pain	*Dolor*
Loss of function	*Functio laesa*

Figure. Pharmacology of Traditional NSAIDs and Selective COX-2 Inhibitors on Prostaglandin Synthesis[6]

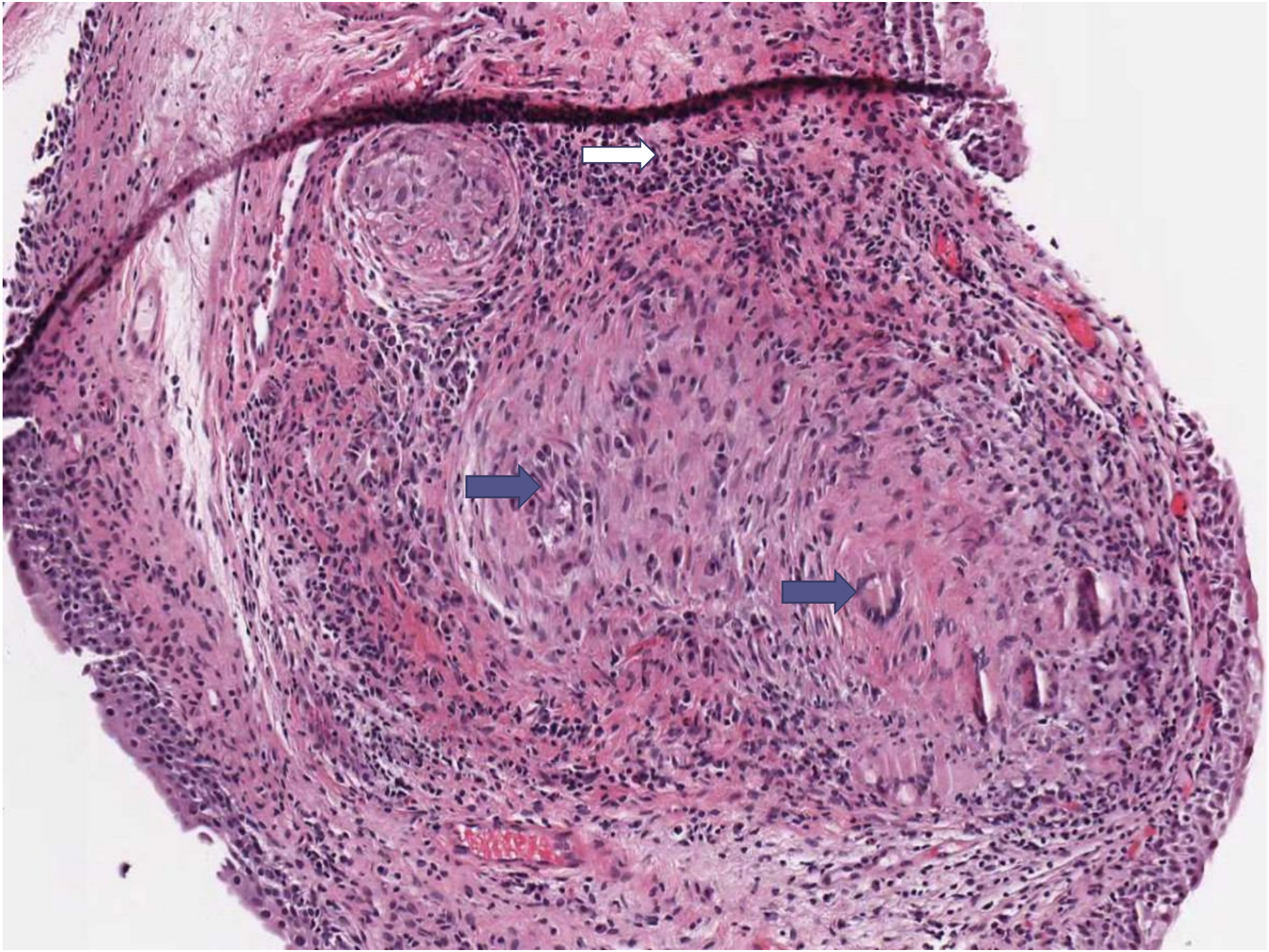


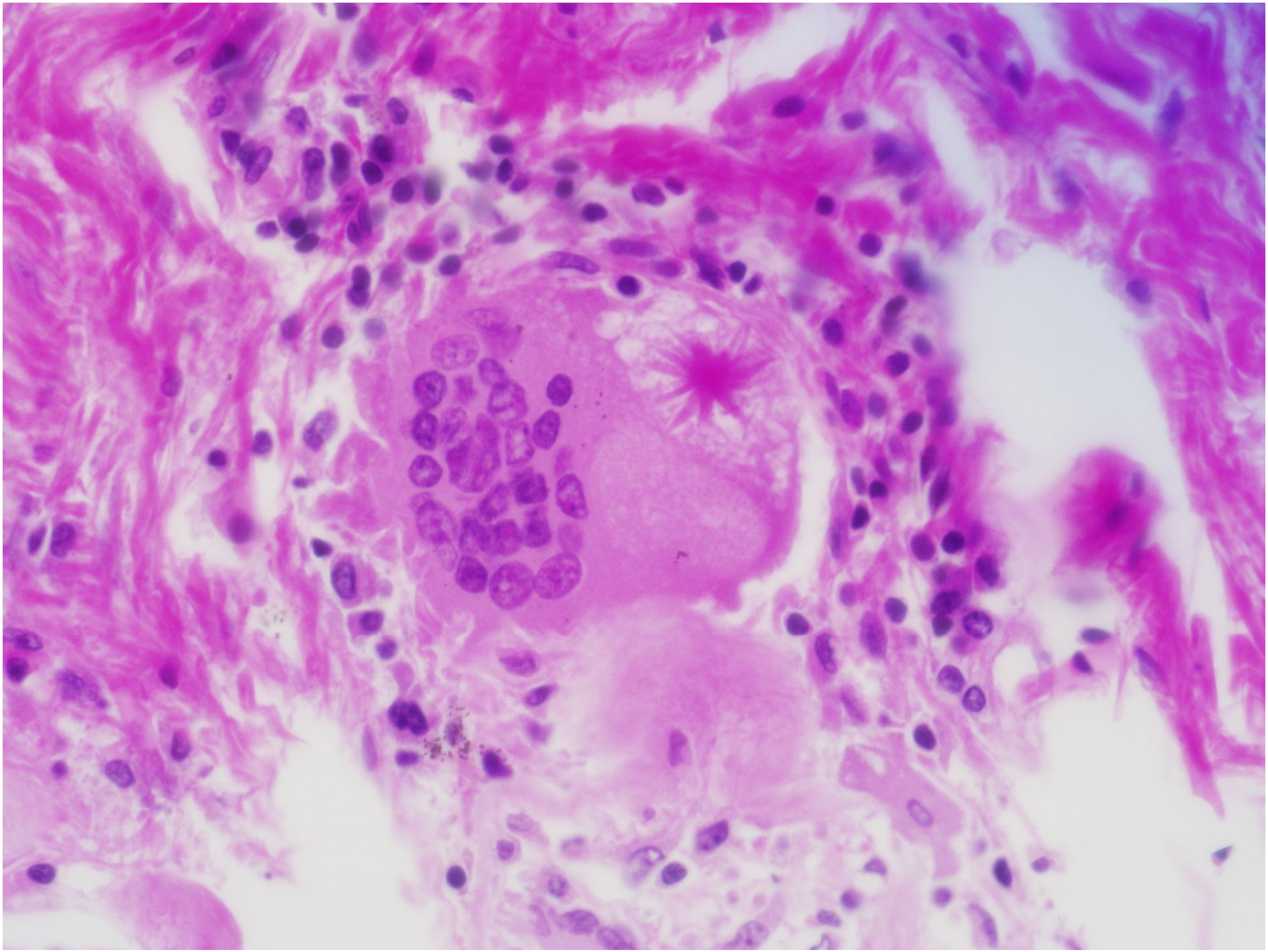
- **acute inflammation** : inflammation, usually of sudden onset, characterized by the classical signs in which the vascular and exudative processes predominate.

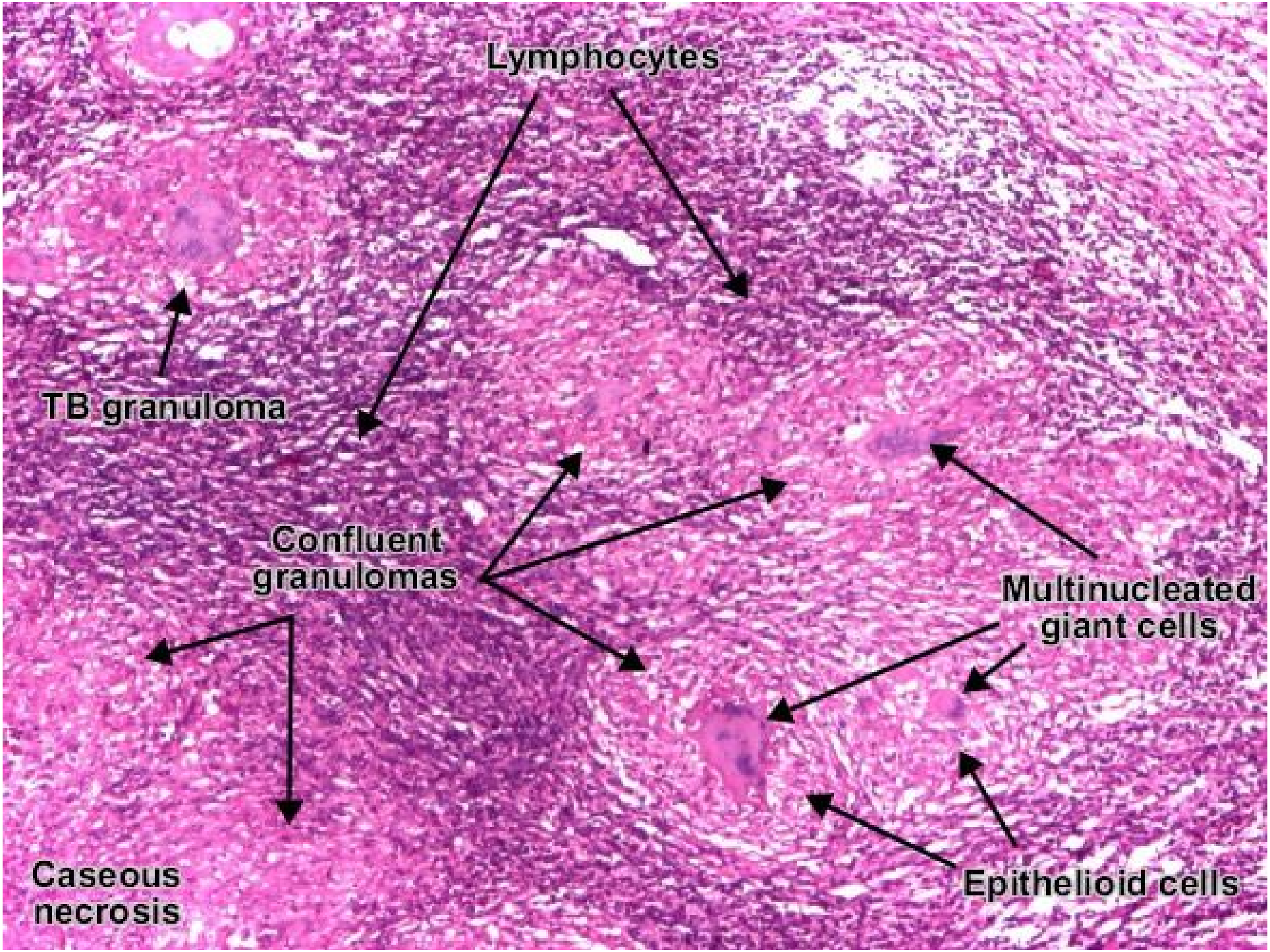
- **subacute inflammation** : a condition intermediate between chronic and acute inflammation, exhibiting some of the characteristics of each.

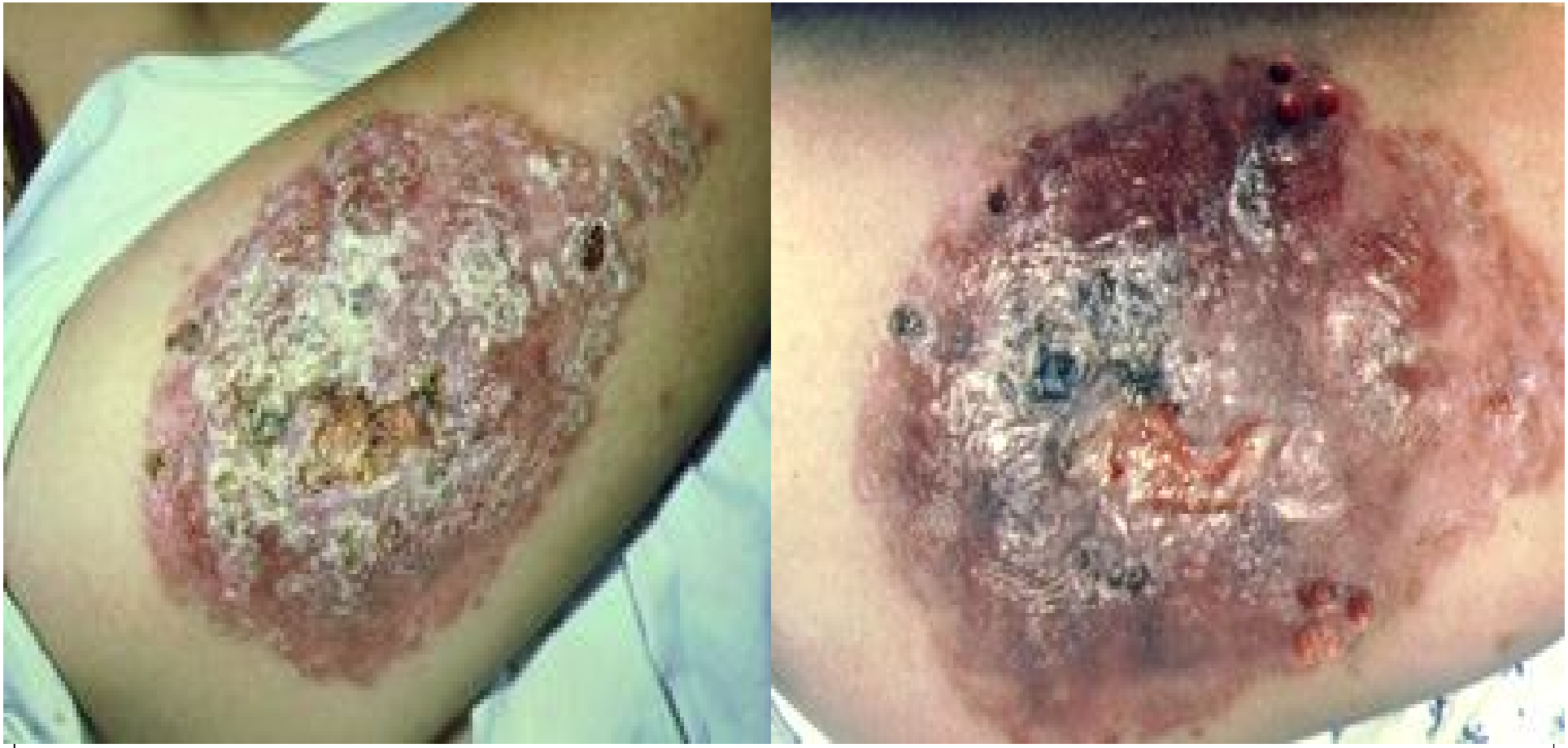
- **chronic inflammation** : inflammation of slow progress and marked chiefly by the formation of new connective tissue; it may be a continuation of an acute form or a prolonged low-grade form, and usually causes permanent tissue damage.

granulomatous inflammation : an inflammation, usually chronic, characterized by the formation of granulomas






Lymphocytes
TB granuloma
Confluent granulomas
Multinucleated giant cells
Caseous necrosis
Epithelioid cells



Inflammation Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid
- Inflammatory mediators:
  - **Kinins, prostaglandins (PGs), complement, and cytokines**
  - **Released by injured tissue, phagocytes, lymphocytes, and mast cells**
  - **Cause local small blood vessels to dilate, resulting in hyperemia**

Toll-like Receptors (TLRs)

- Macrophages and cells lining the gastrointestinal and respiratory tracts bear TLRs
- TLRs recognize specific classes of infecting microbes
- Activated TLRs trigger the release of cytokines that promote inflammation

Inflammatory Response: **Vascular Permeability**

- Chemicals liberated by the inflammatory response increase the permeability of local capillaries
- **Exudate**—fluid containing proteins, clotting factors, and antibodies
  - Exudate seeps into tissue spaces causing local edema (swelling), which contributes to the sensation of pain

Inflammatory Response: **Edema**

- The surge of protein-rich fluids into tissue spaces (edema):
  - **Helps dilute harmful substances**
  - **Brings in large quantities of oxygen and nutrients needed for repair**
  - **Allows entry of clotting proteins, which prevents the spread of bacteria**

Inflammatory Response: **Phagocytic Mobilization**

- Four main phases:
  - **Leukocytosis – neutrophils are released from the bone marrow in response to leukocytosis-inducing factors released by injured cells**
  - **Margination – neutrophils cling to the walls of capillaries in the injured area**
  - **Diapedesis – neutrophils squeeze through capillary walls and begin phagocytosis**
  - **Chemotaxis – inflammatory chemicals attract neutrophils to the injury site**

