

Cardio Vascular
Disease

Allergies

Eye Disorders

Breast Cancer

Asthma

Lung Cancer

Diabetes

Arthritis &
Joint Pain

Inflammation

Colitis & Crohn's
Disease
Inflammation

Infection

Obesity

Injury

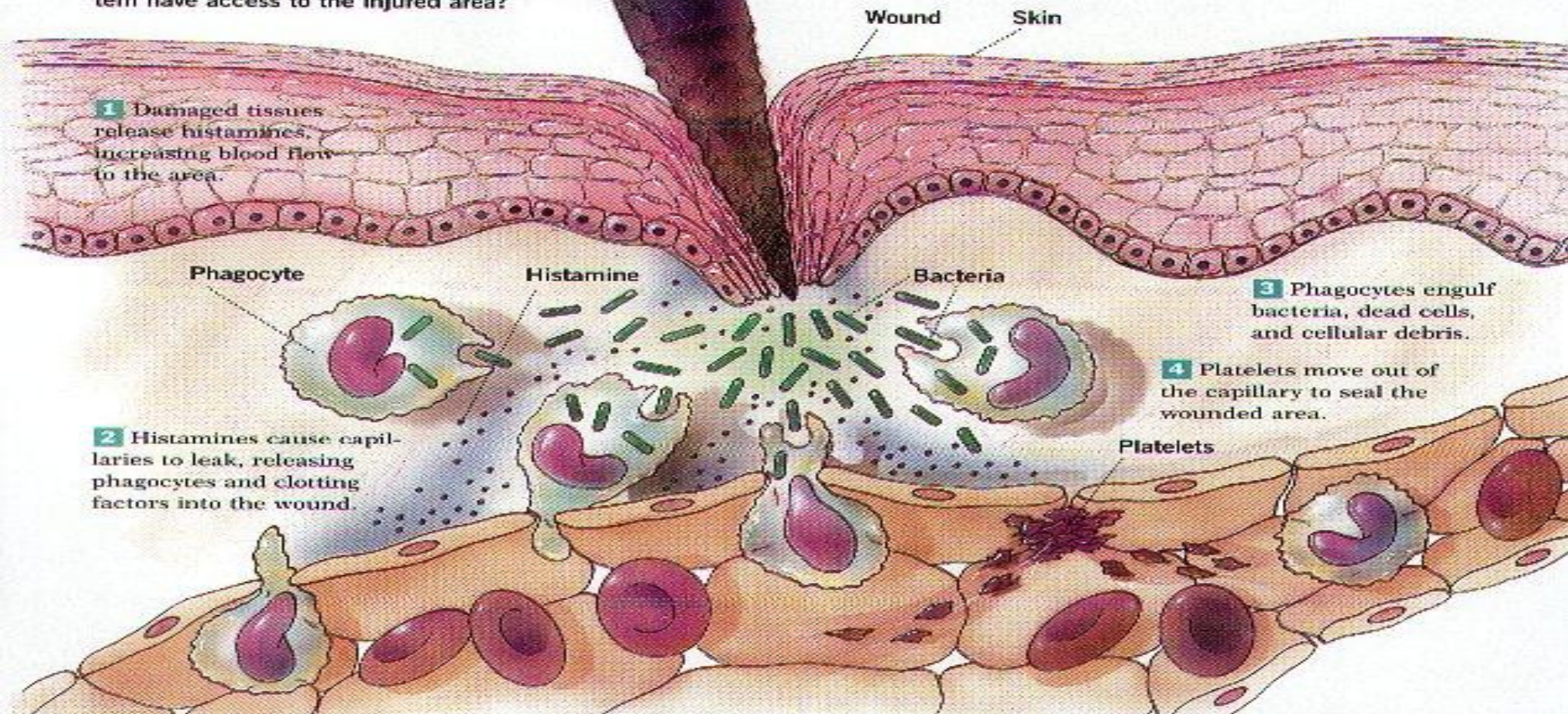
D.HAMMOUDI, MD

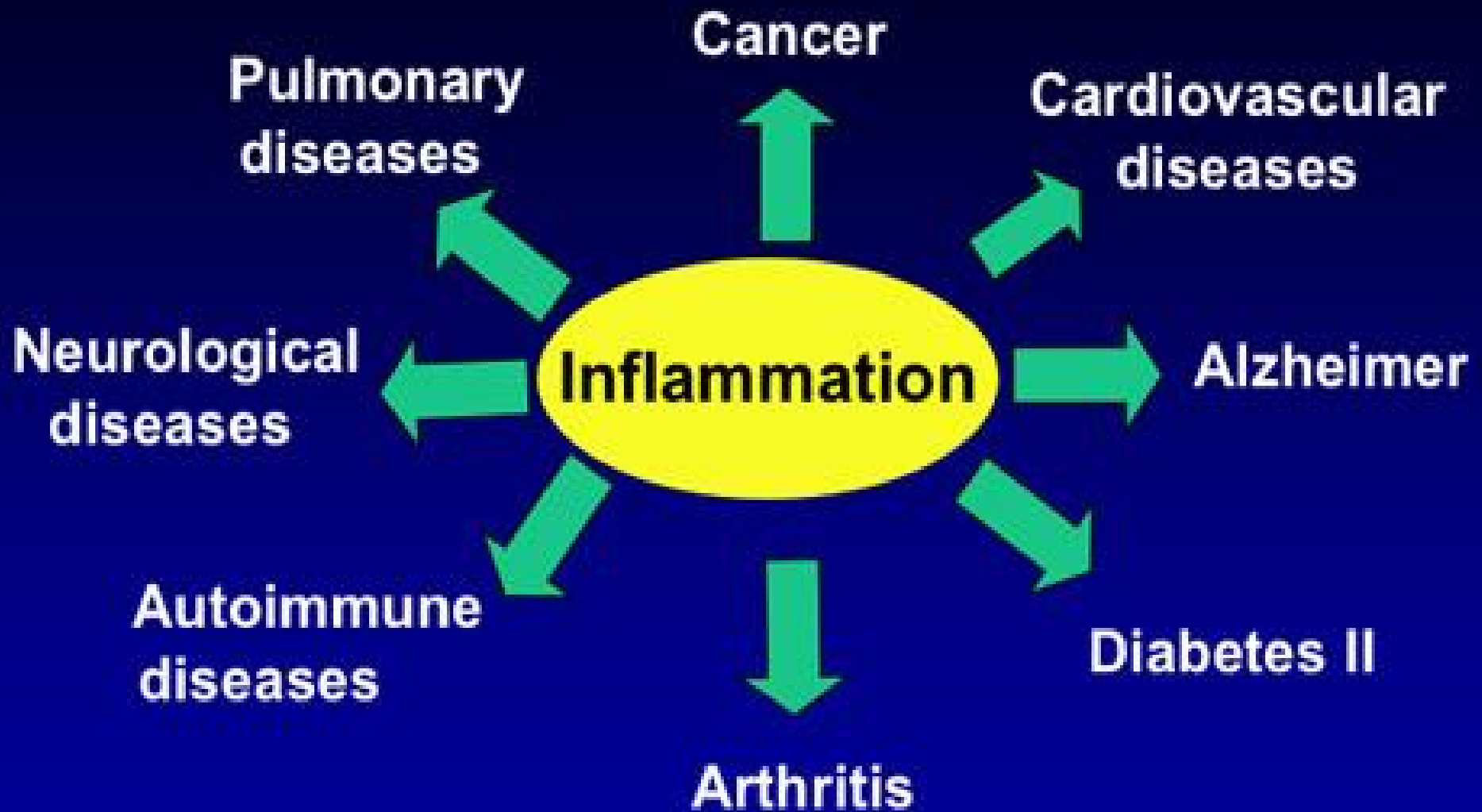


Steps of the Inflammatory Response

The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?