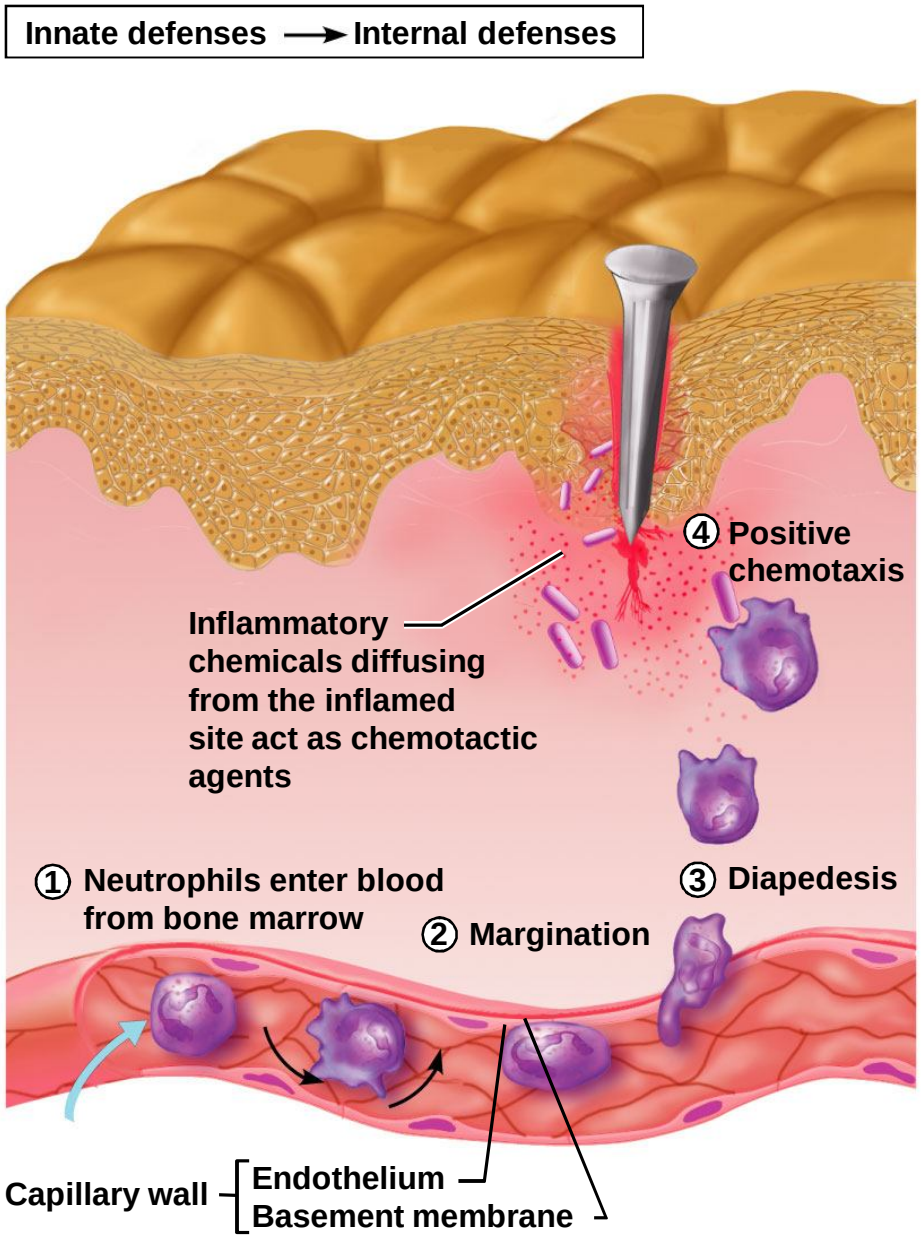
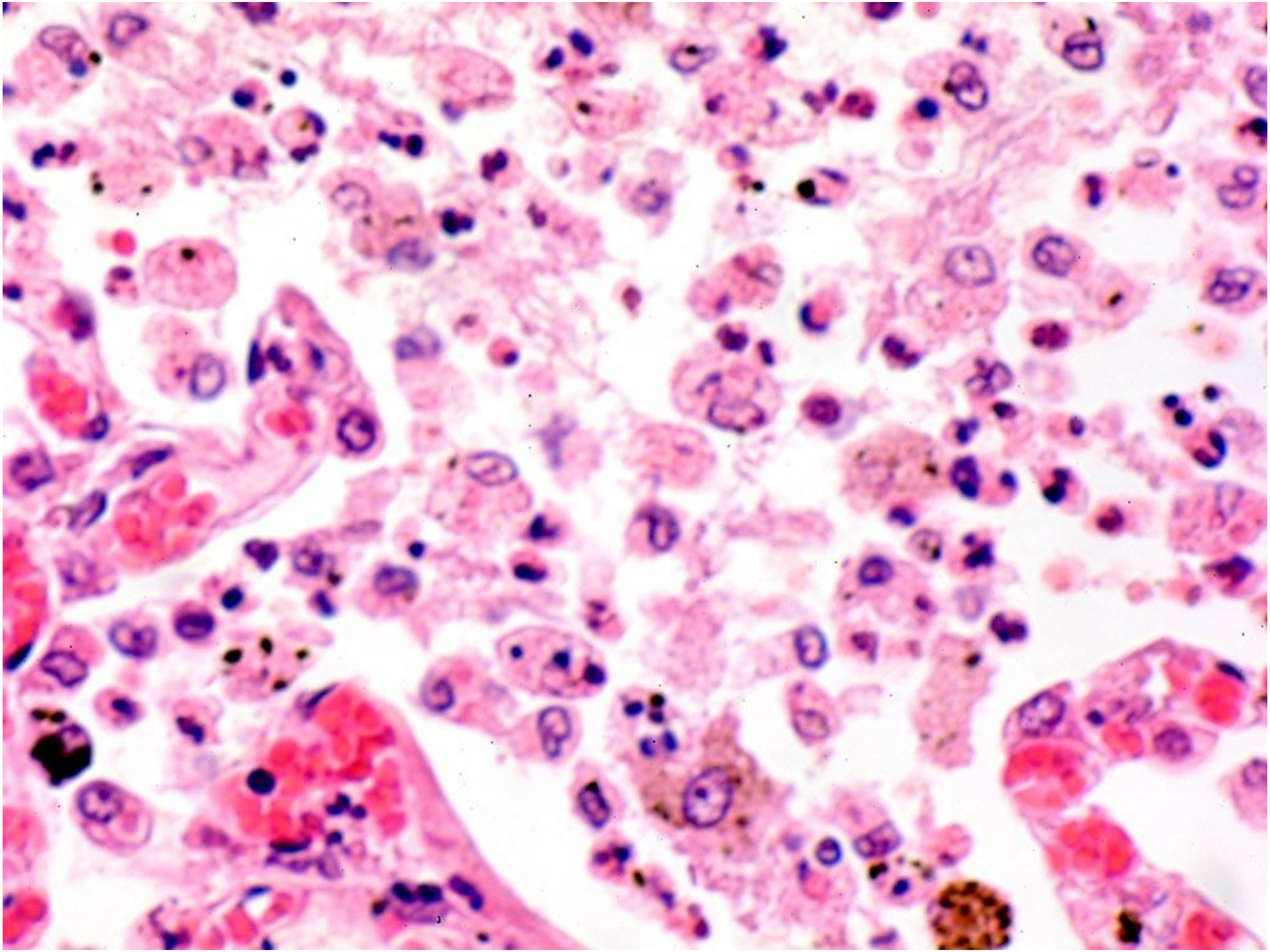
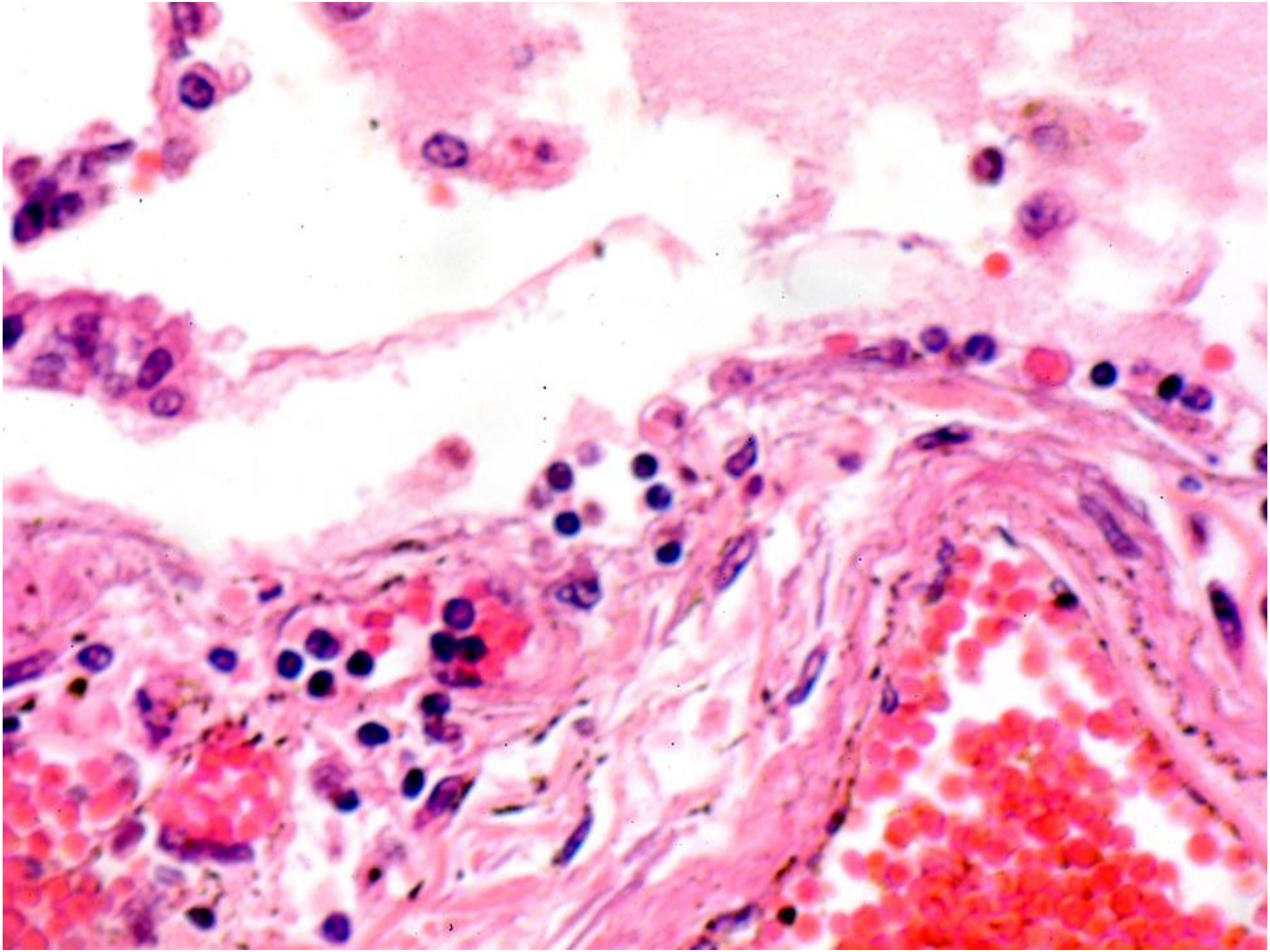
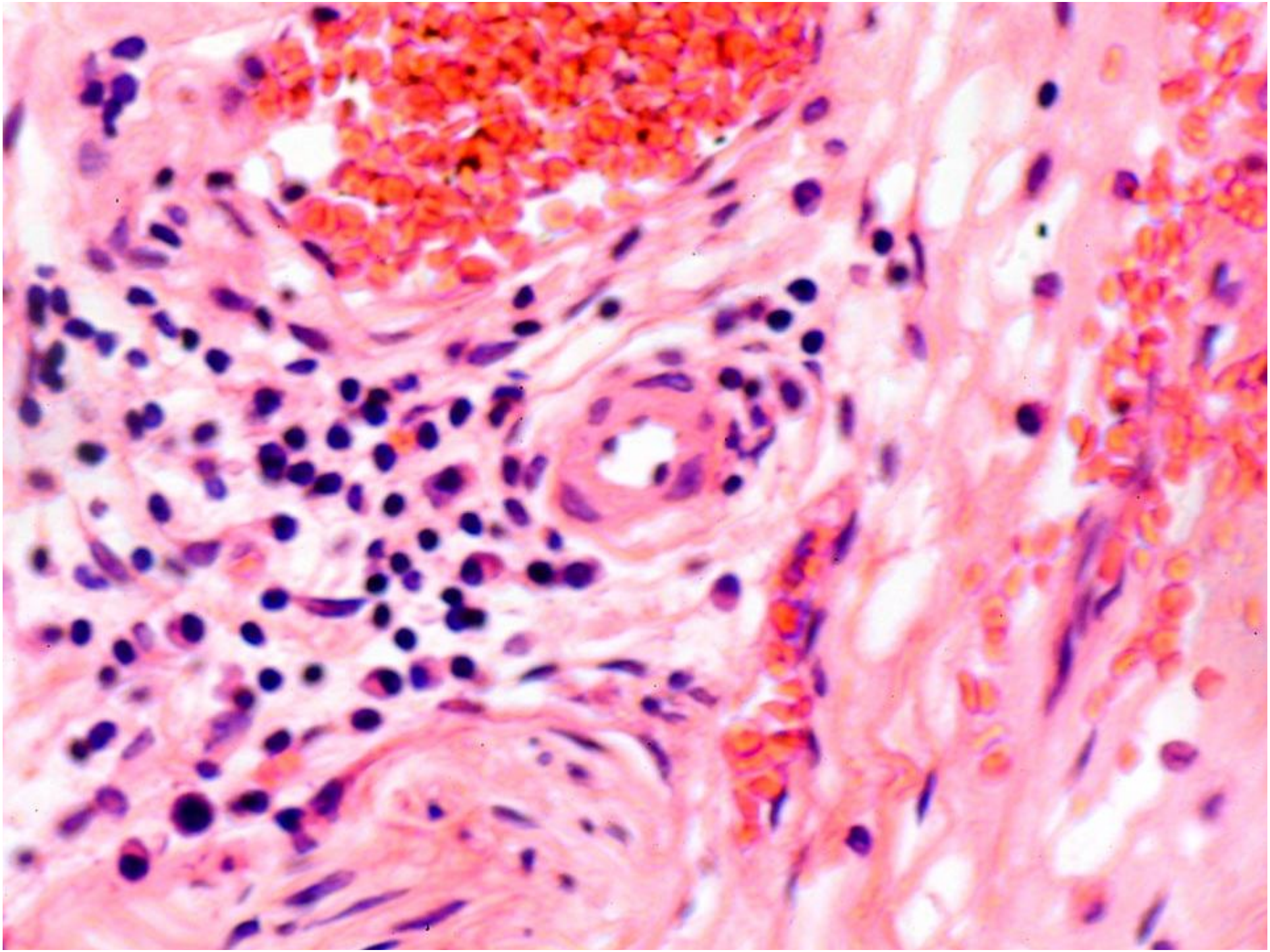
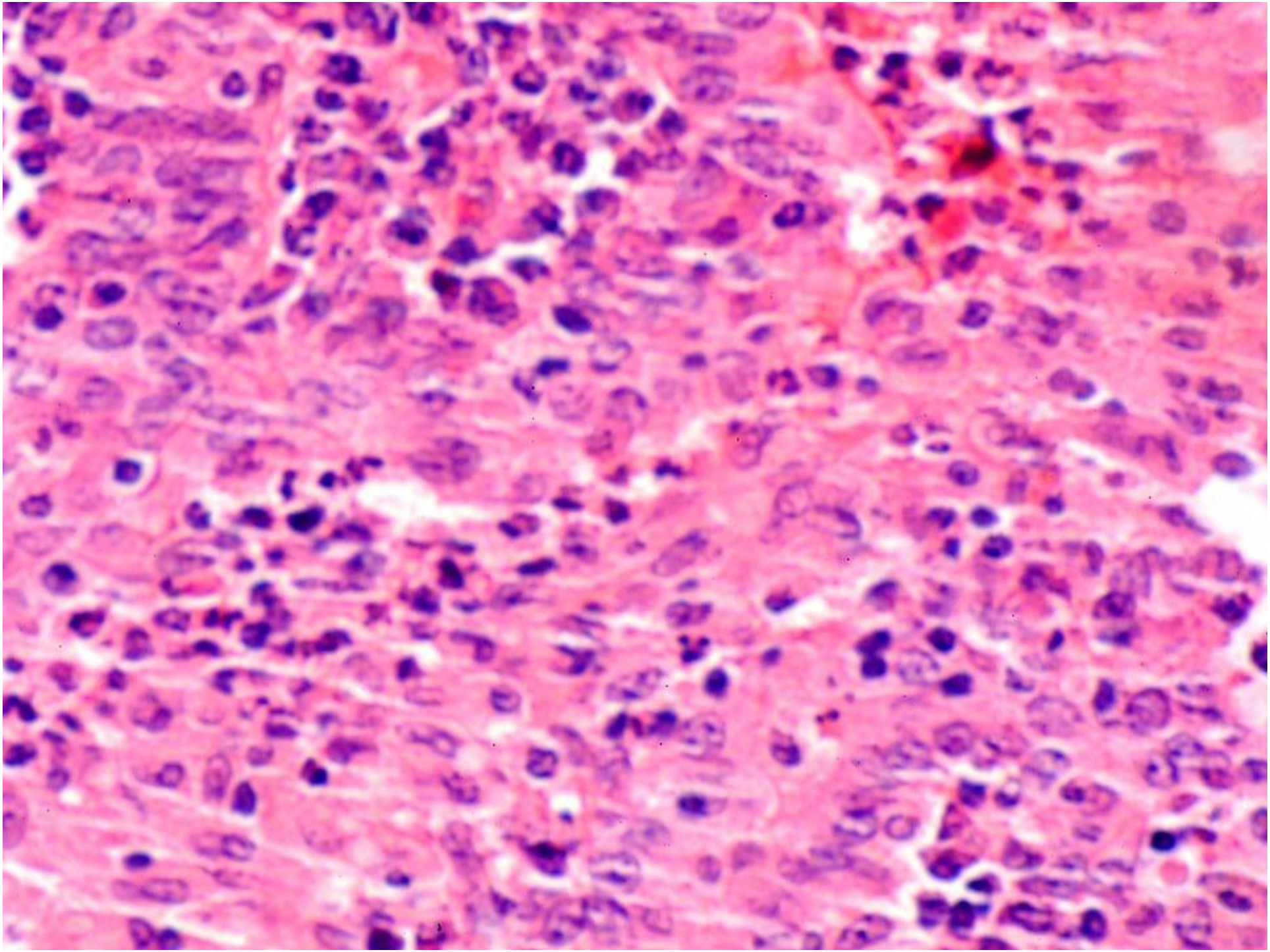

Innate defenses → Internal defenses
④ Positive chemotaxis
Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents
① Neutrophils enter blood from bone marrow
② Margination
③ Diapedesis
Capillary wall
Endothelium
Basement membrane

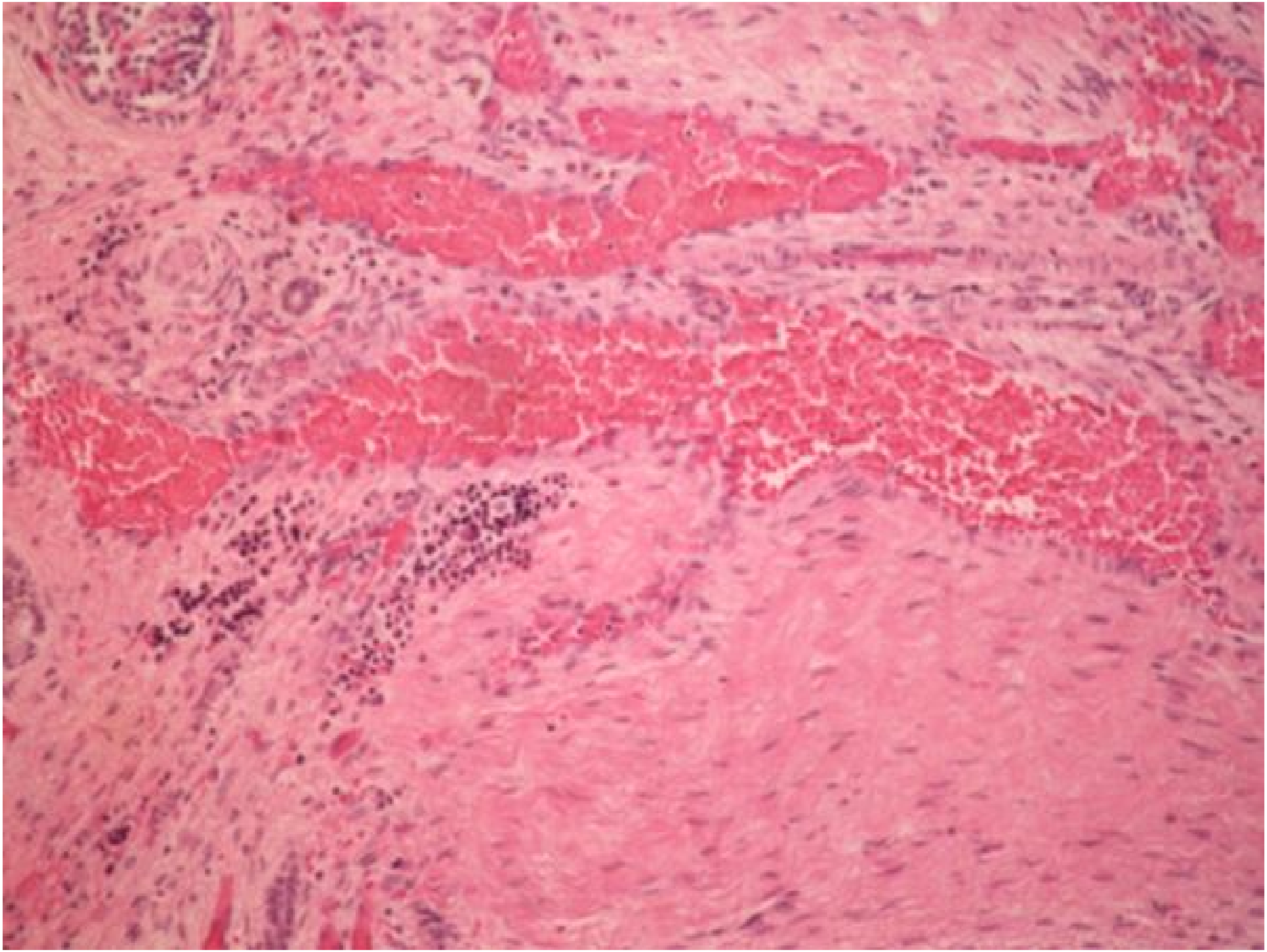
Figure 21.4











Innate defenses → Internal defenses

Tissue injury

Release of chemical mediators (histamine, complement, kinins, prostaglandins, etc.)

Release of leukocytosis-inducing factor

Leukocytosis (increased numbers of white blood cells in bloodstream)

Vasodilation of arterioles

Increased capillary permeability

Attract neutrophils, monocytes, and lymphocytes to area (chemotaxis)

Pain

Migration to injured area

Local hyperemia (increased blood flow to area)

Capillaries leak fluid (exudate formation)

Blood flow slows

Margination (leukocytes cling to capillary walls)

Heat

Redness

Diapedesis (leukocytes pass through capillary walls)

Increased oxygen and nutrients

Leaked protein-rich fluid in tissue spaces

Leaked clotting proteins

Phagocytosis of pathogens and dead tissue cells (by neutrophils, short-term; by macrophages, long-term)

Pain

Swelling

Walling-off process (blood clots wall off area to prevent injury to surrounding area)

Pus may form

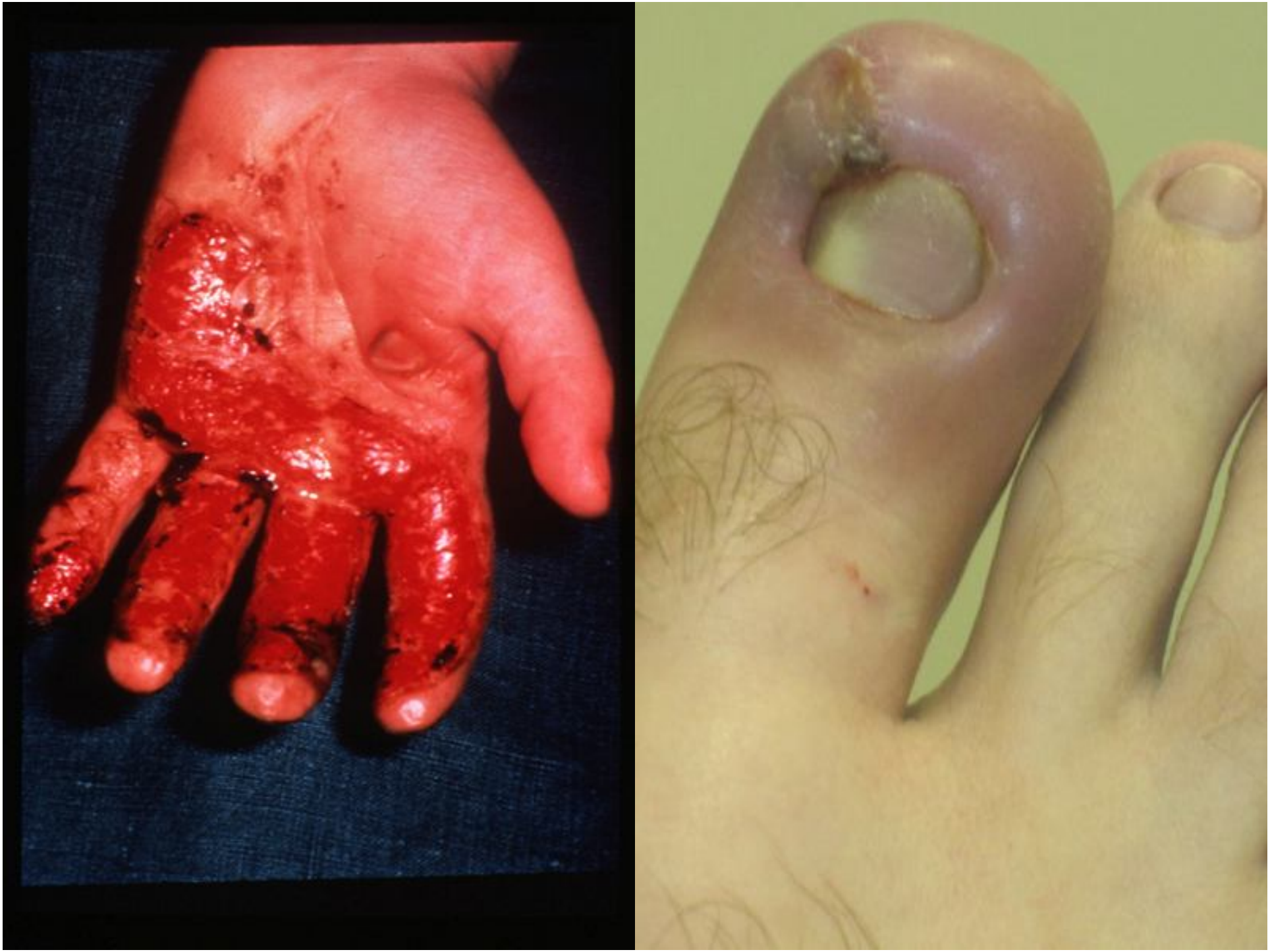
Increased temperature increases metabolic rate of cells

Possible temporary limitation of joint movement

Temporary fibrin patch forms scaffolding for repair

Area cleared of debris

Healing



•**Transudate** is extravascular fluid with

-**low protein** content
-a low specific gravity (< 1.012).
-low nucleated cell counts (less than 500 to 1000 /microlit) and the primary cell types are mononuclear cells: macrophages, lymphocytes and mesothelia cells.

For instance, an ultrafiltrate of blood plasma is transudate.
It results from increased fluid pressures or diminished colloid oncotic forces in the plasma .
In females, transudation is a method of lubrication during sexual arousal.

Exudate [pus like]

– extravascular fluid due to vessel alteration during inflammation (increased permeability, vascular constriction then dilation).

-high protein content,
-cell debris present
-high specific gravity (>1.020).

This is in contrast to transudate where the extracellular fluid is an ultrafiltrate of blood plasma and thus larger molecules such as proteins and cell debris are absent

Exudate **Types**

Purulent or **suppurative** exudate consists of plasma with both active and dead neutrophils, fibrinogen, and necrotic parenchymal cells. This kind of exudate is consistent with more severe infections, and is commonly referred to as pus.

Fibrinous exudate is composed mainly of fibrinogen and fibrin. It is characteristic of **rheumatic carditis**, but is seen in all severe injuries such as strep throat and bacterial pneumonia. Fibrinous inflammation is often difficult to resolve due to the fact that blood vessels grow into the exudate and fill the space that was occupied by fibrin. Often, large amounts of antibiotics are necessary for resolution.

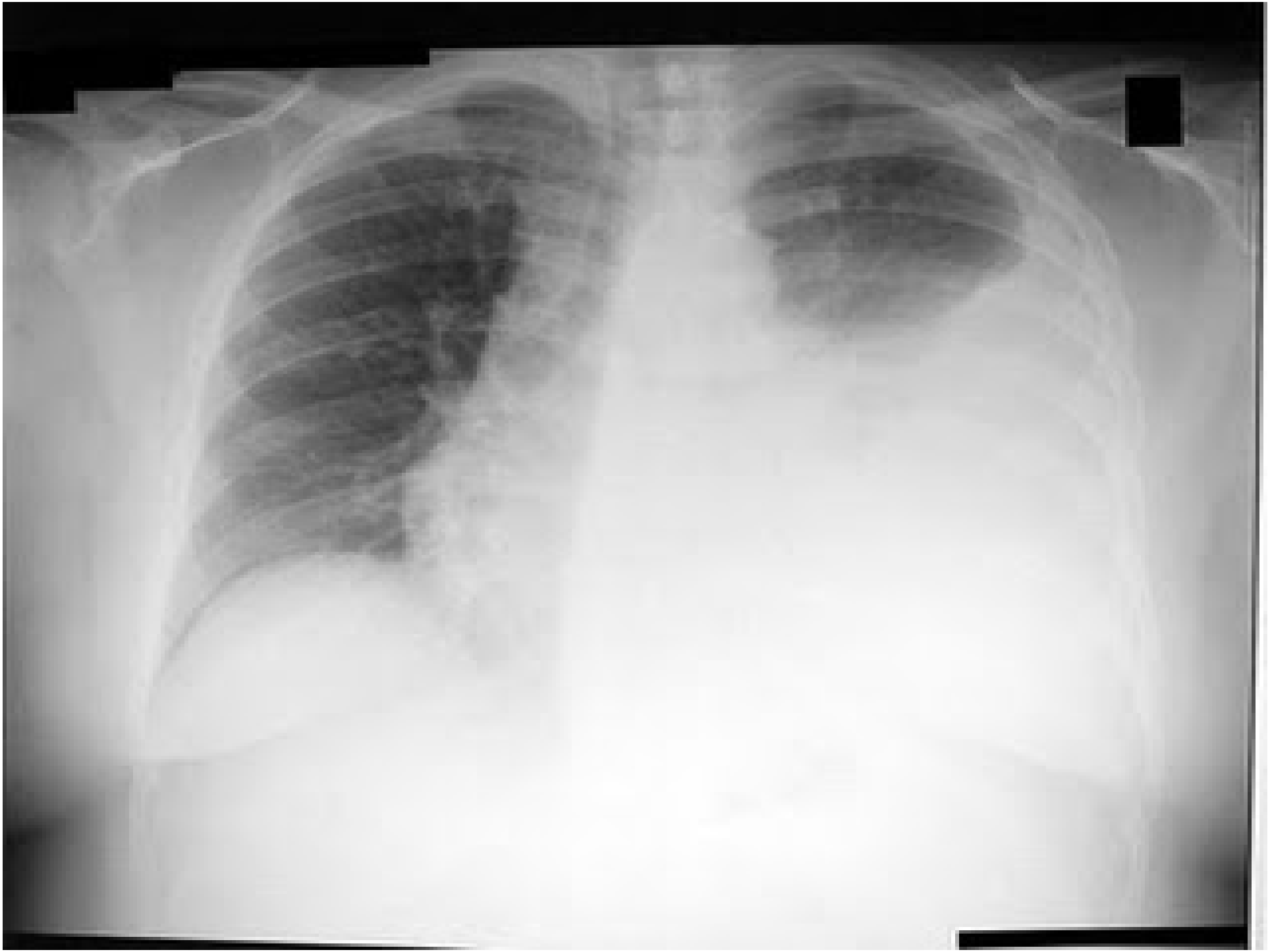
Catarrhal exudate is seen in the nose and throat and is characterized by a high content of mucus.

Serous exudate (sometimes classified as serous transudate) is usually seen in mild inflammation, with little protein content. Its consistency resembles that of serum, and can usually be seen in certain disease states like tuberculosis. (See below for difference between transudate and exudate)

Malignant (or cancerous) pleural effusion is effusion where cancer cells are present. It is usually classified as exudate.

Transudate vs. exudate

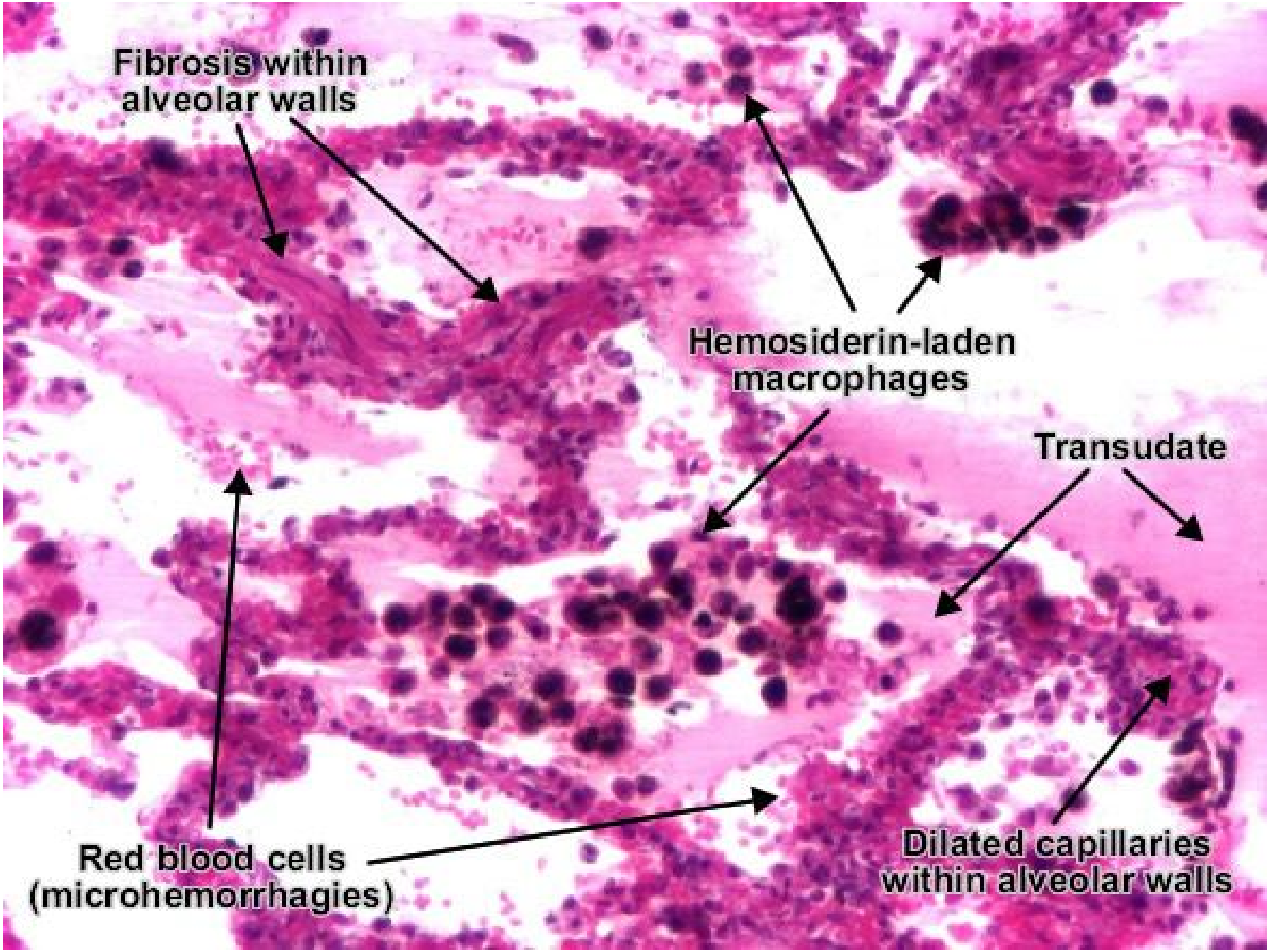
	Transudate	Exudate
Main causes	Increased hydrostatic pressure, Decreased colloid osmotic pressure	Inflammation
Appearance	Clear	Cloudy[
Specific gravity	< 1.012	> 1.020
Protein content	< 2 g/dL	> 2.9 g/dL
$\frac{\text{fluid protein}}{\text{serum protein}}$	< 0.5	> 0.5
Difference of albumin content with blood albumin	> 1.2 g/dL	< 1.2 g/dL
$\frac{\text{fluid LDH}}{\text{upper limit for serum}}$	< 0.6 or < ⅔	> 0.6 or > ⅔
$\frac{\text{fluid glucose}}{\text{serum glucose}}$	< 0.8	> 0.8
Cholesterol content	< 45 mg/dL	> 45 mg/d

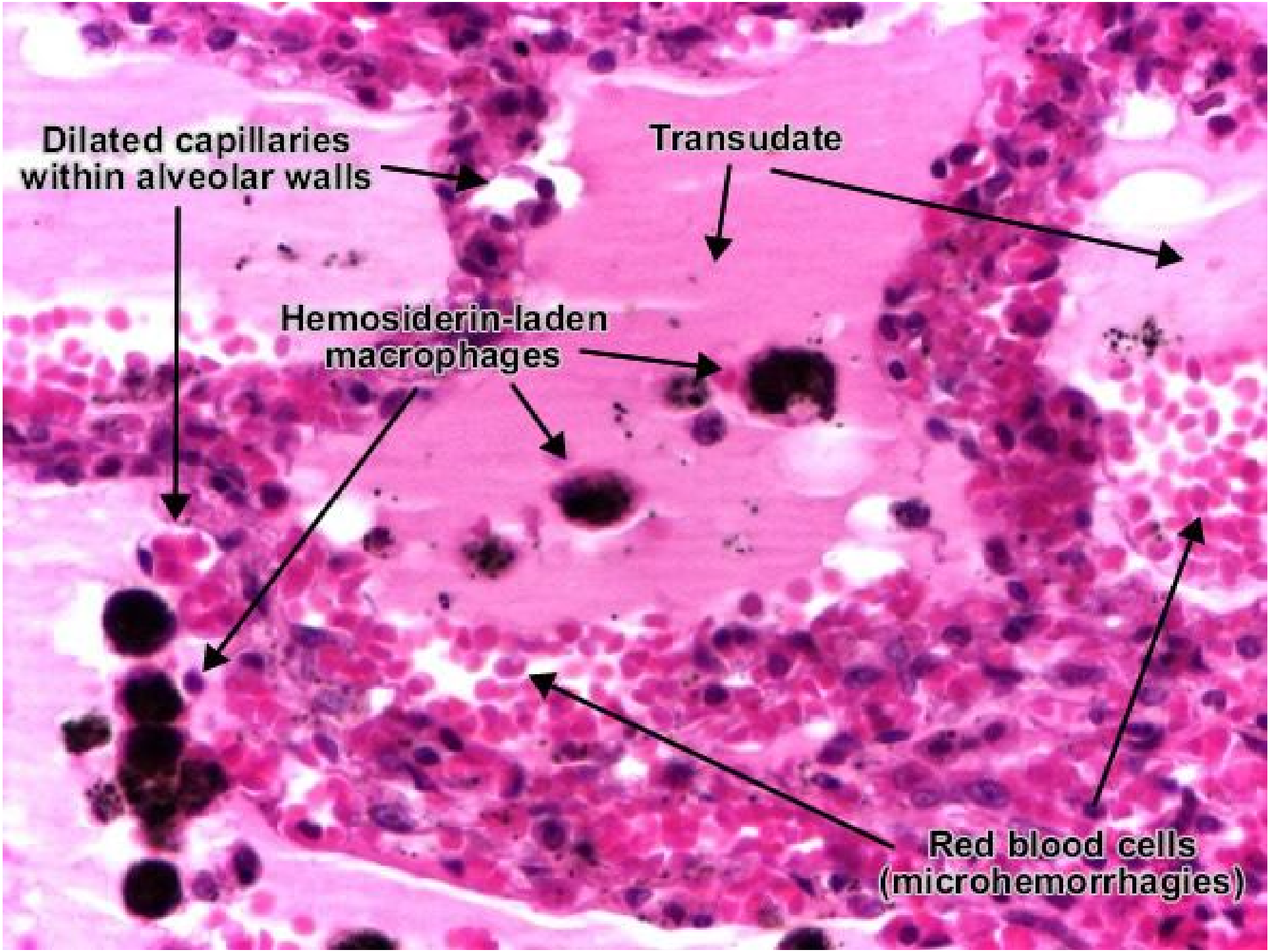


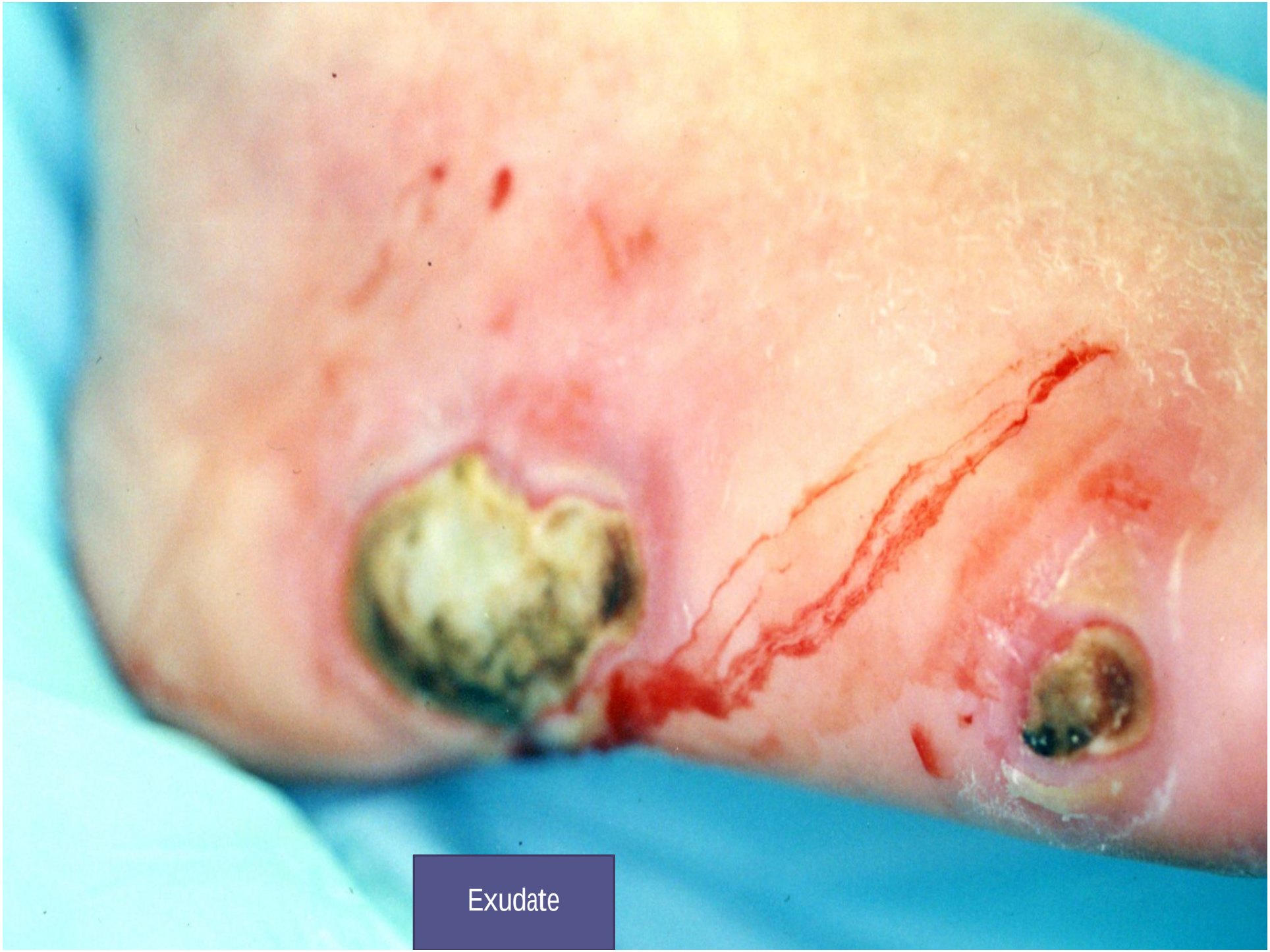
4.56 Blood-stained pleural aspirate. This patient had pleural secondaries from carcinoma of the breast.