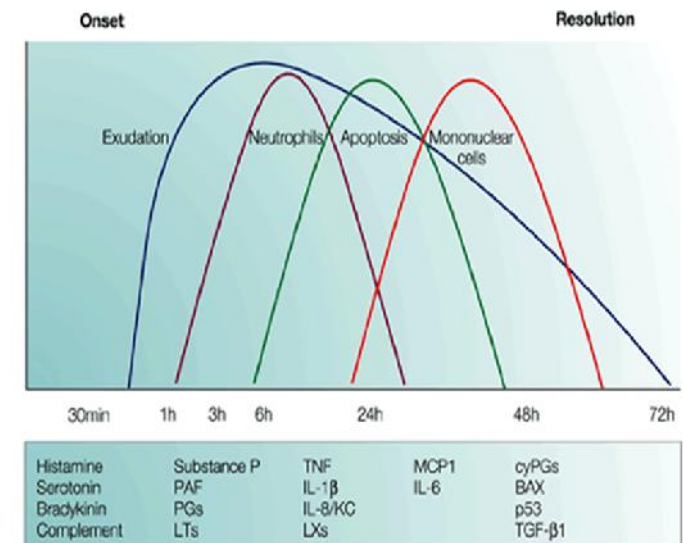
Inflammation





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

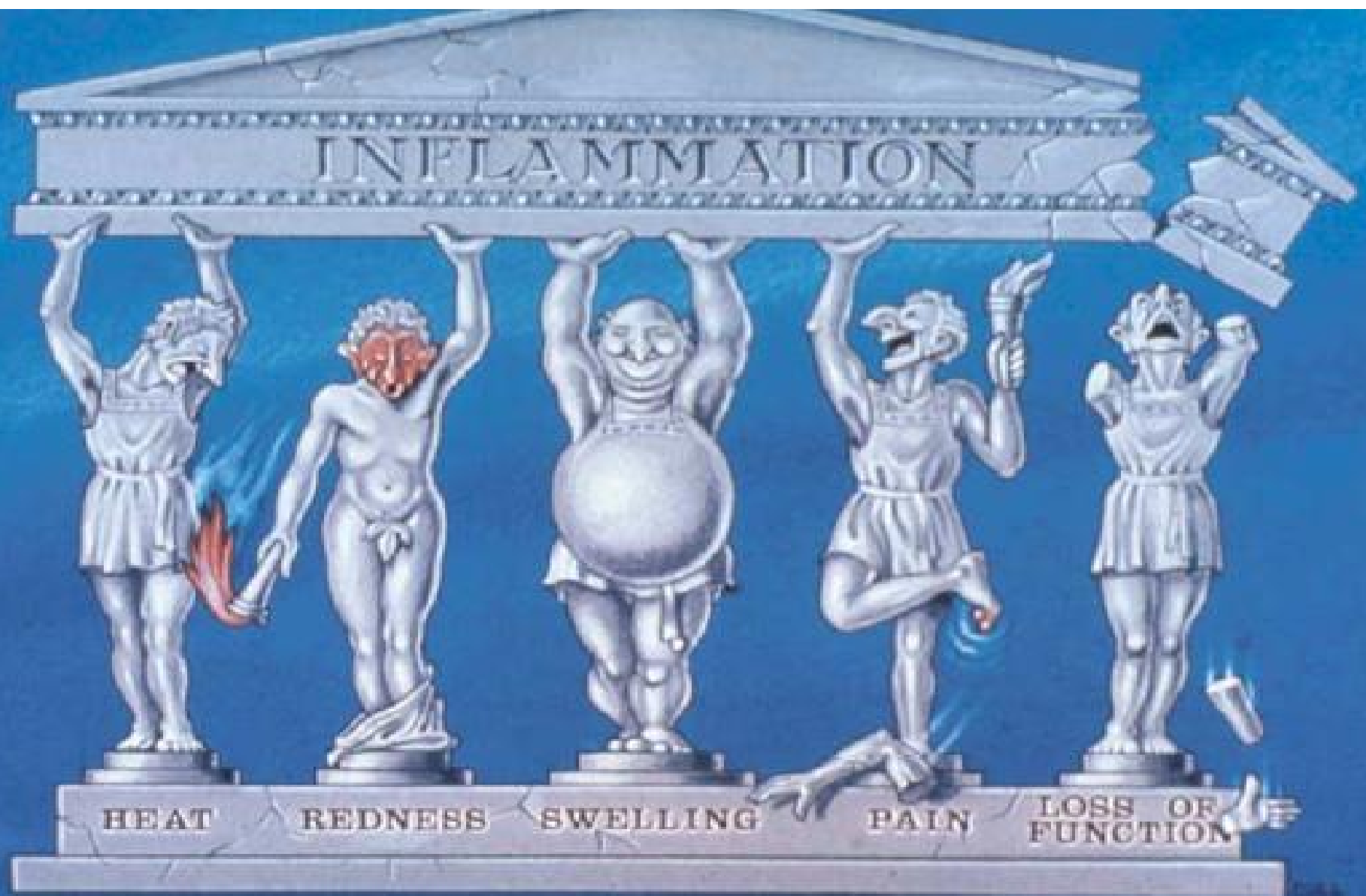


Plasma cascade systems

- 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.

Comparison between acute and chronic inflammation:

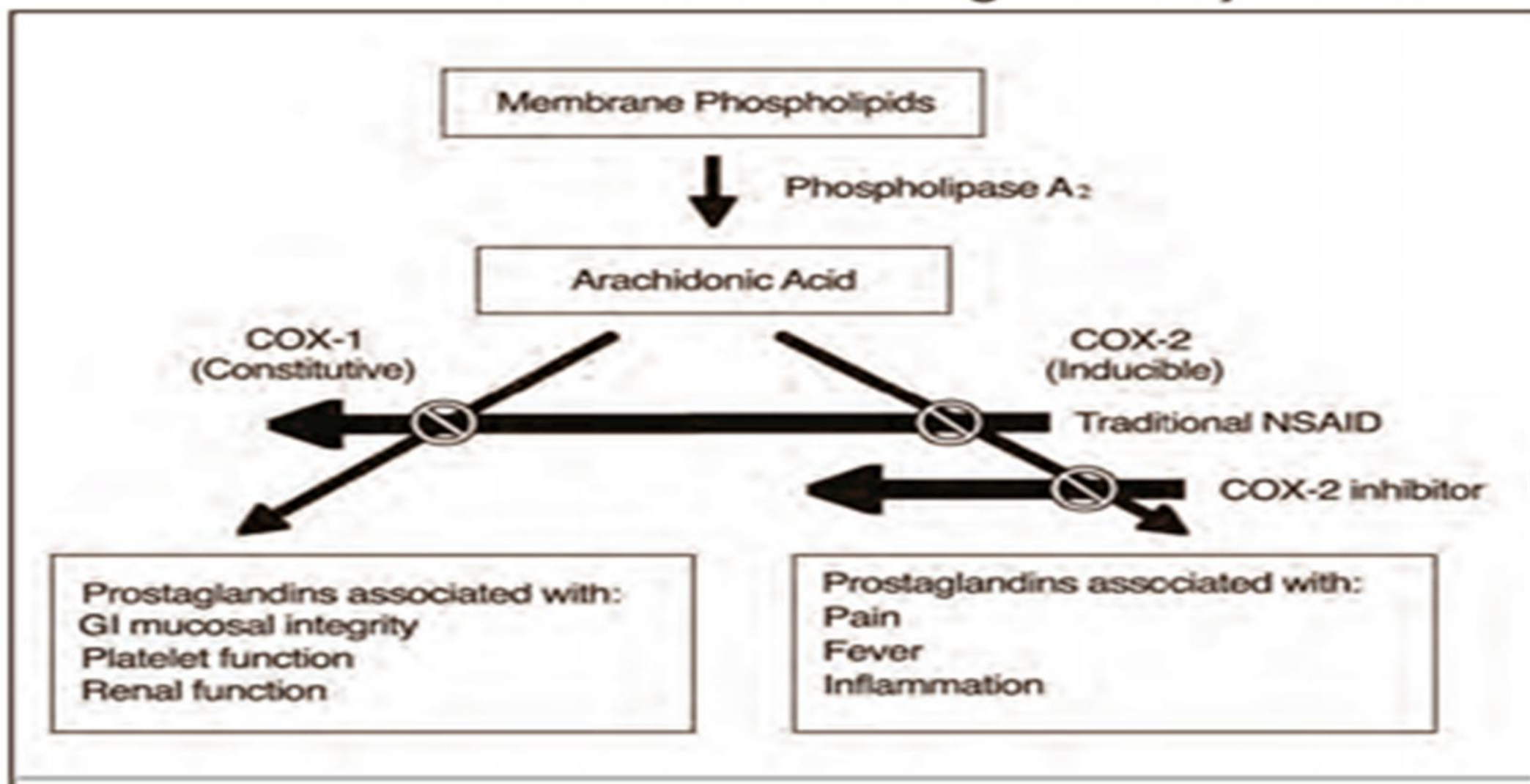
	Acute	Chronic
<i>Causative agent</i>	Pathogens, injured tissues	Persistent acute inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
<i>Major cells involved</i>	Neutrophils, mononuclear cells (monocytes, macrophages)	Mononuclear cells (monocytes, macrophages,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