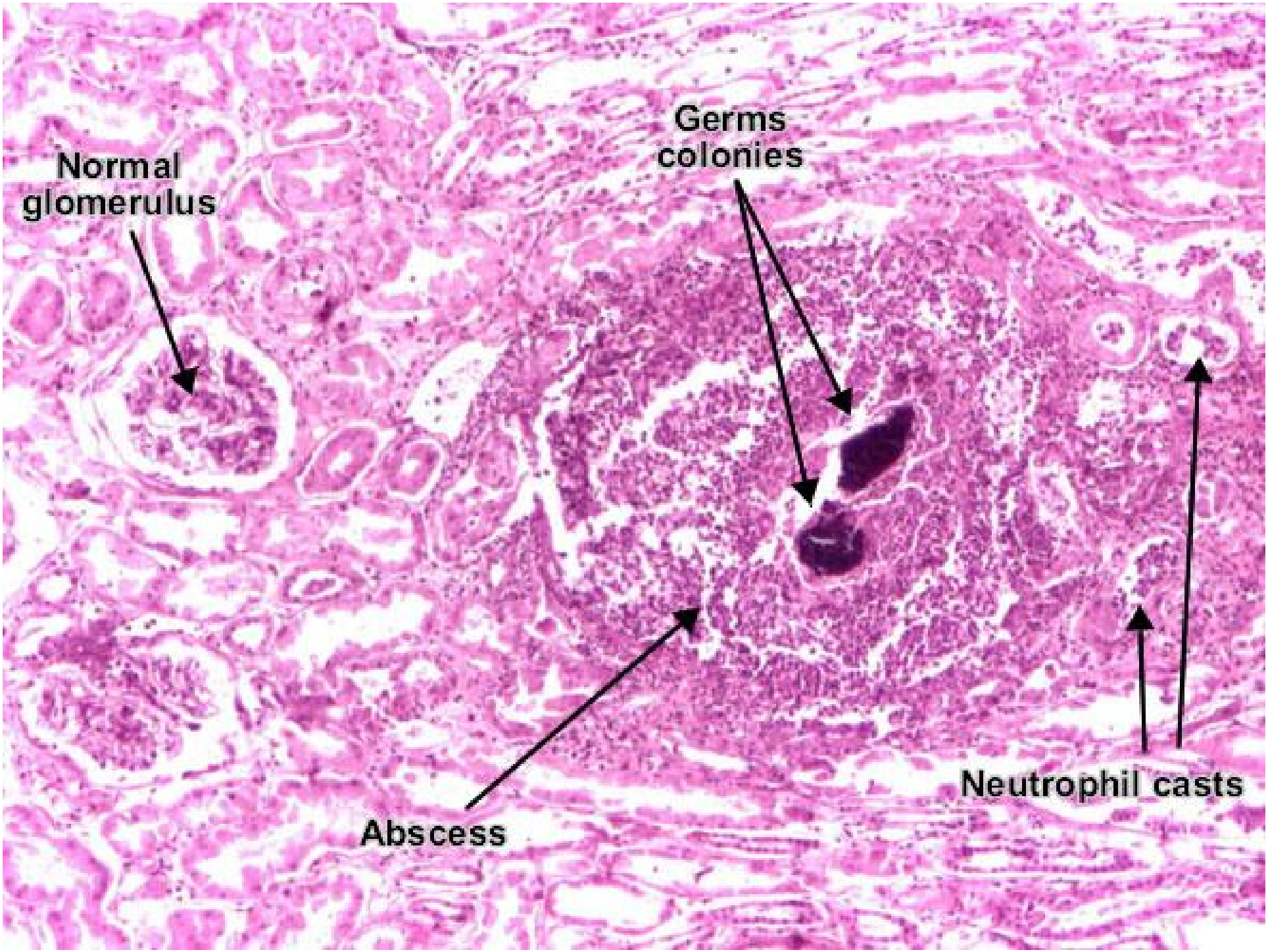
4.57 Chylous pleural effusion. This patient had bronchial carcinoma, which had invaded and obstructed the thoracic duct.

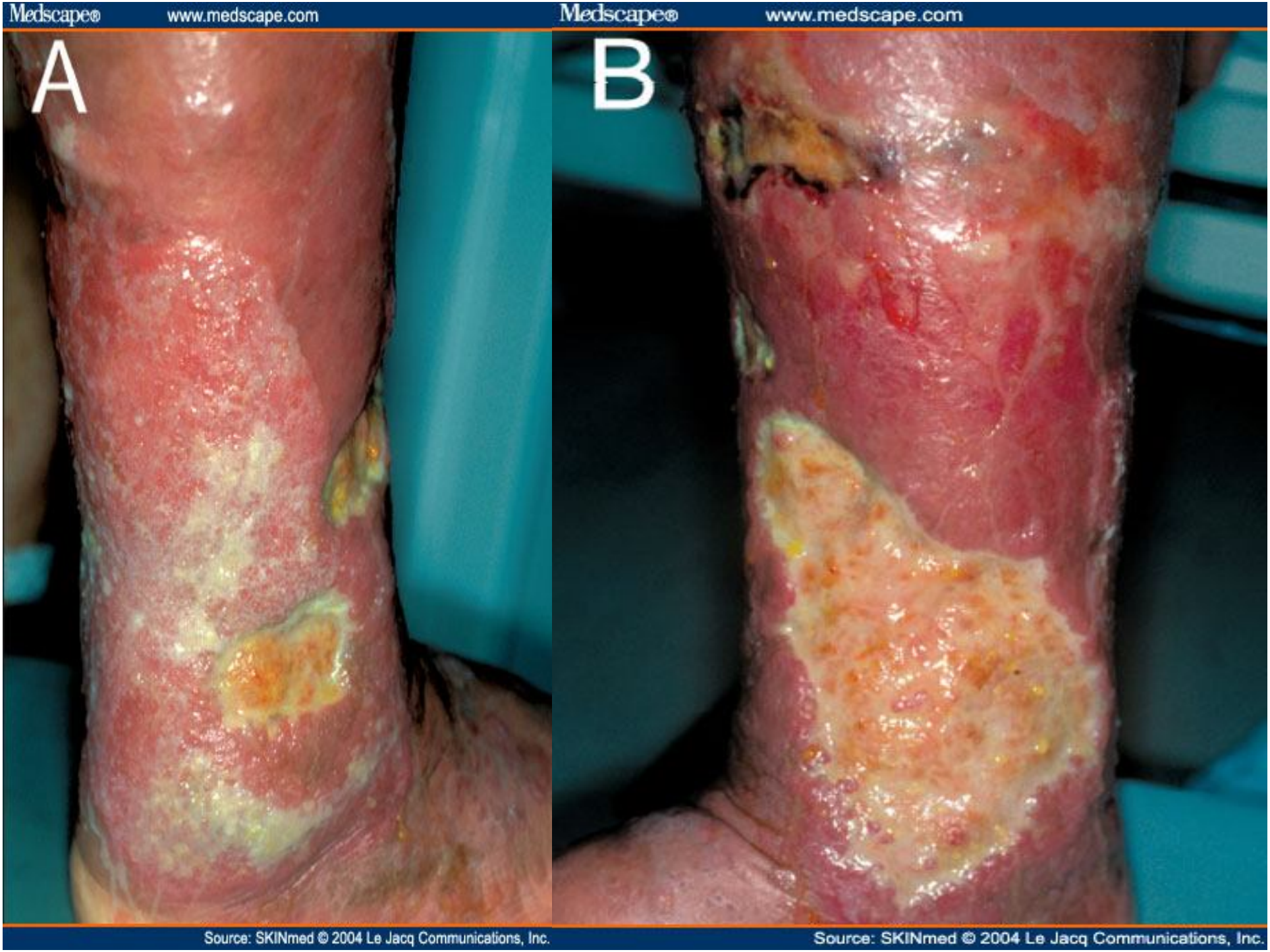
4.58 Pleural transudate. This pale effusion is typically found in patients with heart failure or other causes of generalized oedema.


Fibrosis within alveolar walls
Hemosiderin-laden macrophages
Transudate
Red blood cells (microhemorrhagies)
Dilated capillaries within alveolar walls


Dilated capillaries
within alveolar walls
Transudate
Hemosiderin-laden
macrophages
Red blood cells
(microhemorrhagies)


Exudate


Normal glomerulus
Germs colonies
Abscess
Neutrophil casts


Medscape® www.medscape.com
A
Source: SKINmed © 2004 Le Jacq Communications, Inc.
Medscape® www.medscape.com
B
Source: SKINmed © 2004 Le Jacq Communications, Inc.

Information only

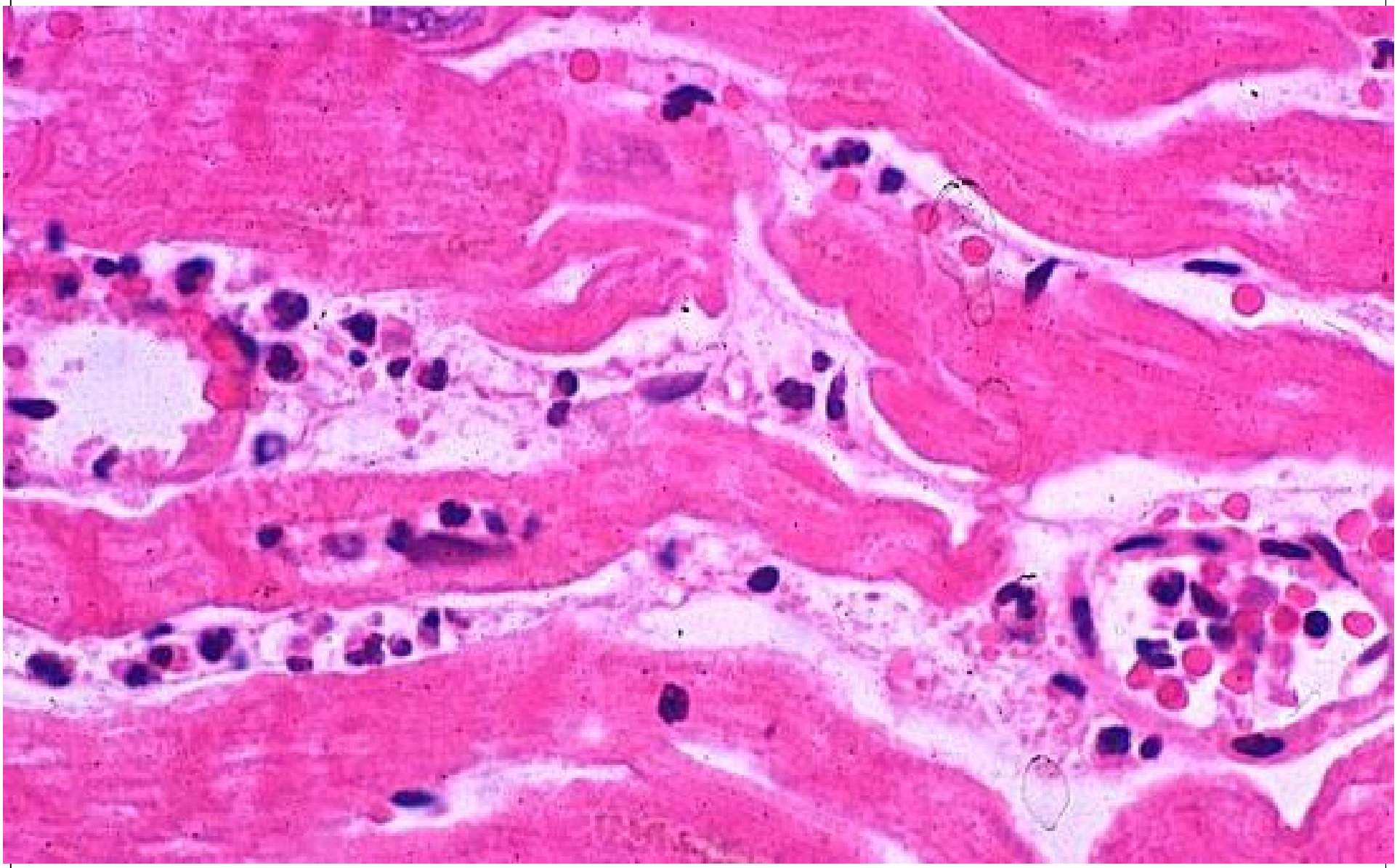
Rivalta test is used in order to differentiate a transudate from an exudate[1]. A test tube is filled with distilled water and acetic acid is added. To this mixture one drop of the effusion to be tested is added. If the drop dissipates, the test is negative, indicating a transudate. If the drop precipitate, the test is positive, indicating an exudate[2].

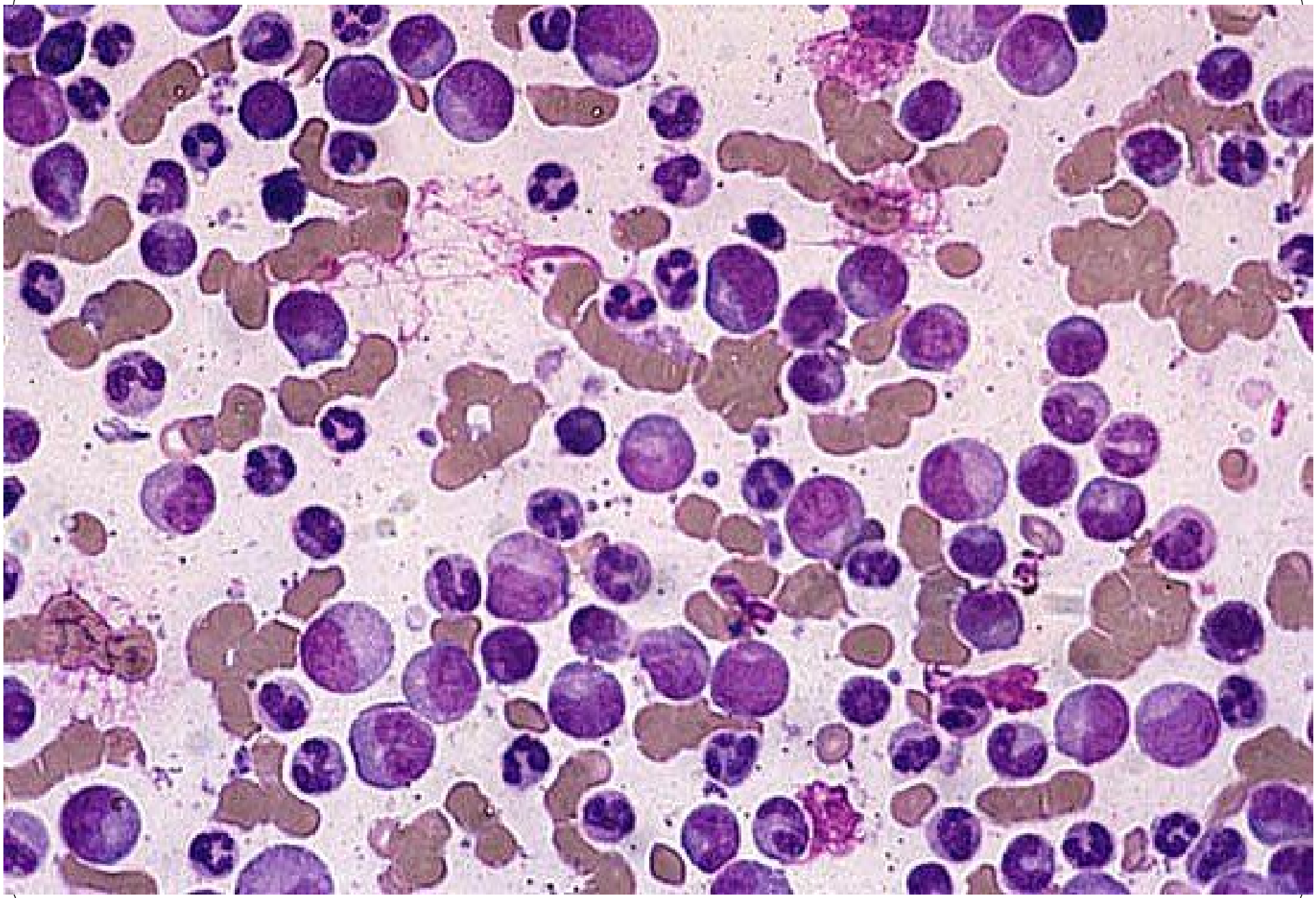
Using a pH 4.0 acetic acid solution, 8 types of proteins were identified in Rivalta reaction-positive turbid precipitates: **C-reactive protein (CRP), Alpha 1-antitrypsin (alpha1-AT), Orosomucoid ((Alpha-1-acid glycoprotein or AGP)), haptoglobin (Hp), transferrin (Tf), ceruloplasmin (Cp), fibrinogen (Fg), and hemopexin (Hpx). Since those are Acute-phase proteins, a positive Rivalta's test may be suggestive of inflammation**

^ Berti-Bock G, Vial F, Premuda L, Rullière R (November 1979). "[Exudates, transudates and the Rivalta reaction (1895). Current status and historical premises]" (in Italian). *Minerva Med.* **70** (52): 3573–80. PMID 392338.

^ "FELINE INFECTIOUS PERITONITIS (FIP) (A SUMMARY)". http://www.marvistavet.com/html/body_fip.html. Retrieved 2009-06-24.

^ Sakai N, Iijima S, Shiba K (November 2004). "Reinvestigation of clinical value of Rivalta reaction of puncture fluid". *Rinsho Byori* **52** (11): 877–82. PMID 15658465.





Antimicrobial Proteins

- Enhance the innate defenses by:
  - Attacking microorganisms directly
  - Hindering microorganisms' ability to reproduce
- The most important antimicrobial proteins are:
  - **Interferon**
  - **Complement proteins**

Interferon (IFN)

- **Genes that synthesize IFN are activated when a host cell is invaded by a virus**
- Interferon molecules leave the infected cell and enter neighboring cells
- Interferon stimulates genes for **PKR (an antiviral protein)**
- **PKR nonspecifically blocks viral reproduction in the neighboring cell**

Interferon Family

- Family of related proteins each with slightly different physiological effects
- **Lymphocytes secrete gamma (γ) interferon, but most other WBCs secrete alpha (α) interferon**
- Fibroblasts secrete beta (β) interferon
- Interferons also activate macrophages and mobilize NKs
- FDA-approved alpha IFN is used:
  - As an antiviral drug against hepatitis C virus
  - To treat genital warts caused by the herpes virus

C-reactive Protein (CRP)

- CRP is produced by the liver in response to inflammatory molecules
- CRP is a clinical marker used to assess:
  - The presence of an acute infection
  - An inflammatory condition and its response to treatment

Functions of C-reactive Protein

- Binds to PC receptor of pathogens and exposed self-antigens
- Plays a surveillance role in targeting damaged cells for disposal
- **Activates complement**

TABLE 21.4 Cells and Molecules of the Adaptive Immune Response *(continued)*

ELEMENT	FUNCTION IN IMMUNE RESPONSE
MOLECULES	
Antibody (immunoglobulin)	Protein produced by B cell or by plasma cell. Antibodies produced by plasma cells are released into body fluids (blood, lymph, saliva, mucus, etc.), where they attach to antigens, causing complement fixation, neutralization, precipitation, or agglutination, which "mark" the antigens for destruction by complement or phagocytes
Perforin, granzymes	Released by T_C cells. Perforin creates large pores in the target cell's membrane, allowing entry of apoptosis-inducing granzymes
Complement	Group of bloodborne proteins activated after binding to antibody-covered antigens or certain molecules on the surface of microorganisms; enhances inflammatory response and causes lysis of some microorganisms
Antigen	Substance capable of provoking an immune response. Typically a large complex molecule (e.g., protein or modified protein) not normally present in the body
CYTOKINES	
Interferons (IFNs)	
▪ Alpha (α) and beta (β)	Secreted by leukocytes, fibroblasts, and other cells; antiviral effects; activate macrophages and NK cells
▪ Gamma (γ)	Secreted by lymphocytes; activates macrophages; stimulates synthesis and expression of more class I and II MHC proteins; promotes differentiation of T_H cells into T_H1
Interleukins (ILs)	
▪ IL-1	Secreted by activated macrophages; promotes inflammation and T cell activation; causes fever (a pyrogen that resets the thermostat of the hypothalamus)
▪ IL-2	Secreted by T cells; stimulates proliferation of T cells; activates NK cells
▪ IL-3	Stimulates production of leukocytes and mast cells

TABLE 21.4 Cells and Molecules of the Adaptive Immune Response *(continued)*

ELEMENT	FUNCTION IN IMMUNE RESPONSE
CYTOKINES	
Interleukins (ILs)	
▪ IL-4	Secreted by T_H cells; promotes differentiation to T_H2; promotes B cell activation; switches antibody production to IgE
▪ IL-5	Secreted by some T_H cells and mast cells; attracts and activates eosinophils; causes plasma cells to secrete IgA antibodies
▪ IL-6	Induces lymphocyte activation and increases antibody production; stimulates liver to secret C-reactive protein, which binds certain bacteria, resulting in complement activation and opsonization
▪ IL-7	Induces lymphocyte proliferation and maturation
▪ IL-8 (also called CXCL8)	Stimulates chemotaxis of neutrophils, basophils, and T cells; promotes angiogenesis
▪ IL-10	Inhibits macrophages and dendritic cells; turns down cellular and innate immune response
▪ IL-12	Secreted by dendritic cells and macrophages; stimulates T_C and NK cell activity; promotes T_H1 differentiation
▪ IL-13	Secreted by T_H cells; switches antibody production to IgE
Migration inhibitory factor (MIF)	Inhibits macrophage migration and keeps them in the area of antigen deposition; a generic term for a number of cytokines
Suppressor factors	A generic term for a number of cytokines that suppress the immune system, for example TGF-β and IL-10
Transforming growth factor beta (TGF-β)	A suppressor factor similar to IL-10
Tumor necrosis factors (TNFs)	Produced by lymphocytes and in large amounts by macrophages. Enhance nonspecific killing; slow tumor growth by selectively damaging tumor blood vessels; enhance granulocyte chemotaxis; help activate T cells, phagocytes, and eosinophils; promote cell death by apoptosis

COMPLEMENT

Complement

Definition : series of heat-labile serum proteins

Site : serum and all tissue fluids except urine and CSF

Synthesis : in liver – appear in fetal circulation during 1st 13 W

Function : Responsible for certain aspects of
immune response and inflammatory response

Activation : antigen-antibody complex or endotoxin, capsule
series of proteins activated sequentially

Inactivation: inhibitors in plasma (short lived)