The classic signs and symptoms of acute inflammation:

Redness	<i>Rubor</i>
Swelling	<i>Tumor/Turgor</i>
Heat	<i>Calor</i>
Pain	<i>Dolor</i>
Loss of function	<i>Functio laesa</i>

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

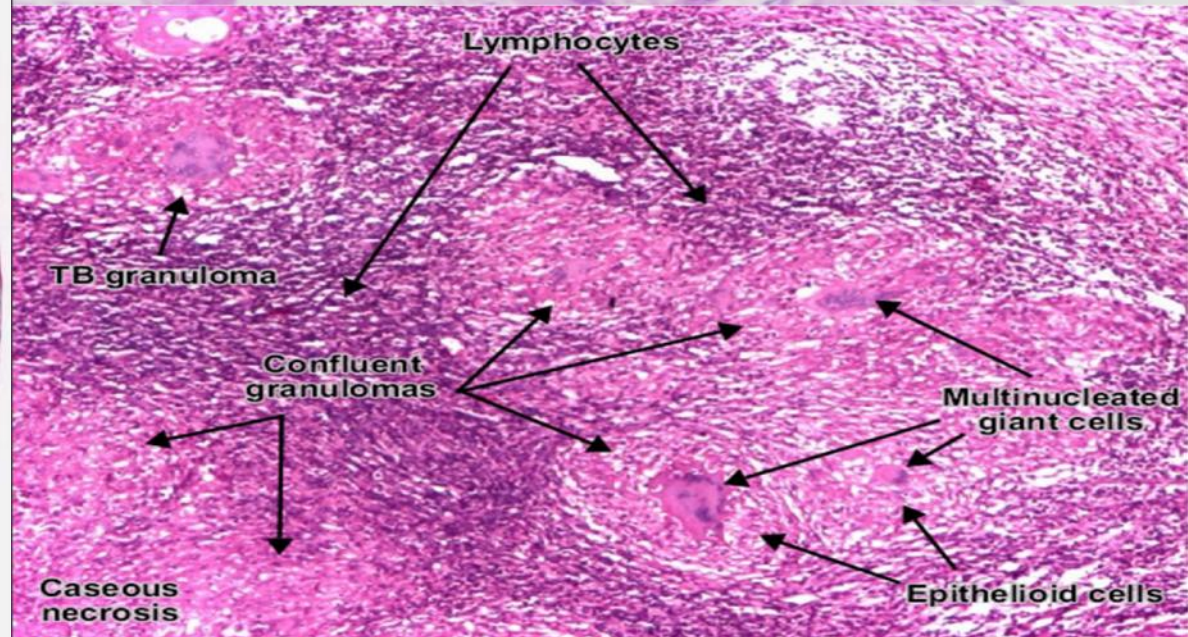
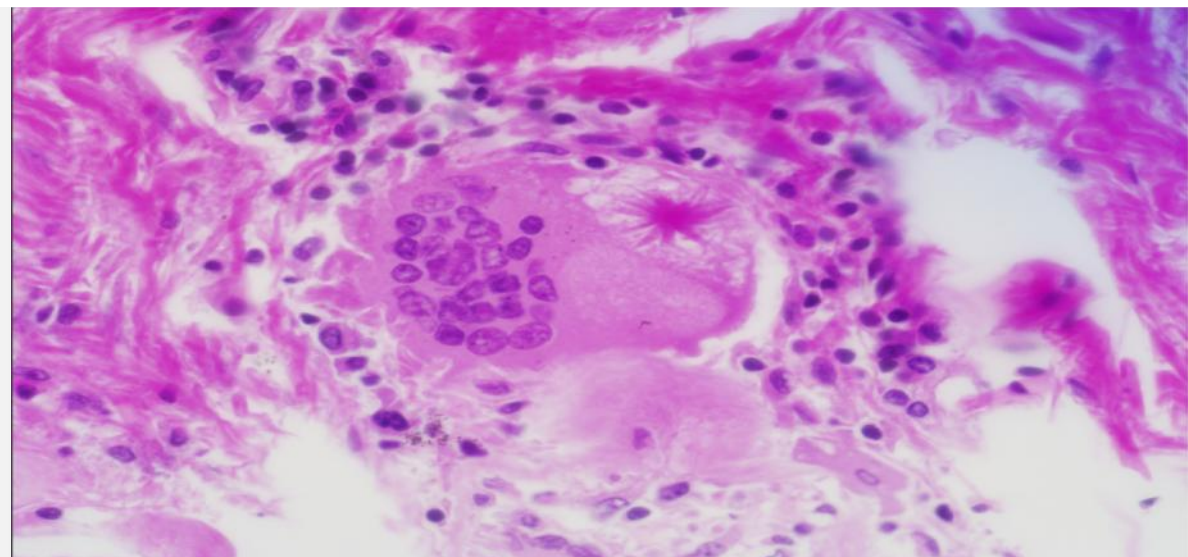


•**acute inflammation** : inflammation, usually of sudden onset, characterized by the classical signs in which the vascular and exudative processes predominate.

•**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





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

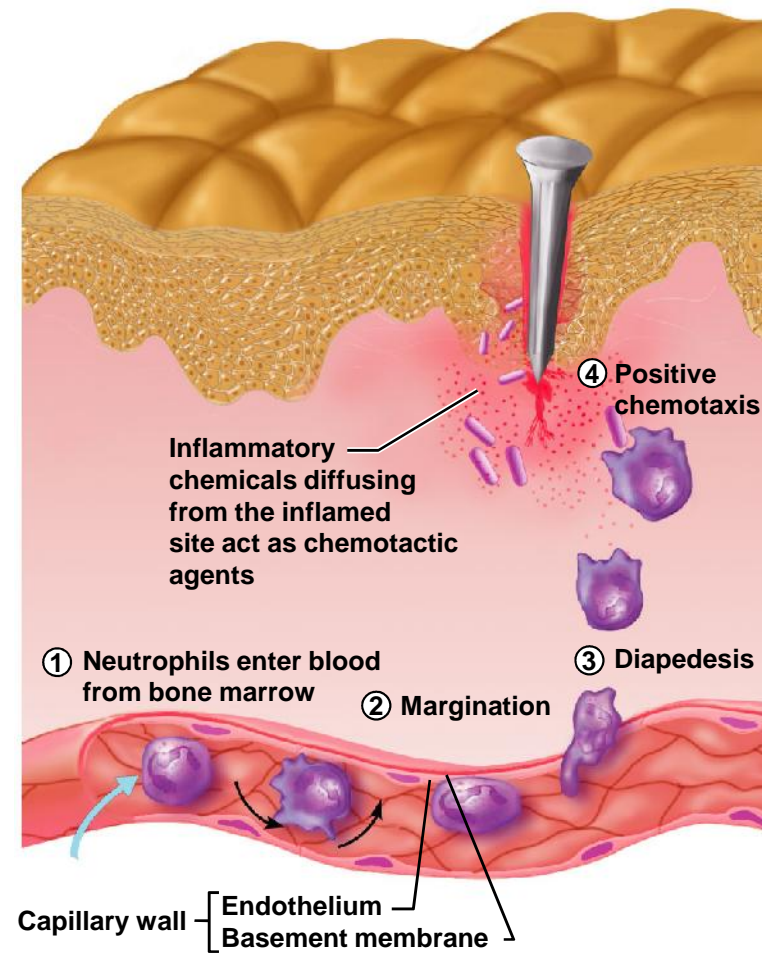
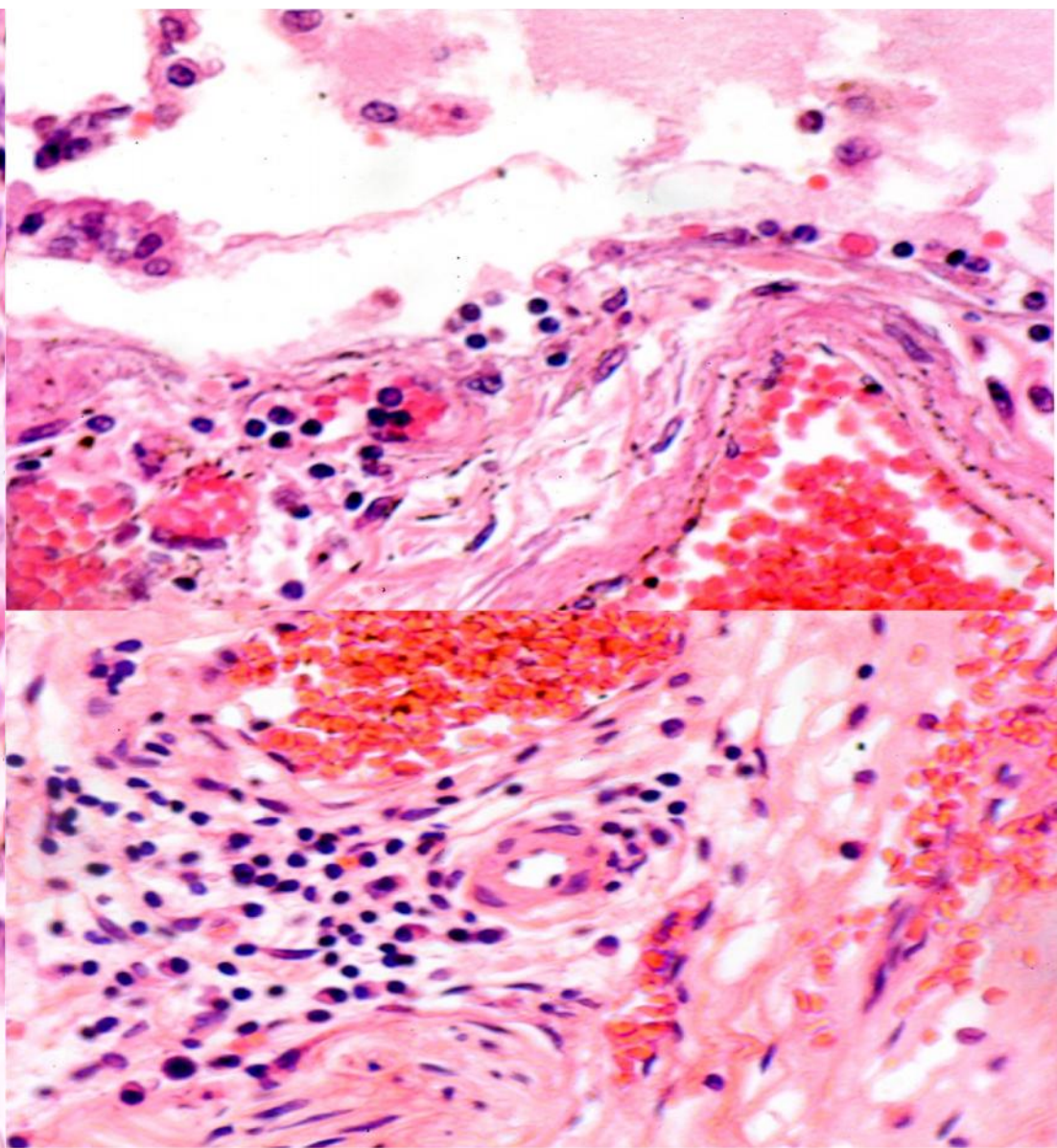
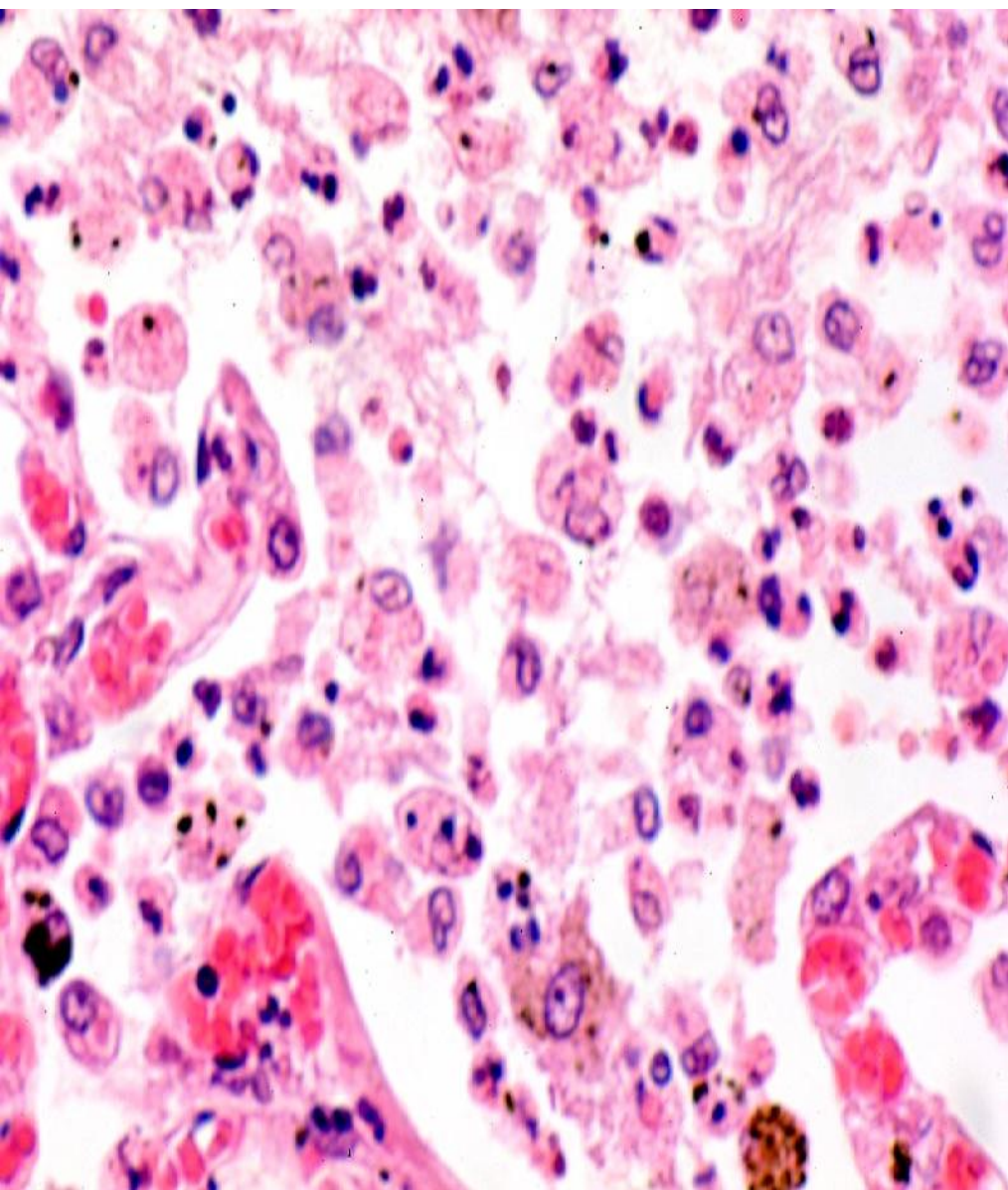
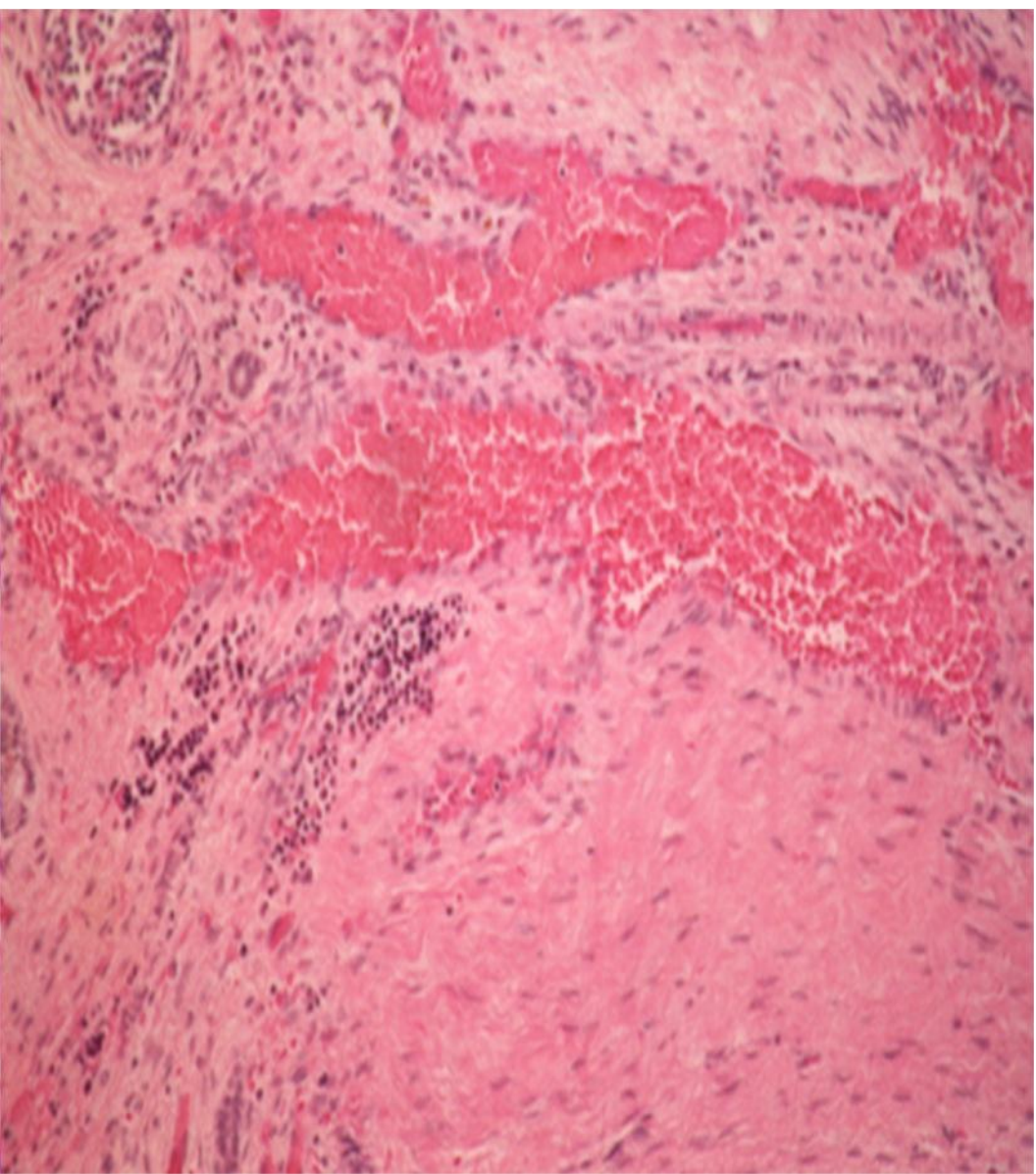