Biological effects: either beneficial or harmful to host

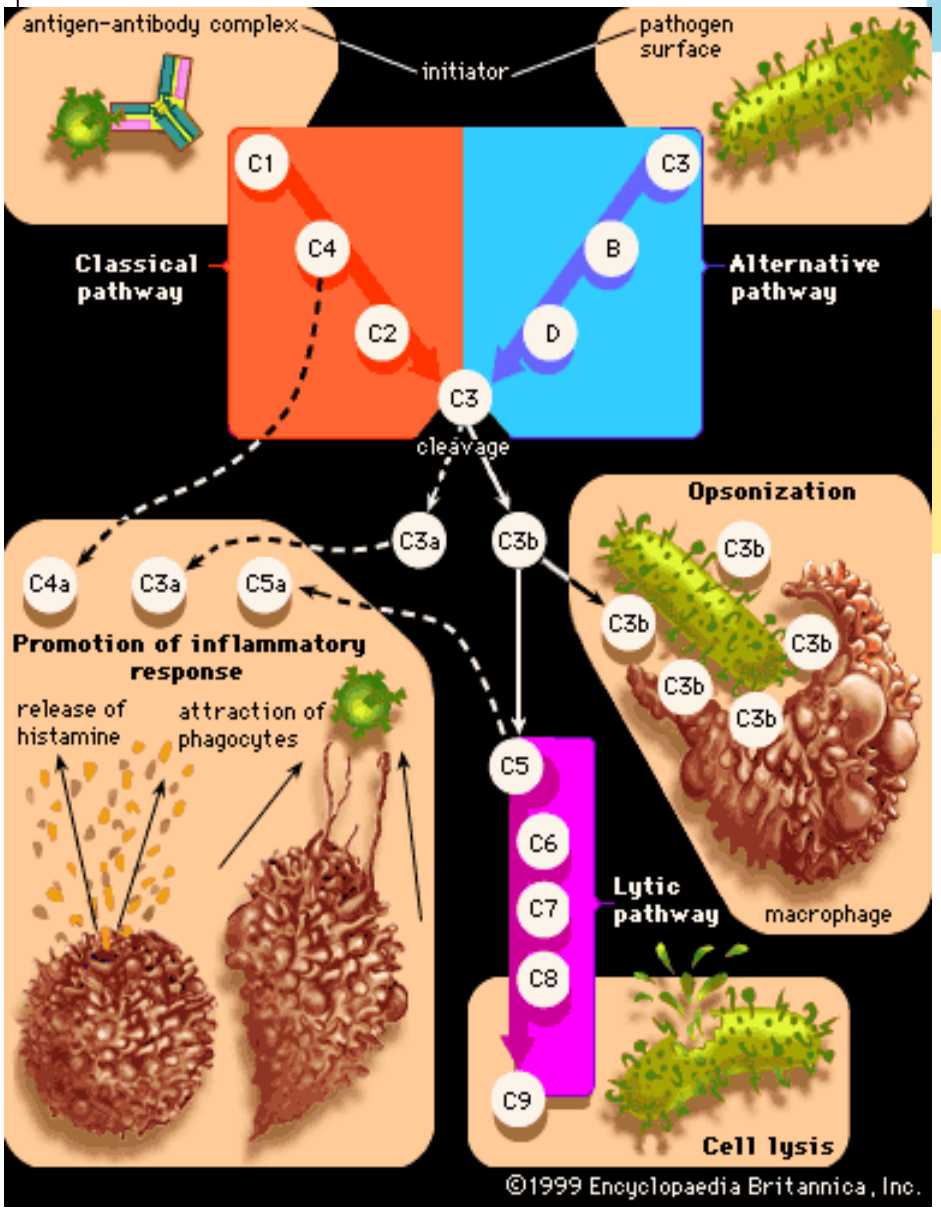
Complement

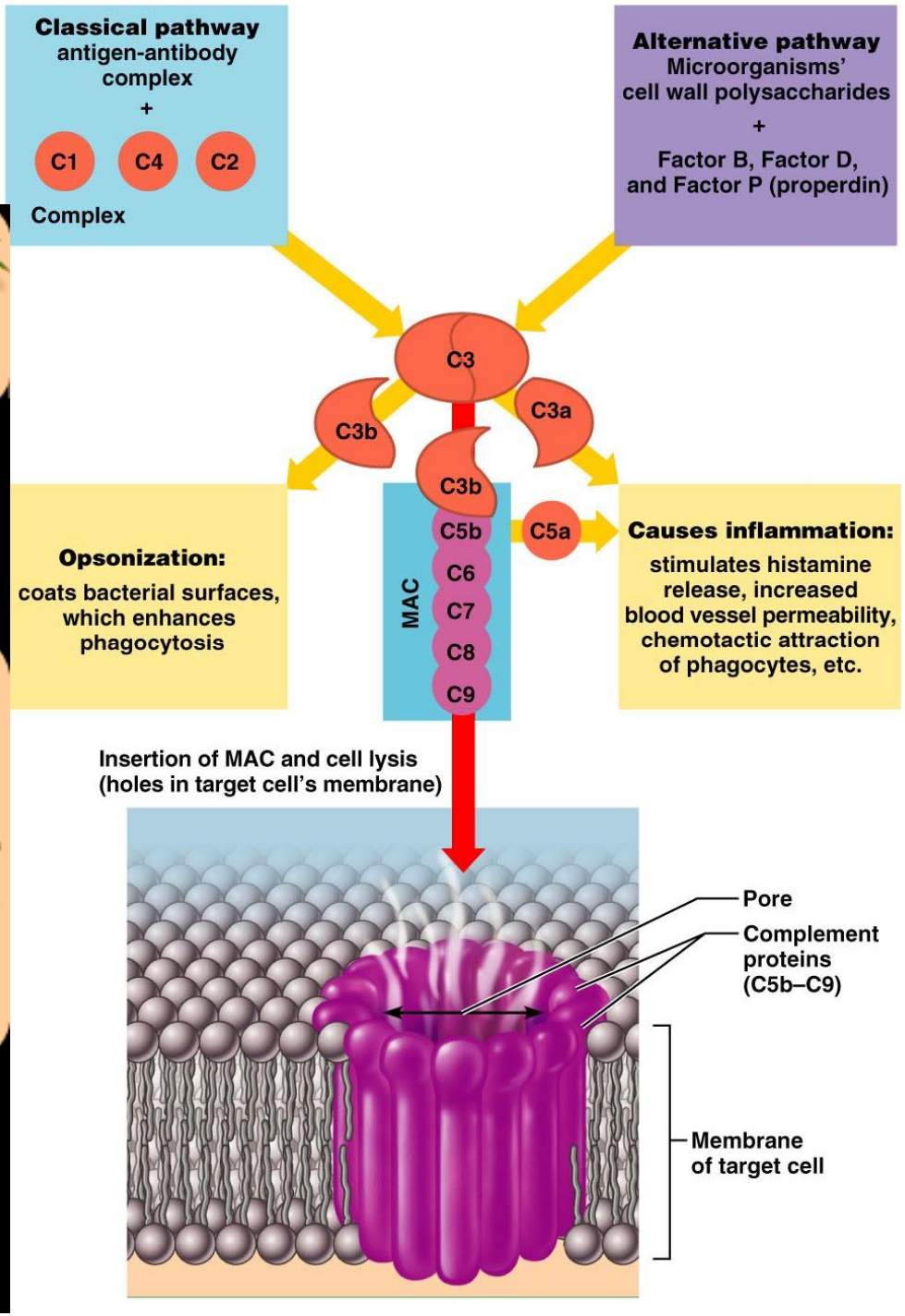
- 20 or so proteins that circulate in the blood in an inactive form
- **Proteins include C1 through C9, factors B, D, and P, and regulatory proteins**
- **Provides a major mechanism for destroying foreign substances in the body**

Complement

- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses

Complement Pathways





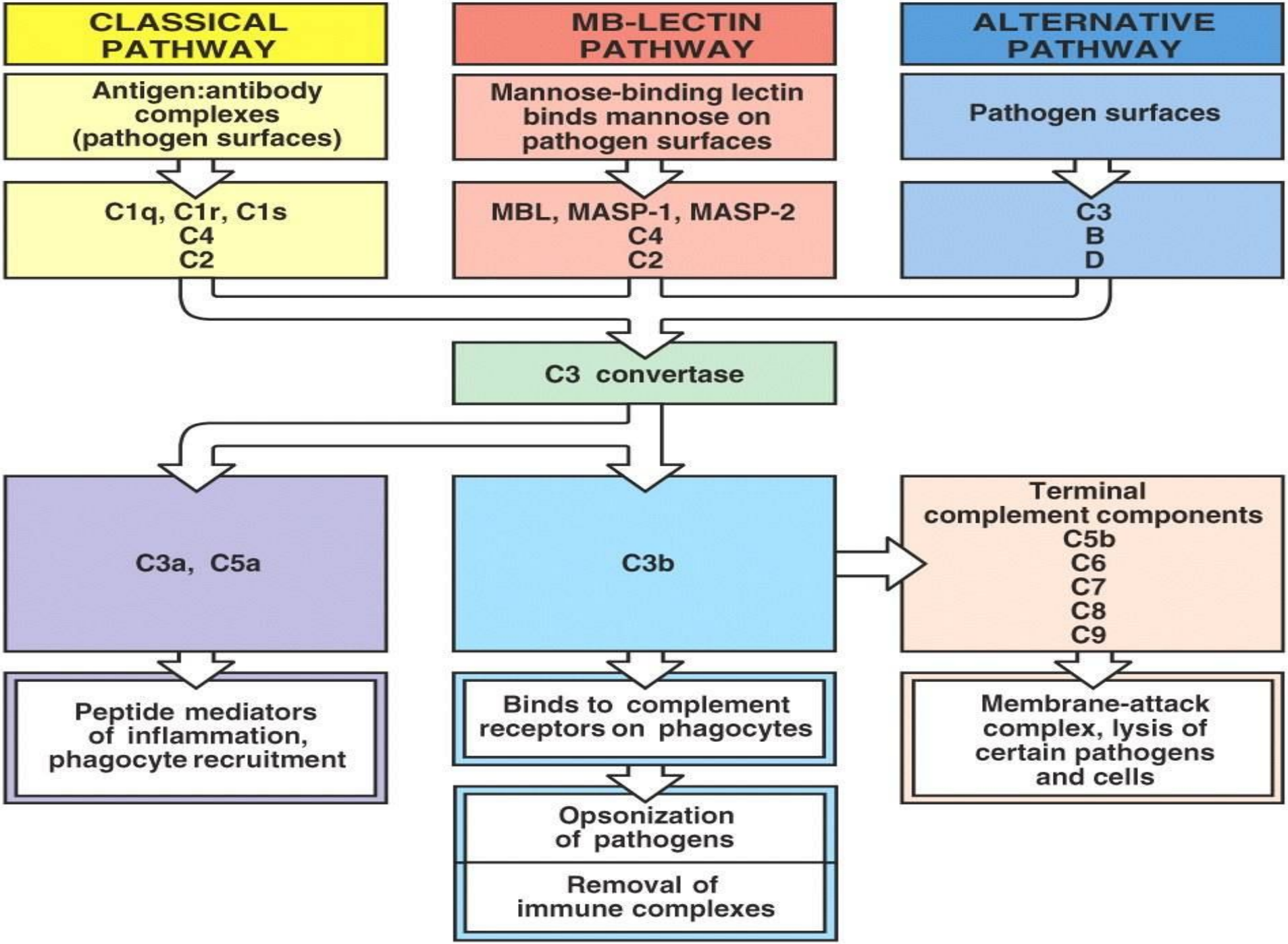


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

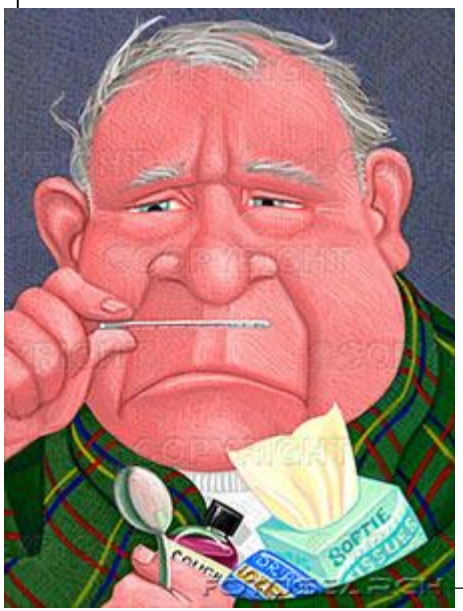
Part v : Fever

Fever = pyrexia

- A systematic, non specific defensive response caused by
  - **infection from bacteria and virus,**
  - **indicated by abnormal high body temperature.**

Beneficial effects of fever:

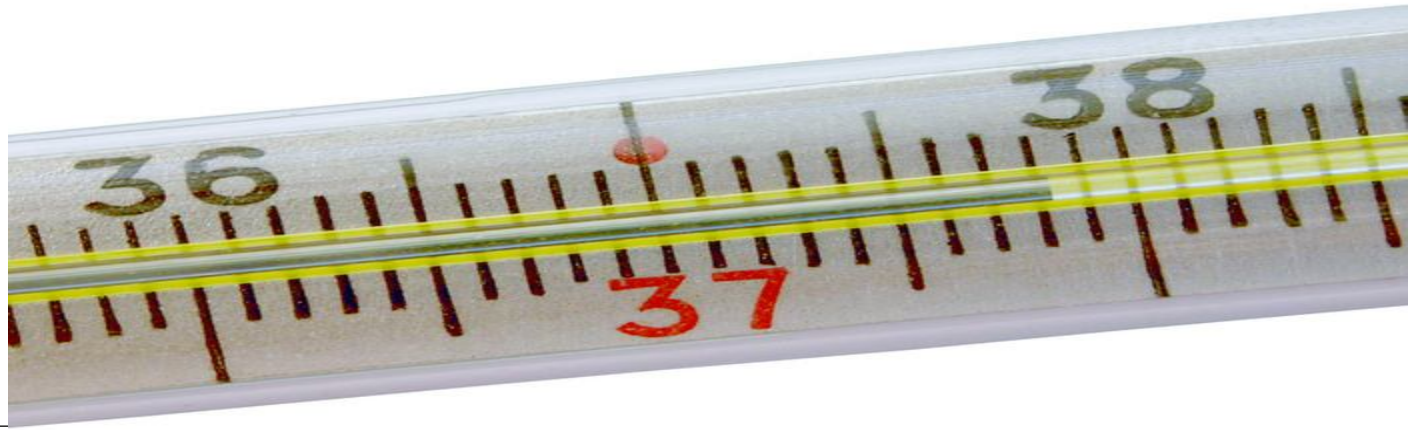
- **Helps set up specific defense (production of T cells)**
- **Speed up metabolism for tissue repair**
- **Increases the antiviral effect of interferons**



- **IFNs are a class of anti-vial proteins that disrupt viral multiplication**
- **Not very effective (short-lived and no effect for infected cells)**
- **Nonspecific to viral types**

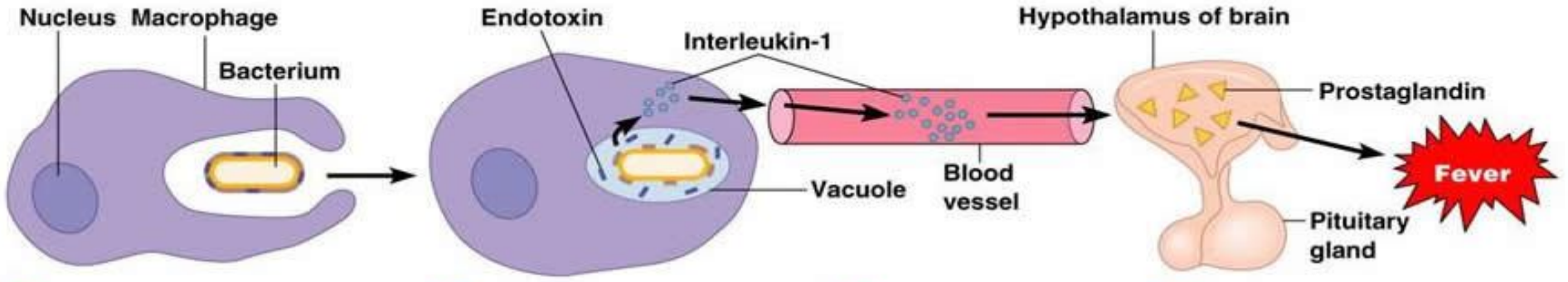
Fever
pyrexia

- The body's thermostat is reset upwards in response to **pyrogens**, chemicals **secreted by leukocytes and macrophages exposed to bacteria** and other foreign substances
- Fever can be classified as low (oral reading of 99° to 100.4° F [37.2° to 38° C]), moderate (100.5° to 104° F [38.1° to 40° C]), or high (above 104° F). Fever over 106° F (41.1° C) causes unconsciousness and, if sustained, leads to **permanent brain damage**.



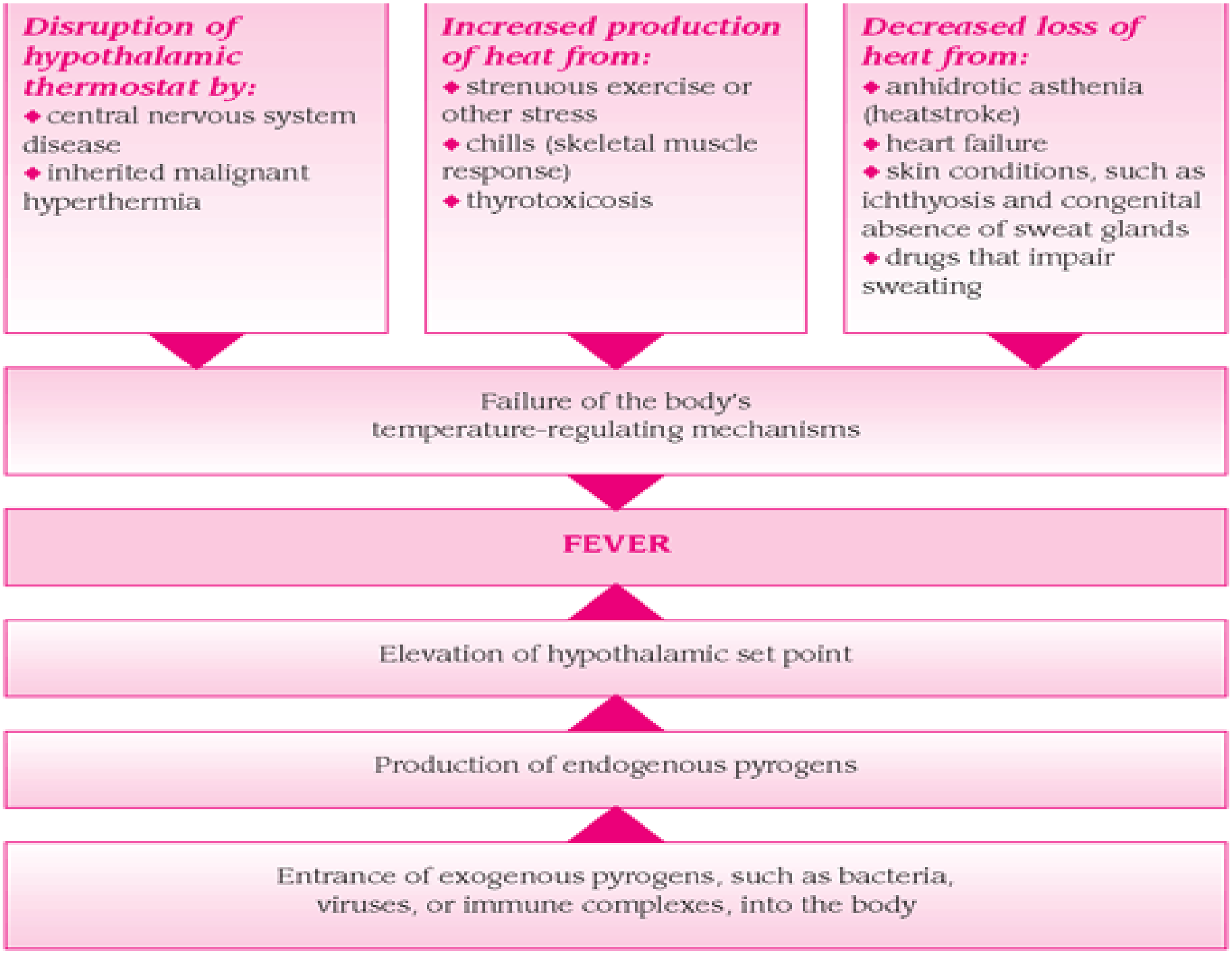
Fever: causes

- Infectious disease is the most common cause of fever in primary patient care.
- Other possible causes of fever are :
  - inflammatory intestinal,
  - joint and connective tissue diseases,
  - allergic reactions,
  - malignant tumours
  - hematological diseases.



Fever

- High fevers are dangerous because they can **denature enzymes**
- Moderate fever can be beneficial, as it causes:
  - **The liver and spleen to sequester iron and zinc (needed by microorganisms)**
  - **An increase in the metabolic rate, which speeds up tissue repair**

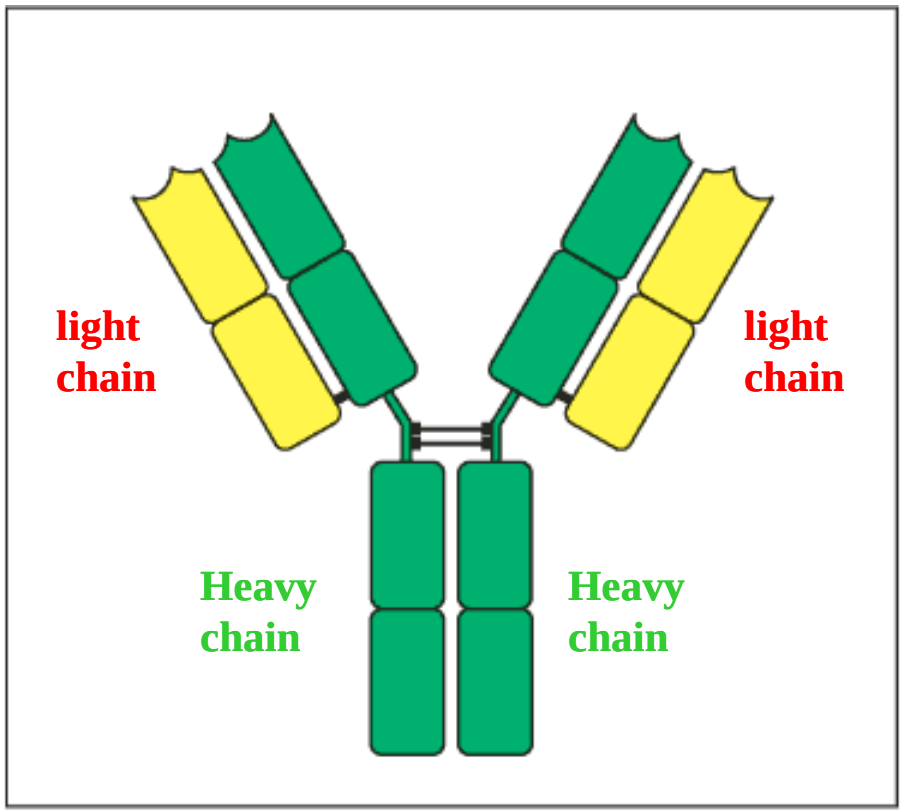

Disruption of hypothalamic thermostat by:
central nervous system disease
inherited malignant hyperthermia
Increased production of heat from:
strenuous exercise or other stress
chills (skeletal muscle response)
thyrotoxicosis
Decreased loss of heat from:
anhidrotic asthenia (heatstroke)
heart failure
skin conditions, such as ichthyosis and congenital absence of sweat glands
drugs that impair sweating
Failure of the body's temperature-regulating mechanisms
FEVER
Elevation of hypothalamic set point
Production of endogenous pyrogens
Entrance of exogenous pyrogens, such as bacteria, viruses, or immune complexes, into the body

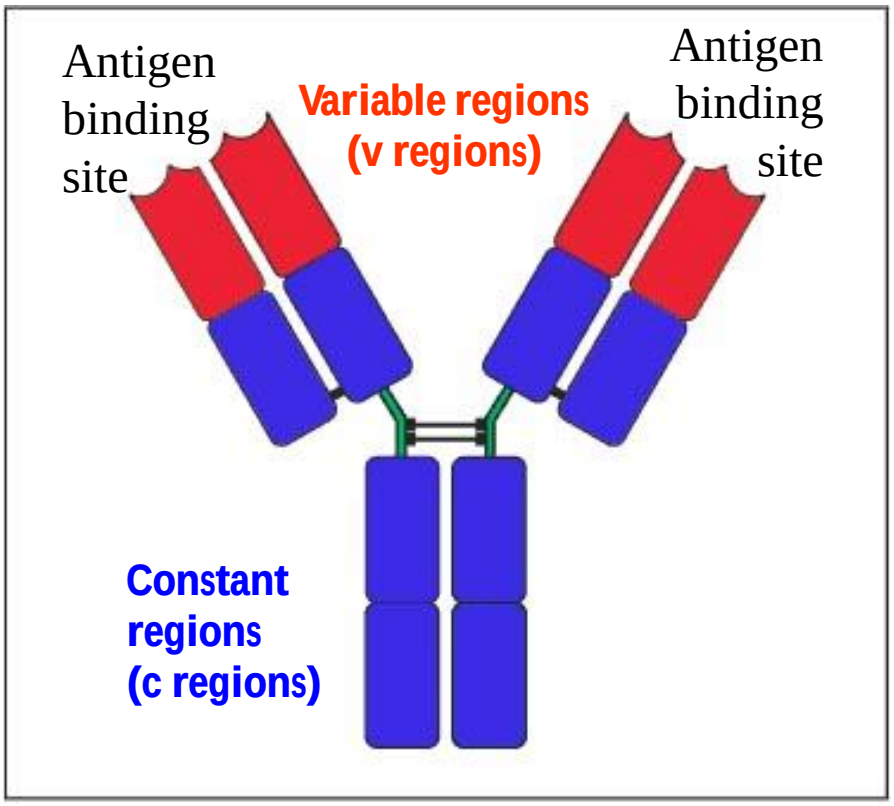
Part VI:Immunoglobulins

Antibodies

- Also called immunoglobulins
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with that antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE

Immunoglobulins (i.e., antibodies)

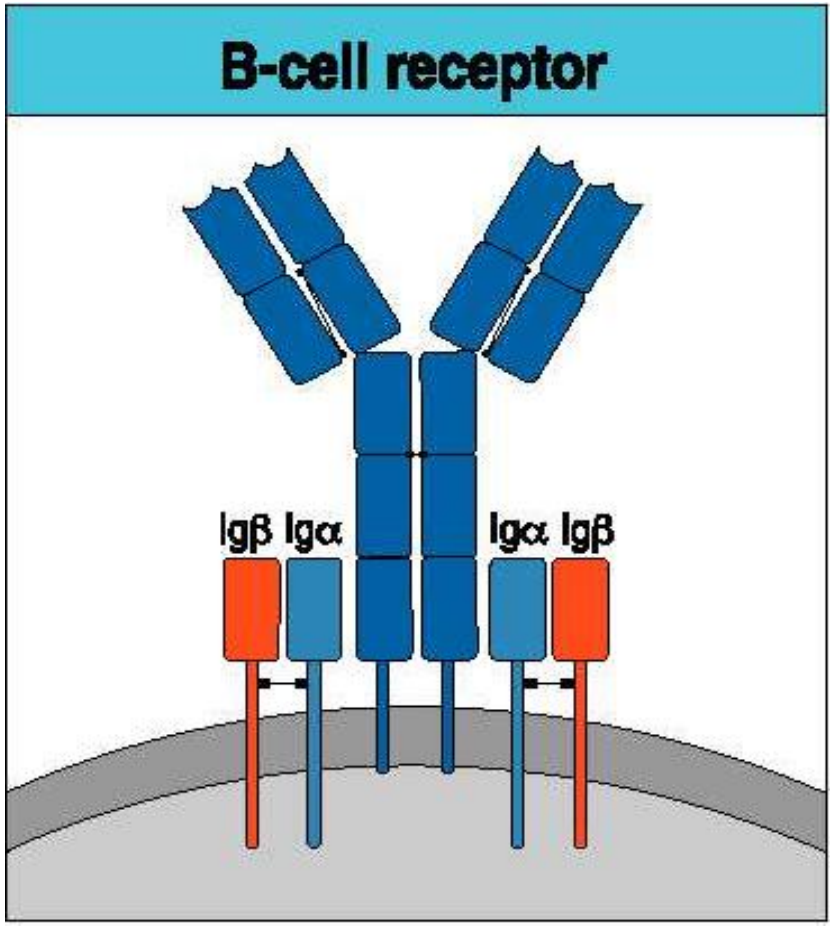




Antibodies with different specificities differ in the amino acid sequence of the variable regions of the heavy and light chains

The two heavy chains are identical and the two light chains are identical so the **<u>two antigen binding sites are identical</u>**

Two Forms of Immunoglobulin



Membrane-bound receptor

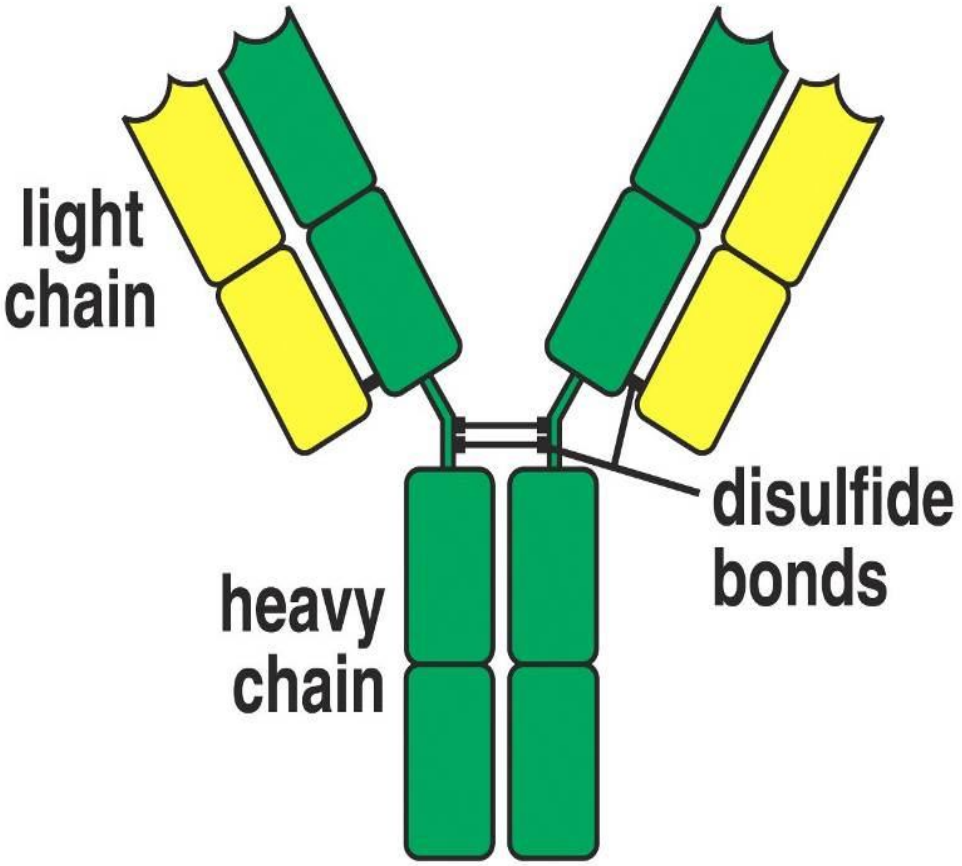


Figure 3-2 Immunobiology, 6/e. (© Garland Science 2005)

Soluble antibody

Immunoglobulin Classes

I. IgG

- Structure: Monomer
- Percentage serum antibodies: 80%
- Location: Blood, lymph, intestine
- Half-life in serum: 23 days
- Complement Fixation: Yes
- Placental Transfer: Yes
- Known Functions: Enhances phagocytosis, neutralizes toxins and viruses, protects fetus and newborn.

Immunoglobulin Classes

II. IgM

- Structure: Pentamer
- Percentage serum antibodies: 5-10%
- Location: Blood, lymph, B cell surface (monomer)
- Half-life in serum: 5 days
- Complement Fixation: Yes
- Placental Transfer: No
- Known Functions: First antibodies produced during an infection. Effective against microbes and agglutinating antigens.

Immunoglobulin Classes

III. IgA

- Structure: Dimer
- Percentage serum antibodies: 10-15%
- Location: Secretions (tears, saliva, intestine, milk), blood and lymph.
- Half-life in serum: 6 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Localized protection of *mucosal* surfaces. Provides immunity to infant digestive tract.

Immunoglobulin Classes

IV. IgD

- Structure: Monomer
- Percentage serum antibodies: 0.2%
- Location: B-cell surface, blood, and lymph
- Half-life in serum: 3 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: In serum function is unknown. On B cell surface, initiate immune response.

Immunoglobulin Classes

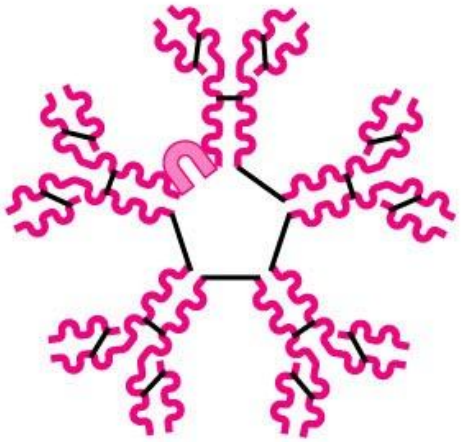
V. IgE

- Structure: Monomer
- Percentage serum antibodies: 0.002%
- Location: Bound to mast cells and basophils throughout body. Blood.
- Half-life in serum: 2 days
- Complement Fixation: No
- Placental Transfer: No
- Known Functions: Allergic reactions. Possibly lysis of worms.

TABLE 21.3 Immunoglobulin Classes

IgD (monomer)

IgD is virtually always attached to the external surface of a B cell, where it functions as the antigen receptor of the B cell; important in B cell activation.



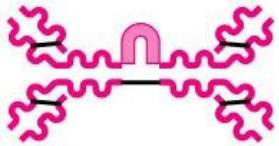
IgM (pentamer)

IgM exists in monomer and pentamer (five united monomers) forms. The monomer, which is attached to the B cell surface, serves as an antigen receptor. The pentamer (illustrated) circulates in blood plasma and is the first Ig class released by plasma cells during the primary response. (This fact is diagnostically useful because presence of IgM in plasma usually indicates current infection by the pathogen eliciting IgM's formation.) Because of its numerous antigen-binding sites, IgM is a potent agglutinating agent and readily fixes and activates complement.

TABLE 21.3 Immunoglobulin Classes *(continued)*

IgG (monomer)

IgG is the most abundant and diverse antibody in plasma, accounting for 75–85% of circulating antibodies. It protects against bacteria, viruses, and toxins circulating in blood and lymph, readily fixes complement, and is the main antibody of both secondary and late primary responses. It crosses the placenta and confers passive immunity from the mother to the fetus.



IgA (dimer)

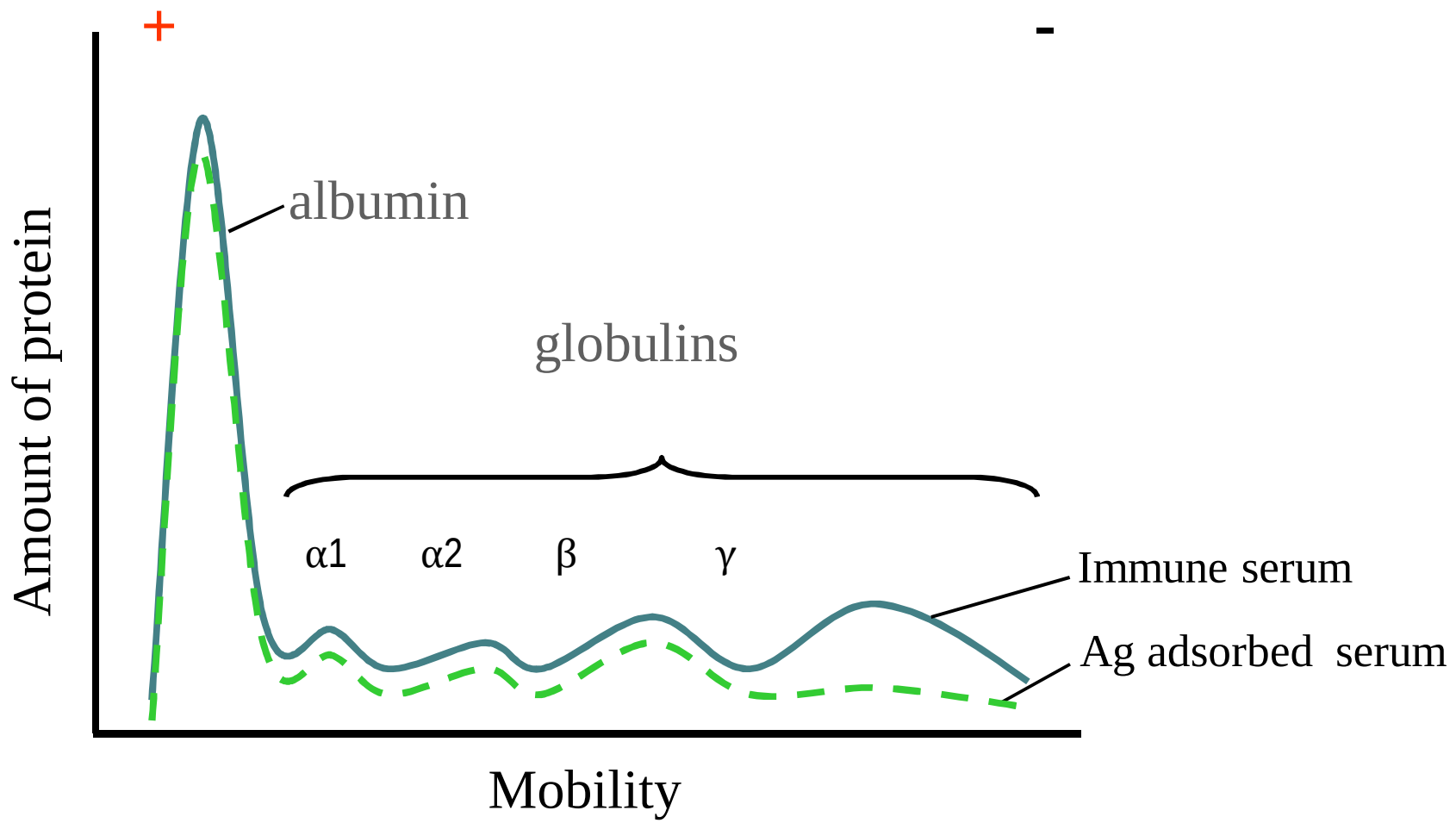
IgA monomer exists in limited amounts in plasma. The dimer (illustrated), referred to as secretory IgA, is found in body secretions such as saliva, sweat, intestinal juice, and milk, and helps prevent attachment of pathogens to epithelial cell surfaces (including mucous membranes and the epidermis).

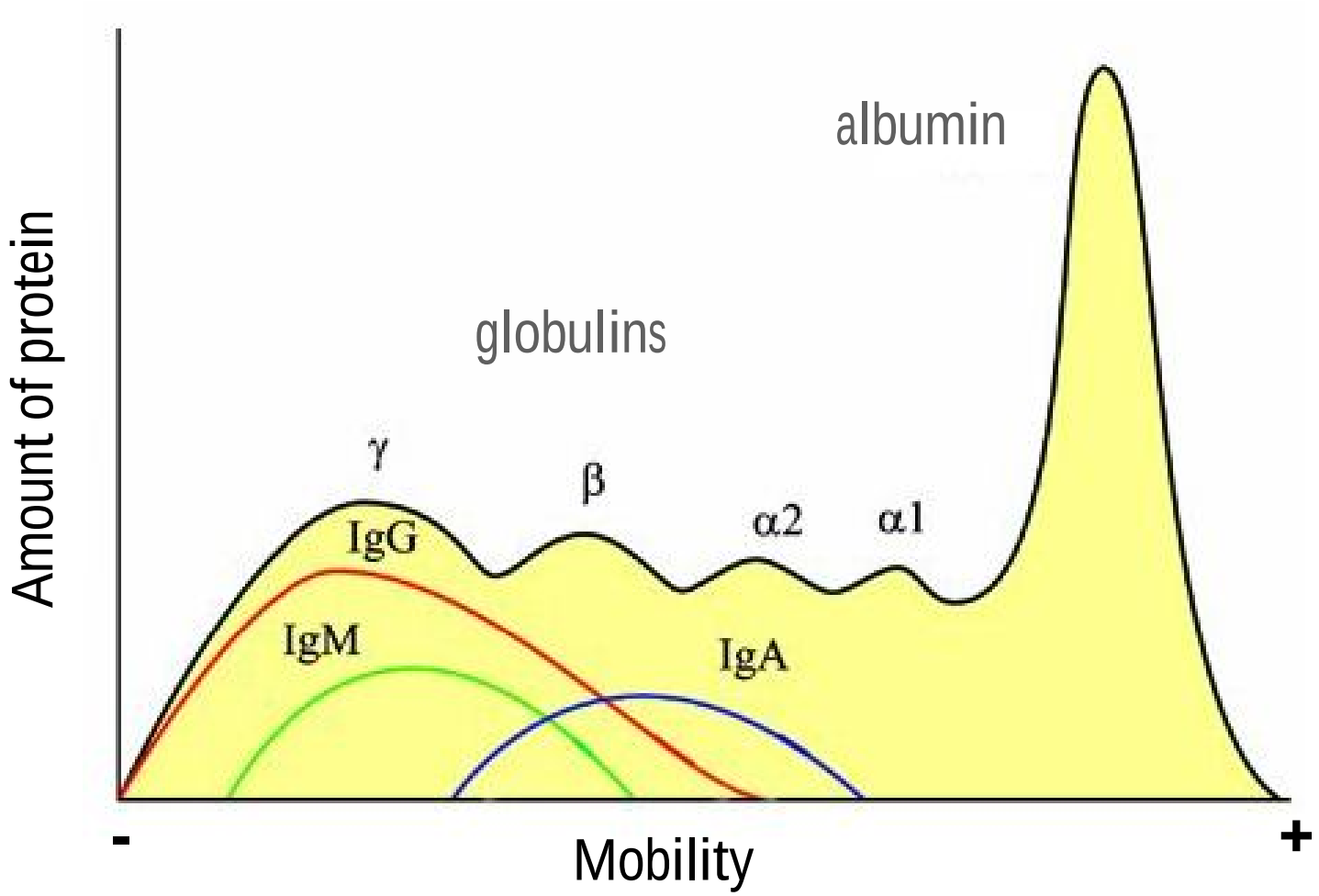
IgE (monomer)

IgE is slightly larger than the IgG antibody. It is secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. Its stem region becomes bound to mast cells and basophils, and when its receptor ends are triggered by an antigen, it causes the cells to release histamine and other chemicals that mediate inflammation and an allergic reaction. Typically only traces of IgE are found in plasma, but levels rise during severe allergic attacks or chronic parasitic infections of the gastrointestinal tract.

Immunoglobulin, Ig

- Definition: Glycoprotein molecules that are produced by **plasma cells** in response to an immunogen and which function as **antibodies**.
- The immunoglobulins are a group of glycoproteins present in the serum and tissue fluids of all mammals.


+
-
albumin
globulins
α1
α2
β
γ
Immune serum
Ag adsorbed serum
Amount of protein
Mobility


albumin
globulins
γ
β
α2
α1
IgG
IgM
IgA
Amount of protein
-
+
Mobility

ADAPTIVE IMMUNE SYSTEM

T-lymphocytes

T-cytotoxic → Cytoyoxic

B-lymphocytes

Plasma cells → Antibodies

Response takes 7 to 10 days

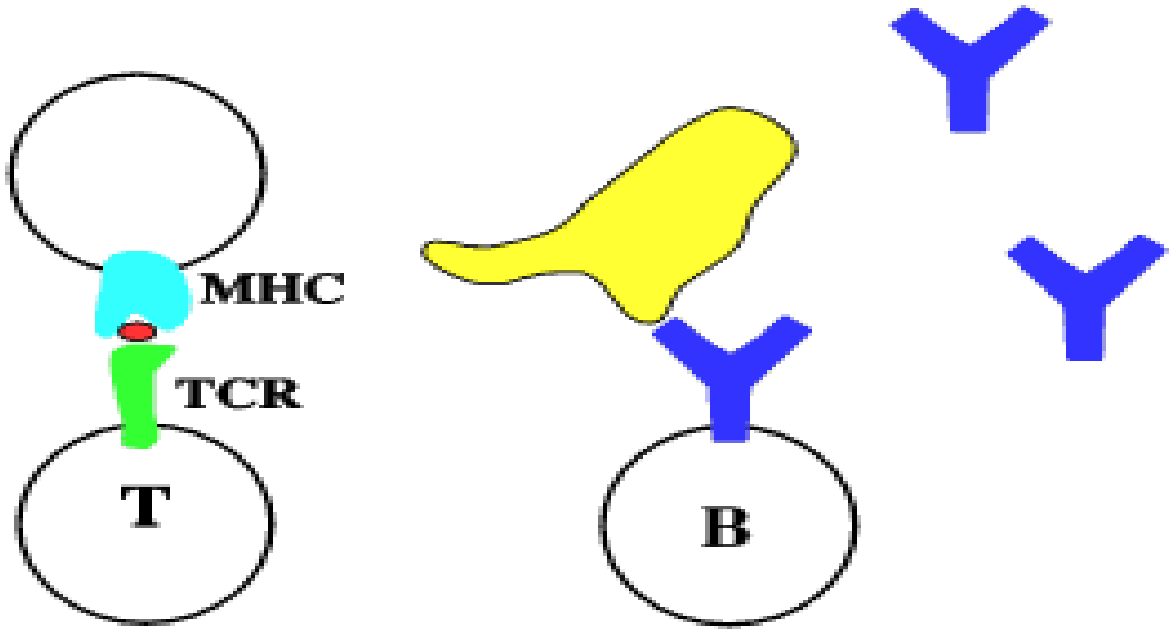
Adaptive Immune System

- T and B Lymphocytes
- Highly specific for pathogen
- Response improves with repeated exposure
- Memory
- Life-long immunity

T versus B cell Response

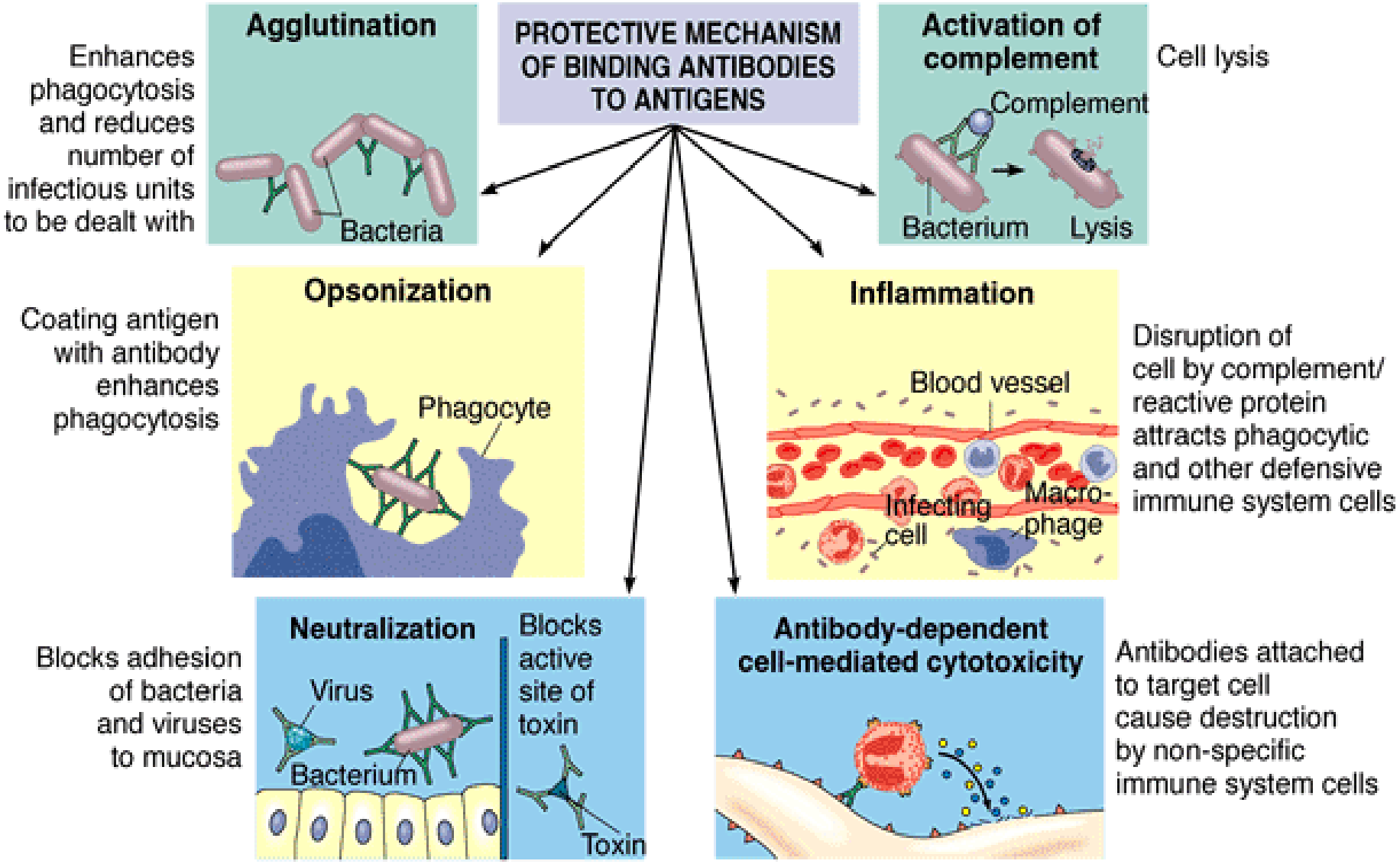
B cells recognise native antigen

T cells recognise processed antigen



Part VII: Antibodies - Antigens

Consequences of Antibody Binding



Consequences of Antigen-Antibody Binding

Antigen-Antibody Complex: Formed when an antibody binds to an antigen it recognizes.

Affinity: A measure of binding strength.

1. **Agglutination**: Antibodies cause antigens (microbes) to clump together.
   - IgM (decavalent) is more effective that IgG (bivalent).
   - **Hemagglutination:** Agglutination of red blood cells. Used to determine ABO blood types and to detect influenza and measles viruses.
2. **Opsonization: Antigen (microbe) is covered with antibodies that** enhances its ingestion and lysis by phagocytic cells.

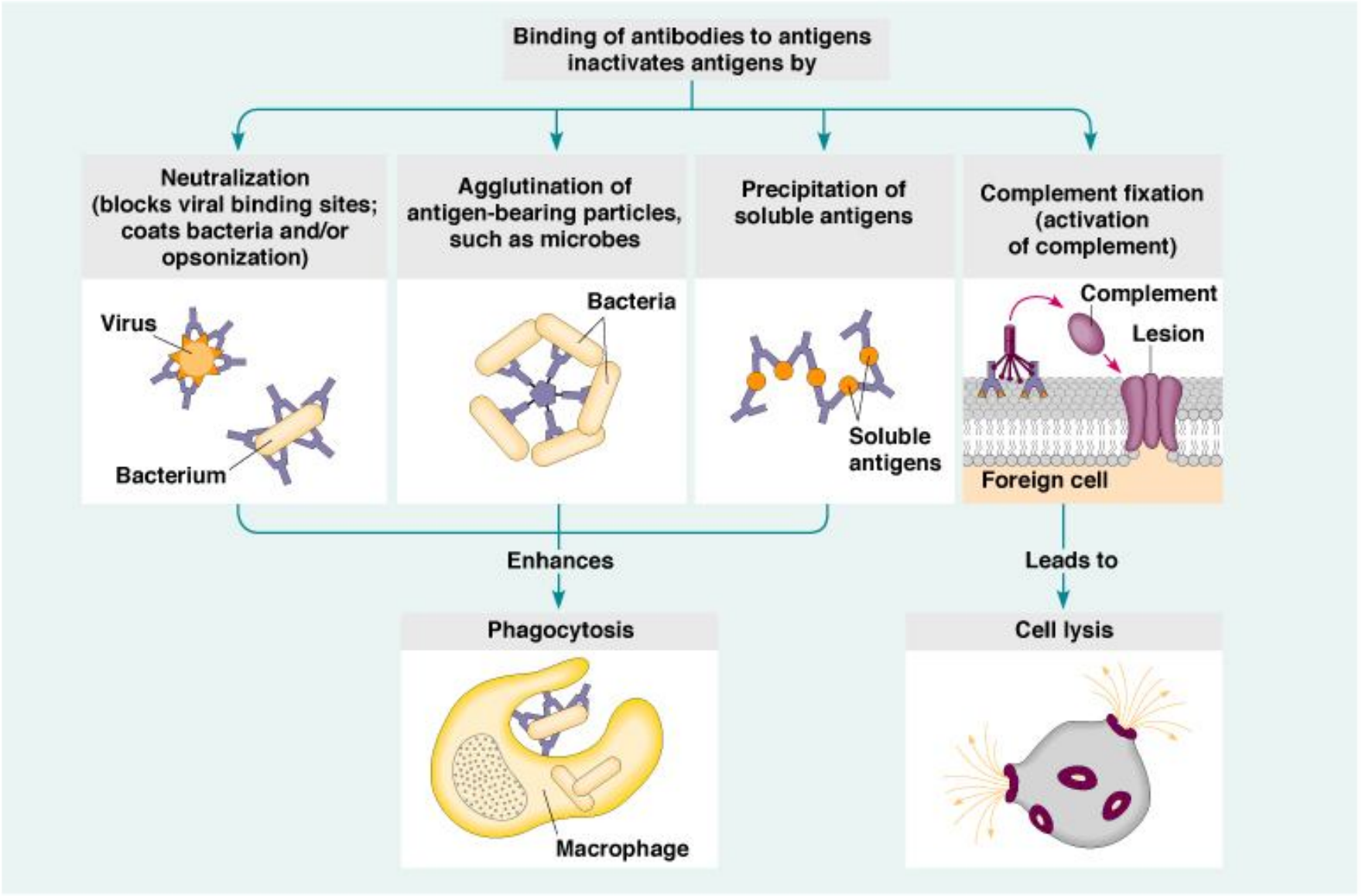
Humoral Immunity (Continued)

3. **Neutralization:** IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.

4. **Antibody-dependent cell-mediated cytotoxicity:** Used to destroy large organisms (e.g.: worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific immune cells.

5. **Complement Activation:** Both IgG and IgM trigger the complement system which results in cell lysis and inflammation.

Consequences of Antibody Binding



Vaccination

* Vaccination prevents and control such diseases as cholera, rabies, poliomyelitis, diphtheria, tetanus, measles, and typhoid fever

* Vaccines can be:

a- **prophylactic** (e.g. to prevent the effects of a future infection by any natural or "wild" pathogen

b- Therapeupic (e.g. vaccines against cancer are also being investigated)

Dr. Schreiber of San Augustine giving a typhoid inoculation at a rural school, San Augustine County, Texas. Transfer from U.S. Office of War Information, 1944.

Vaccination

Vaccination:

*Producing immunity against pathogens (viruses and bacteria) by the introduction of live, killed, or altered antigens that stimulate the body to produce antibodies against more dangerous forms

*Vaccines work with the immune system's ability to recognize and destroy foreign proteins (antigens)

Vaccination

Immunization of young children and adolescents:

- Hepatitis B (HepB) and Hepatitis A (HepA)

- Diphtheria, tetanus and pertussis (whooping cough) given together as DTaP (formerly DTP)

- *Haemophilus influenzae b* (Hib)

- Poliomyelitis (IPV)

- Measles, Mumps, and Rubella, given together as MMR

- Chicken pox (Var)

- *Neisseria meningitidis* (meningococcal meningitis)

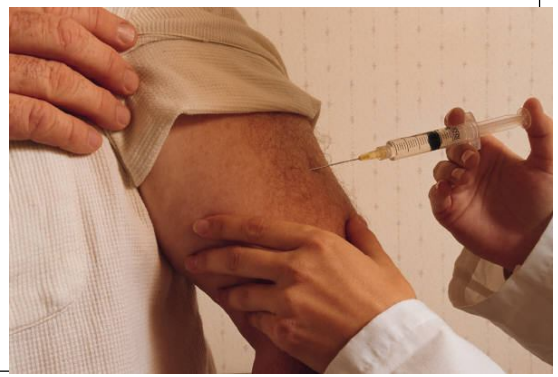


TABLE 1. Catch-up schedule for children aged 4 months–6 years

Dose one (minimum age)	Minimum interval between doses			
	Dose one to dose two	Dose two to dose three	Dose three to dose four	Dose four to dose five
DTaP (6 wks)	**4 wks**	**4 wks**	**6 mos**	**6 mos**[1]
IPV (6 wks)	**4 wks**	**4 wks**	**4 wks**[2]	
HepB[3] (birth)	**4 wks**	**8 wks** (and 16 weeks after first dose)		
MMR (12 mos)	**4 wks**[4]			
Varicella (12 mos)				
Hib[5] (6 wks)	**4 wks:** if 1st dose given at age <12 mos **8 wks (as final dose):** if 1st dose given at age 12–24 mos **No further doses needed:** if 1st dose given at age ≥15 mos	**4 wks**[6]**:** if current age <12 mos **8 wks (as final dose)**[6]**:** if current age ≥12 mos and 2nd dose given at age <15 mos **No further doses needed:** if previous dose given at age ≥15 mos	**8 wks (as final dose):** this dose only necessary for children aged 12 mos–5 yrs who received 3 doses before age 12 mos	
PCV[7] (6 wks)	**4 wks:** if 1st dose given at age <12 mos and current age <24 mos **8 wks (as final dose):** if 1st dose given at age ≥12 mos or current age 24–59 mos **No further doses needed:** for healthy children if 1st dose given at age ≥24 mos	**4 wks:** if current age <12 mos **8 wks (as final dose):** if current age ≥12 mos **No further doses needed:** for healthy children if previous dose given at age ≥24 mos	**8 wks (as final dose):** this dose only necessary for children aged 12 mos–5 yrs who received 3 doses before age 12 mos	

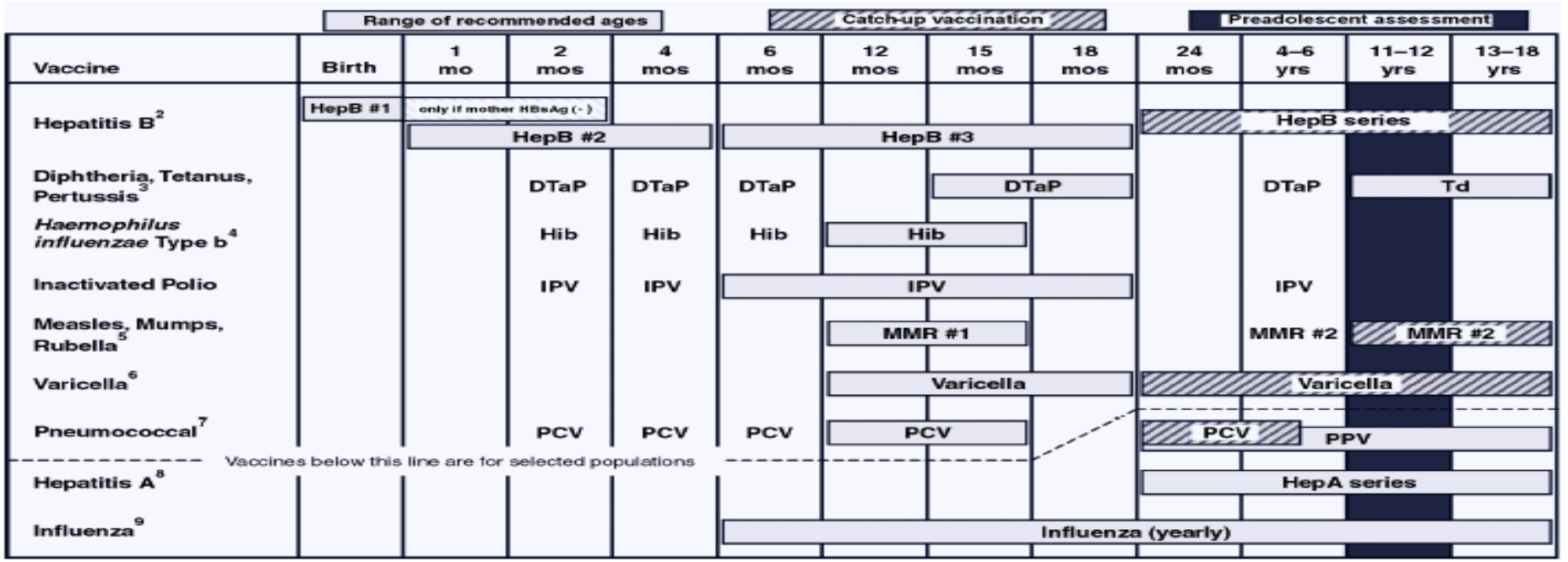
1. **Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP):** The fifth dose is not necessary if the fourth dose was given after the fourth birthday.
2. **Inactivated Polio (IPV):** For children who received an all-IPV or all-OPV series, a fourth dose is not necessary if third dose was given at age ≥4 years. If both OPV and IPV were given as part of a series, a total of 4 doses should be given, regardless of the child's current age.
3. **Hepatitis B vaccine (HepB):** All children and adolescents who have not been vaccinated against hepatitis B should begin the hepatitis B vaccination series during any visit. Providers should make special efforts to immunize children who were born in, or whose parents were born in, areas of the world where hepatitis B virus infection is moderately or highly endemic.
4. **Measles, mumps, and rubella vaccine (MMR):** The second dose of MMR is recommended routinely at age 4–6 years, but may be given earlier if desired.
5. ***Haemophilus influenzae* type b (Hib):** Vaccine is not recommended generally for children aged ≥5 years.
6. **Hib:** If current age is <12 months and the first 2 doses were PRP-OMP (PedvaxHIB® or ComVax [Merck]®), the third (and final) dose should be given at age 12–15 months and at least 8 weeks after the second dose.
7. **Pneumococcal conjugate vaccine (PCV):** Vaccine is not recommended generally for children aged ≥5 years.

TABLE 2. Catch-up schedule for children aged 7–18 years

Minimum interval between doses		
Dose one to dose two	**Dose two to dose three**	**Dose three to booster dose**
Td: 4 wks	**Td:** 6 mos	**Td**[1]: **6 mos:** if 1st dose given at age <12 mos and current age <11 yrs **5 yrs:** if 1st dose given at age ≥12 mos and 3rd dose given at age <7 yrs and current age ≥11 yrs **10 yrs:** if 3rd dose given at age ≥7 yrs
IPV[2]**:** 4 wks	**IPV**[2]**:** 4 wks	**IPV**[2]
HepB: 4 wks	**HepB:** 8 wks (and 16 wks after 1st dose)	
MMR: 4 wks		
Varicella[3]**:** 4 wks		

1. **Tetanus toxoid:** For children aged 7–10 years, the interval between the third and booster dose is determined by the age when the first dose was given. For adolescents aged 11–18 years, the interval is determined by the age when the third dose was given.
2. **Inactivated Polio (IPV):** Vaccine is not recommended generally for persons aged ≥18 years.
3. **Varicella:** Give 2-dose series to all susceptible adolescents aged ≥13 years.

FIGURE. Recommended childhood and adolescent immunization schedule[1] — United States, 2003



1. Indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2002, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. ▨ Indicates age groups that warrant special effort to administer those vaccines not given previously. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

2. **Hepatitis B vaccine (HepB).** All infants should receive the first dose of HepB vaccine soon after birth and before hospital discharge; the first dose also may be given by age 2 months if the infant's mother is HBsAg-negative. Only monovalent HepB vaccine can be used for the birth dose. Monovalent or combination vaccine containing HepB may be used to complete the series; 4 doses of vaccine may be administered when a birth dose is given. The second dose should be given at least 4 weeks after the first dose except for combination vaccines, which cannot be administered before age 6 weeks. The third dose should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose. The last dose in the vaccination series (third or fourth dose) should not be administered before age 6 months. Infants born to HBsAg-positive mothers should receive HepB vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1–2 months. The last dose in the vaccination series should not be administered before age 6 months. These infants should be tested for HBsAg and anti-HBs at 9–15 months of age. Infants born to mothers whose HBsAg status is unknown should receive the first dose of the HepB vaccine series within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The second dose is recommended at age 1–2 months. The last dose in the vaccination series should not be administered before age 6 months.

3. **Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** The fourth dose of DTaP may be administered at age 12 months provided that 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. **Tetanus and diphtheria toxoids (Td)** is recommended at age 11–12 years if at least 5 years have elapsed since the last dose of Td-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

4. ***Haemophilus influenzae* type b (Hib) conjugate vaccine.** Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at age 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary vaccination in infants at age 2, 4, or 6 months but can be used as boosters following any Hib vaccine.

5. **Measles, mumps, and rubella vaccine (MMR).** The second dose of MMR is recommended routinely at age 4–6 years but may be administered during any visit provided that at least 4 weeks have elapsed since the first dose and that both doses are administered beginning at or after age 12 months. Those who have not received the second dose previously should complete the schedule by the visit at age 11–12 years.

6. **Varicella vaccine.** Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons aged ≥13 years should receive 2 doses given at least 4 weeks apart.

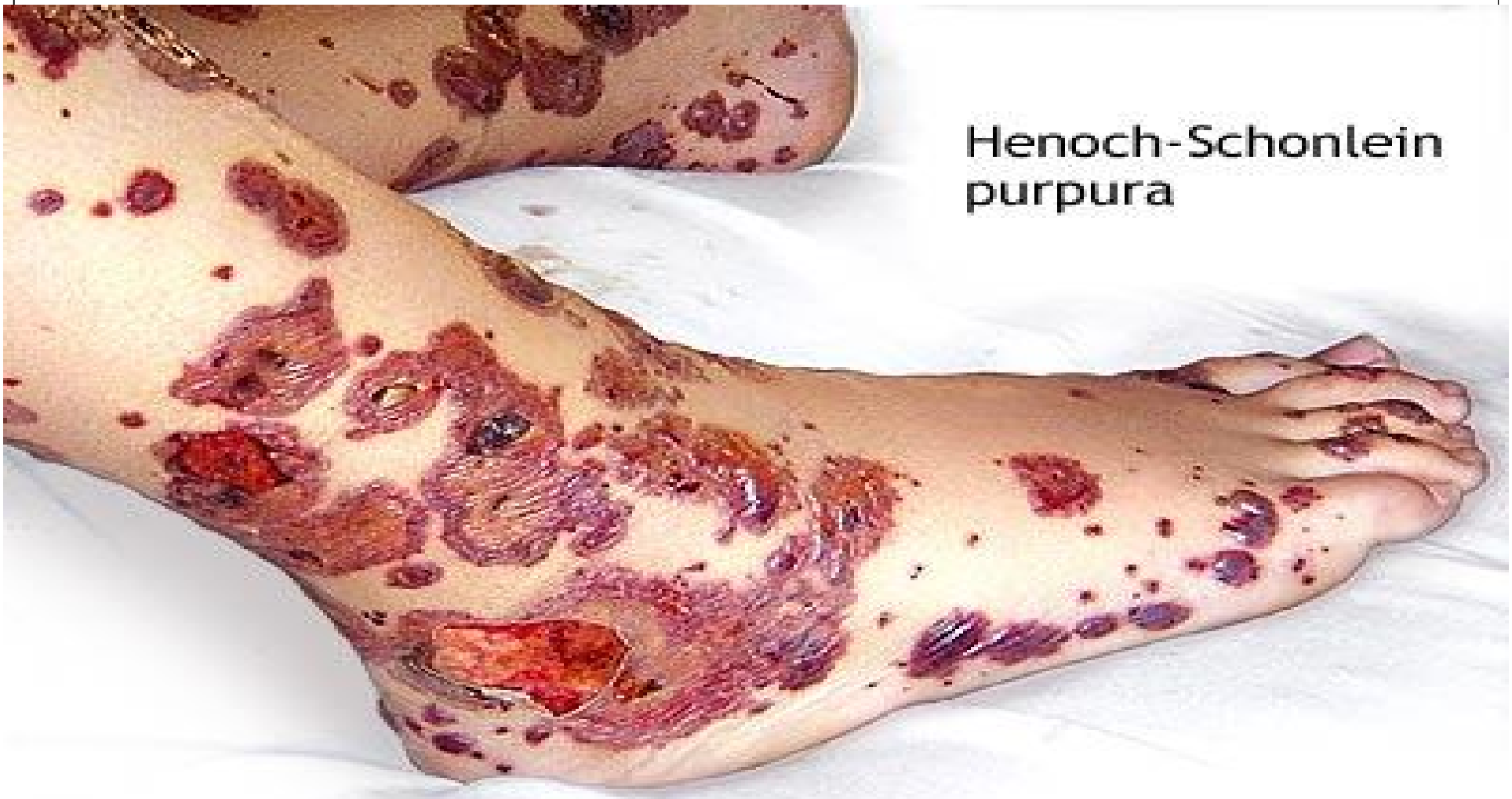
7. **Pneumococcal vaccine.** The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children aged 2–23 months and for certain children aged 24–59 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000;49(No. RR-9):1–37.

8. **Hepatitis A vaccine.** Hepatitis A vaccine is recommended for children and adolescents in selected states and regions, and for certain high-risk groups. Consult local public health authority and *MMWR* 1999;48(No. RR-12):1–37. Children and adolescents in these states, regions, and high-risk groups who have not been immunized against hepatitis A can begin the hepatitis A vaccination series during any visit. The two doses in the series should be administered at least 6 months apart.

9. **Influenza vaccine.** Influenza vaccine is recommended annually for children aged ≥6 months with certain risk factors (including but not limited to asthma, cardiac disease, sickle cell disease, HIV, and diabetes, and household members of persons in groups at high risk (see *MMWR* 2002;51[No. RR-3]:1–31), and can be administered to all others wishing to obtain immunity. In addition, healthy children age 6–23 months are encouraged to receive influenza vaccine if feasible because children in this age group are at substantially increased risk for influenza-related hospitalizations. Children aged ≤12 years should receive vaccine in a dosage appropriate for their age (0.25 mL if 6–35 months or 0.5 mL if ≥3 years). Children aged ≤8 years who are receiving influenza vaccine for the first time should receive 2 doses separated by at least 4 weeks.

Additional information about vaccines, including precautions and contraindications for vaccination and vaccine shortages, is available at http://www.cdc.gov/nip or at the National Immunization information hotline, telephone 800-232-2522 (English) or 800-232-0233 (Spanish). Copies of the schedule can be obtained at http://www.cdc.gov/nip/recs/child-schedule.htm. Approved by the **Advisory Committee on Immunization Practices** (http://www.cdc.gov/nip/acip), the **American Academy of Pediatrics** (http://www.aap.org), and the **American Academy of Family Physicians** (http://www.aafp.org).

Hypersensitivity Reaction



Hypersensitivity Reaction

Hypersensitivity or allergy

* An immune response results in exaggerated reactions harmful to the host

* There **are four types** of hypersensitivity reactions:

Type I, Type II, Type III, Type IV

* Types I, II and III are antibody mediated

* Type IV is cell mediated

Type I: Immediate hypersensitivity

* An antigen reacts with cell **fixed antibody (Ig E)**
  leading to release of soluble molecules
  An antigen (allergen)
  soluble molecules (mediators)

* Soluble molecules cause the manifestation of disease

* **Systemic life threatening; anaphylactic shock**

* Local atopic allergies; bronchial asthma, hay fever and food allergies

Pathogenic mechanisms

* Three classes of mediators **derived from mast cells**:

  !) Preformed mediators stored in granules (histamine)

  2) Newly sensitized mediators:
  leukotrienes, prostaglandins, platelets activating factor

  3) Cytokines produced by activated mast cells, basophils
  e.g. TNF, IL3, IL-4, IL-5 IL-13, chemokines

* These mediators cause: ↑ smooth muscle contraction,
  mucous secretion and bronchial spasm, vasodilatation,
  ↑ vascular permeability and edema

Anaphylaxis

* Systemic form of Type I hypersensitivity

* Exposure to allergen to which a person is previously sensitized

* Allergens:

  Drugs: penicillin

  Serum injection : anti-diphtheritic or ant-tetanic serum

  anesthesia or insect venom

* Clinical picture:

  Shock due to sudden decrease of blood pressure, respiratory distress due to bronhospasm, cyanosis, edema, urticaria

* Treatment: corticosteroids injection, epinephrine, antihistamines

Atopy

* Local form of type I hypersensitivity

* Exposure to certain allergens that induce production of specific Ig E

* Allergens :
  Inhalants: dust mite feces, tree or pollens, mould spor.
  Ingestants: milk, egg, fish, chocolate
  Contactants: wool, nylon, animal fur
  Drugs: penicillin, salicylates, anesthesia insect venom

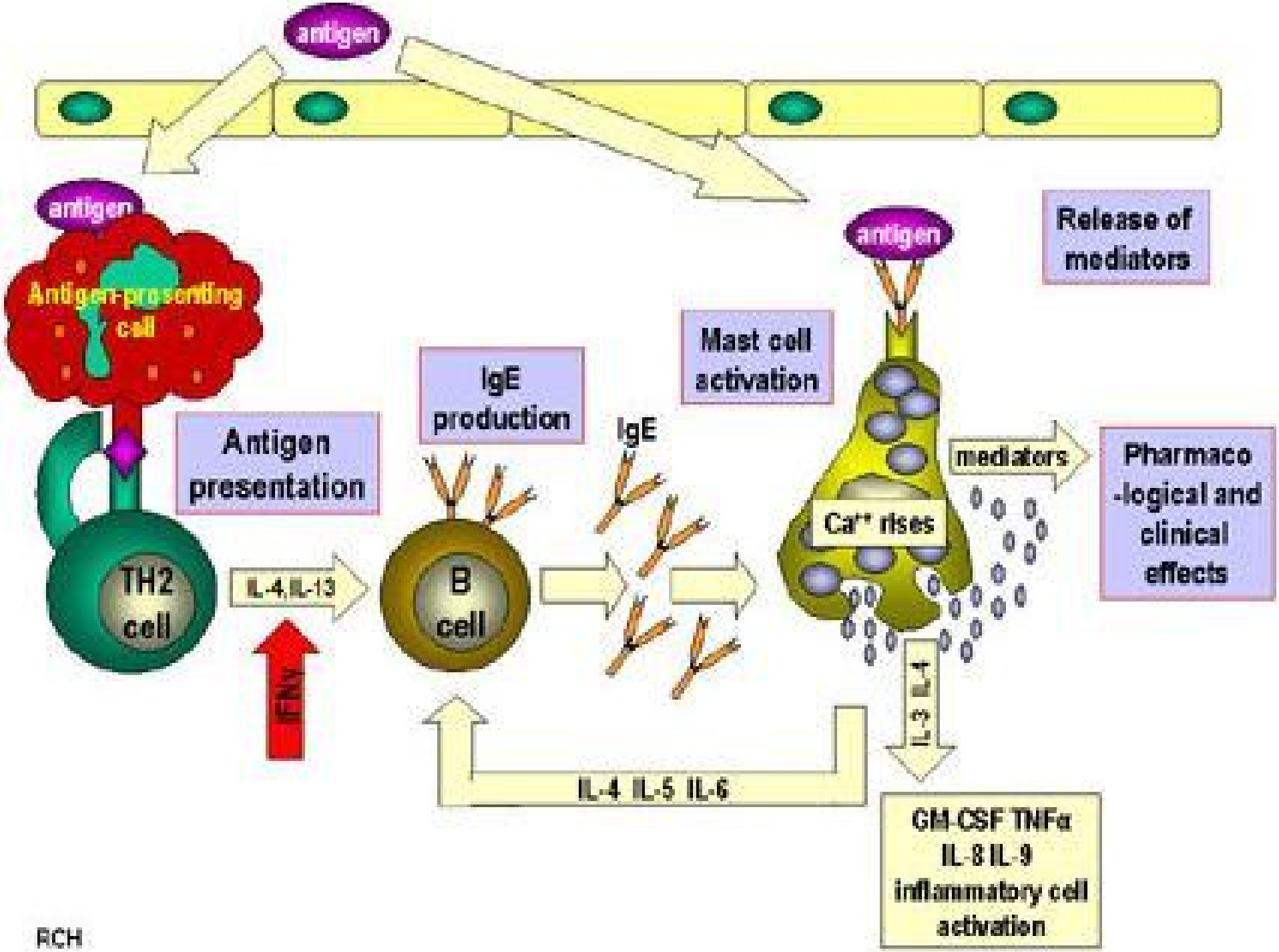
* There is a strong familial predisposition to atopic allergy

* The predisposition is genetically determined

Type II: Cytotoxic or Cytolytic Reactions

* An antibody (Ig G or Ig M) reacts with antigen on the cell surface

* This antigen may be part of cell membrane or circulating antigen (or hapten) that attaches to cell membrane


antigen
antigen
Antigen-presenting cell
Antigen presentation
TH2 cell
IL-4,IL-13
IFNγ
IgE production
B cell
IgE
Mast cell activation
antigen
Ca++ rises
mediators
Release of mediators
Pharmaco -logical and clinical effects
IL-3 IL-4
IL-4 IL-5 IL-6
GM-CSF TNFα IL-8 IL-9 inflammatory cell activation
RCH

Clinical Conditions

1) Transfusion reaction due to ABO incompatibility

2) Rh-incompatability (Haemolytic disease of the newborn)

3) Autoimmune diseases

The mechanism of tissue damage is cytotoxic reactions

e.g. SLE, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrotoxic nephritis, Hashimoto's thyroiditis

4) A non-cytotoxic Type II hypersensitivity is Graves's disea

It is a form of thyroditits in which antibodies are produced against TSH surface receptor

This lead to mimic the effect of TSH and stimulate cells to over- produce thyroid hormones

Clinical Conditions

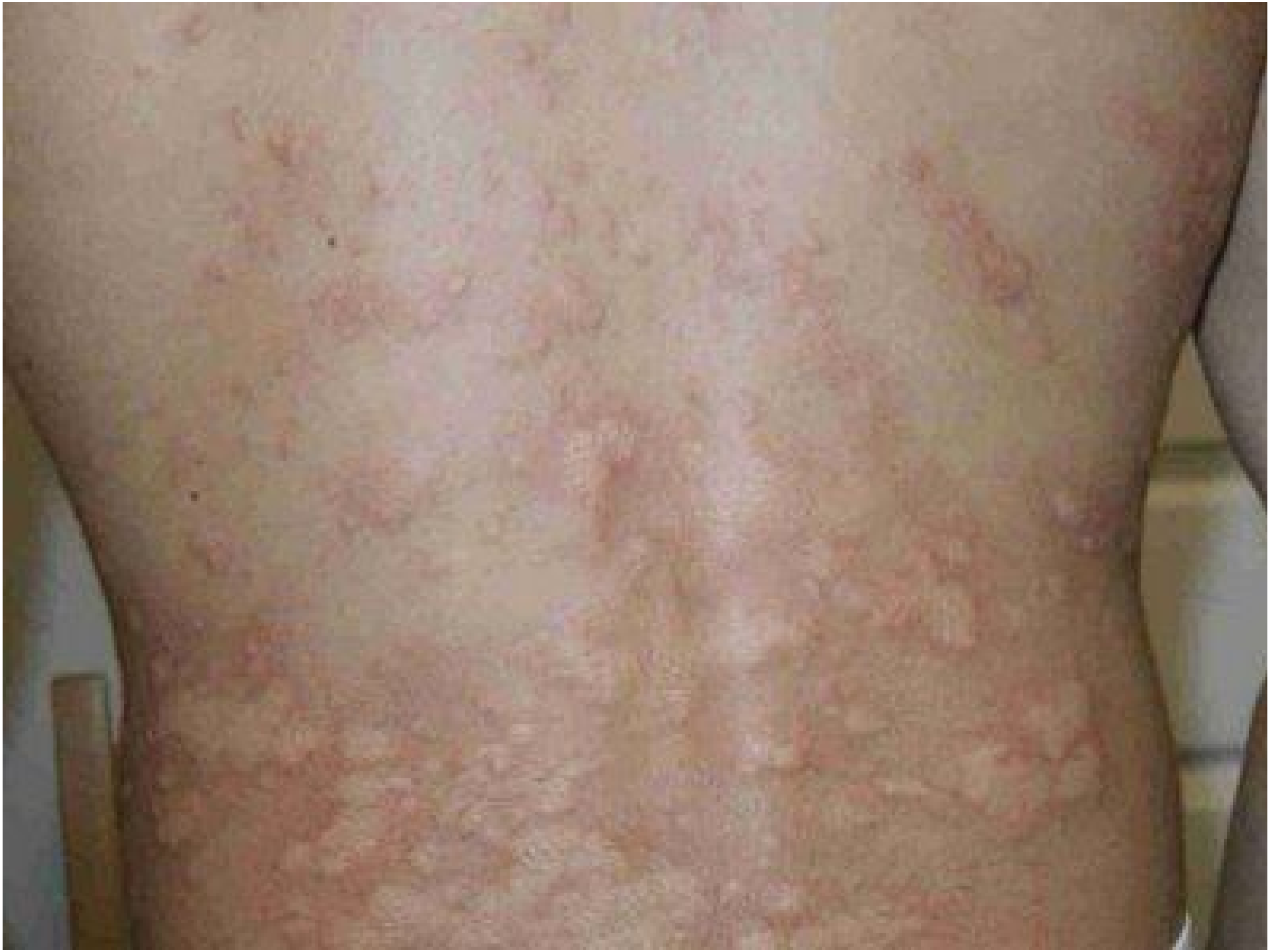
5- Graft rejection cytotoxic reactions:

In hyperacute rejection the recipient already has performed antibody against the graft

6- Drug reaction:

Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis

Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura




Penicillin Allergy
Emory U. / Dr. Sellers

Type III Hypersensitivity

Immune Complex Mediated Reaction

Type III: Immune Complex Mediated Reaction

*When antibodies (Ig G or Ig M) and antigen coexist immune complexes are formed

*Immune complexes are removed by reticuloendoth. syst.

*Some immune complexes escape phagocytosis

*Immune complexes deposited in tissues on the basement membrane of blood vessels and cause tissue injury

Mechanism Of Tissue Injury

Immune complexes trigger inflammatory processes:

1) Immune complexes —activate→ the complement —release→ anaphylatoxins C3a, C5a

→ stimulate degranulation of basophiles and mast cells —release→ histamine

Histamine ↑ vascular permeability and help deposition of immune complexes

2) Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammat. Pro.

3) Platelets are aggregated with two consequences

a- release of histamine

b- form of microthrombi which lead to ischemia

Clinical conditions of Type III Hypersensitivity

Diseases produced by immune complexes are those in which antigens persists without being eliminated as:

a- Repeated exposure to extrinsic antigen

b- injection of large amounts of antigens

c- Persistent infections

d- Autoimmunity to self components

1- Arthus Reaction

* This is a local immune complex deposition phenomenon
  e.g. diabetic patients receiving insulin subcutaneously

* Local reactions in the form of → edema, erythema, necrosis

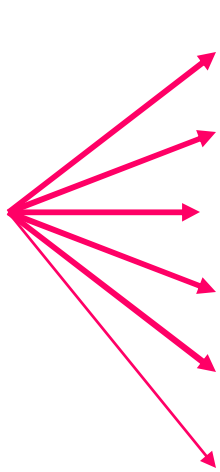
* Immune complexes → deposited → in small blood vessels

leading to → vasculitis, microthrombi formation, vascular occlusion, necrosis

2- Serum Sickness

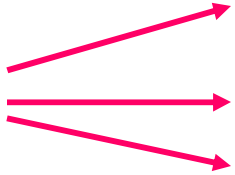
* A systemic immune complex phenomenon
* Injection of large doses of foreign serum
* Antigen is slowly cleared from circulation
* Immune complexes are deposited in various sites

* 10 days after injection



- fever
- urticaria
- arthralgia
- lymphadenopathy
- splenomegaly
- glomerulonephritis

e.g. treatment with



- antidiphtheritic serum
- penicillin
- sulphonamides

Type IV
Cell Mediated
Delayed Type Hypersensitivity

Type IV: Cell Mediated Delayed Type Hypersensitivity

* T-cells cause tissue injury by
  - triggering DTH reactions by TH1
  - or
  - directly killing target cells by CD8

* TH1 and CD8 T cells secrete cytokines (IFN-γ and TNF)

* Cytokines
  - attract lymphocytes
  - activate macrophages
  - induce inflammation

* Tissue damage results from products of activated macrophages

Tuberculin –Type Hypersensitivity

* When PPD is injected intradermally in sensitized person

* Local indurated area appears injection site (48-72 hs)

* Indurations due to accumulation Of:
  macrophages and lymphocytes

* Similar reactions observed in diseases
  e.g. brucellosis, lepromin test in leprosy, Frei's test in lymphogranuloma venereum

THERE IS MORE TO IT

The end

- Stop complaining, it has been resumed

It can be worst