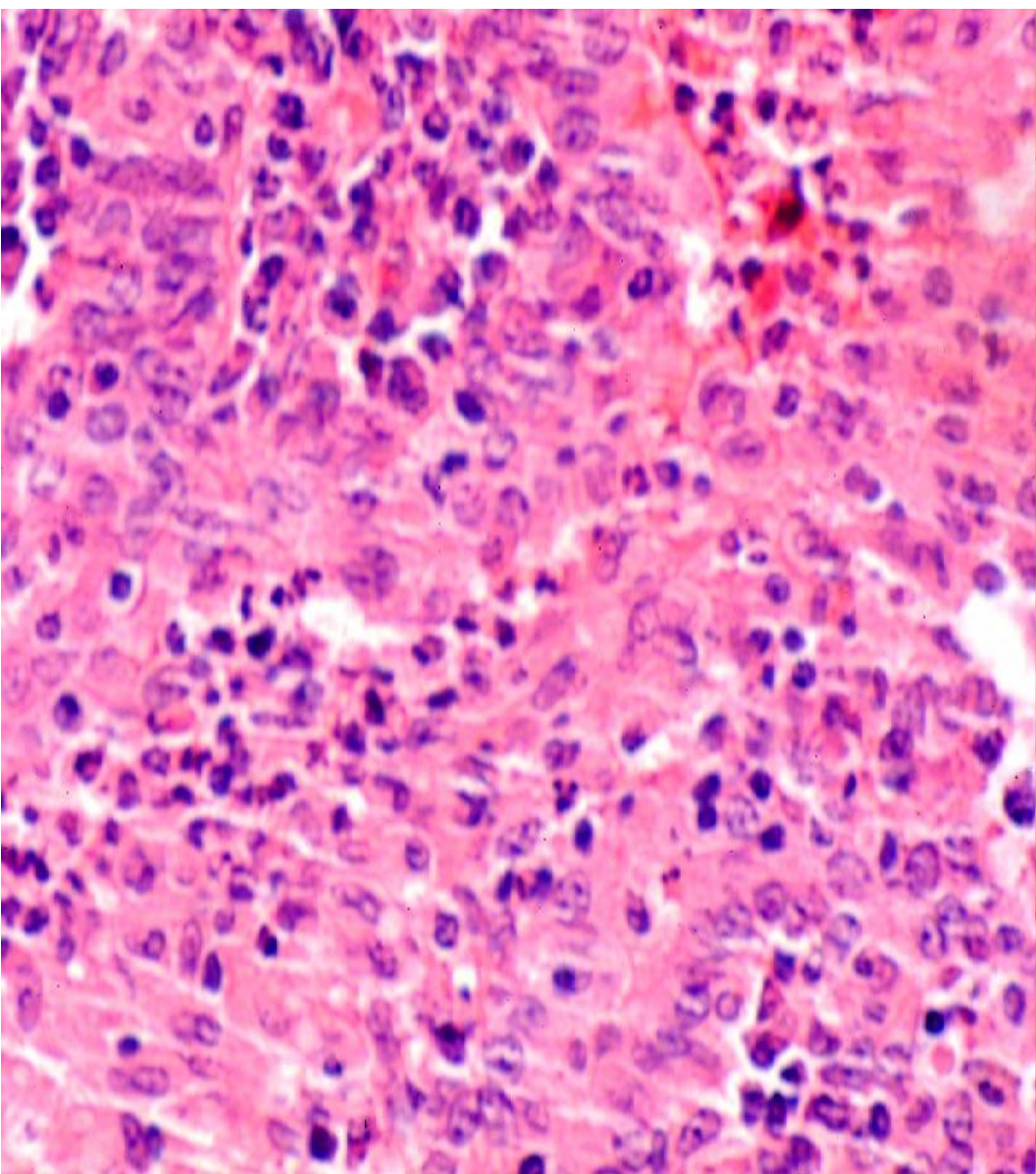
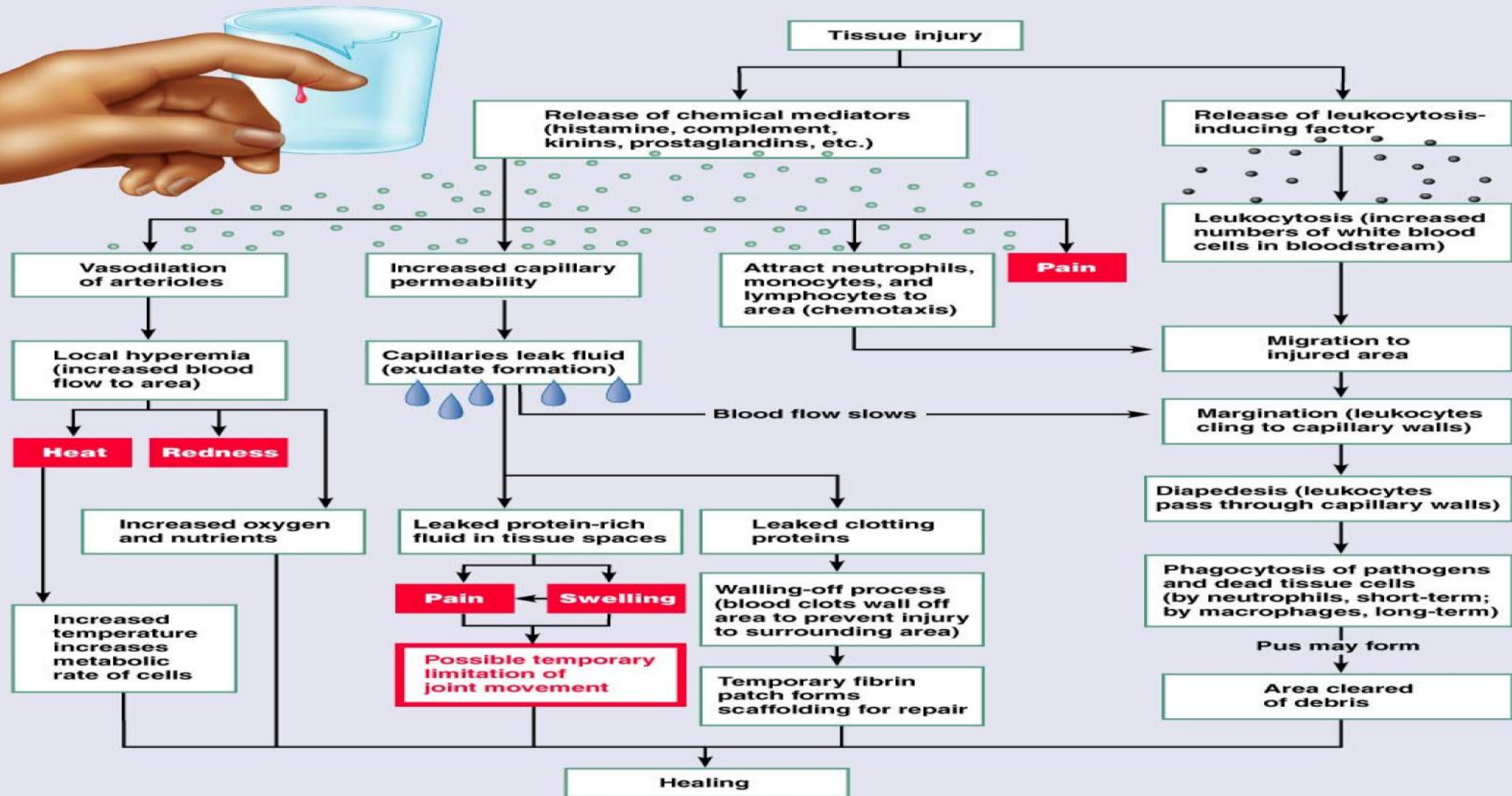


Figure 21.4





Innate defenses → Internal defenses





• **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 mesothelial 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.

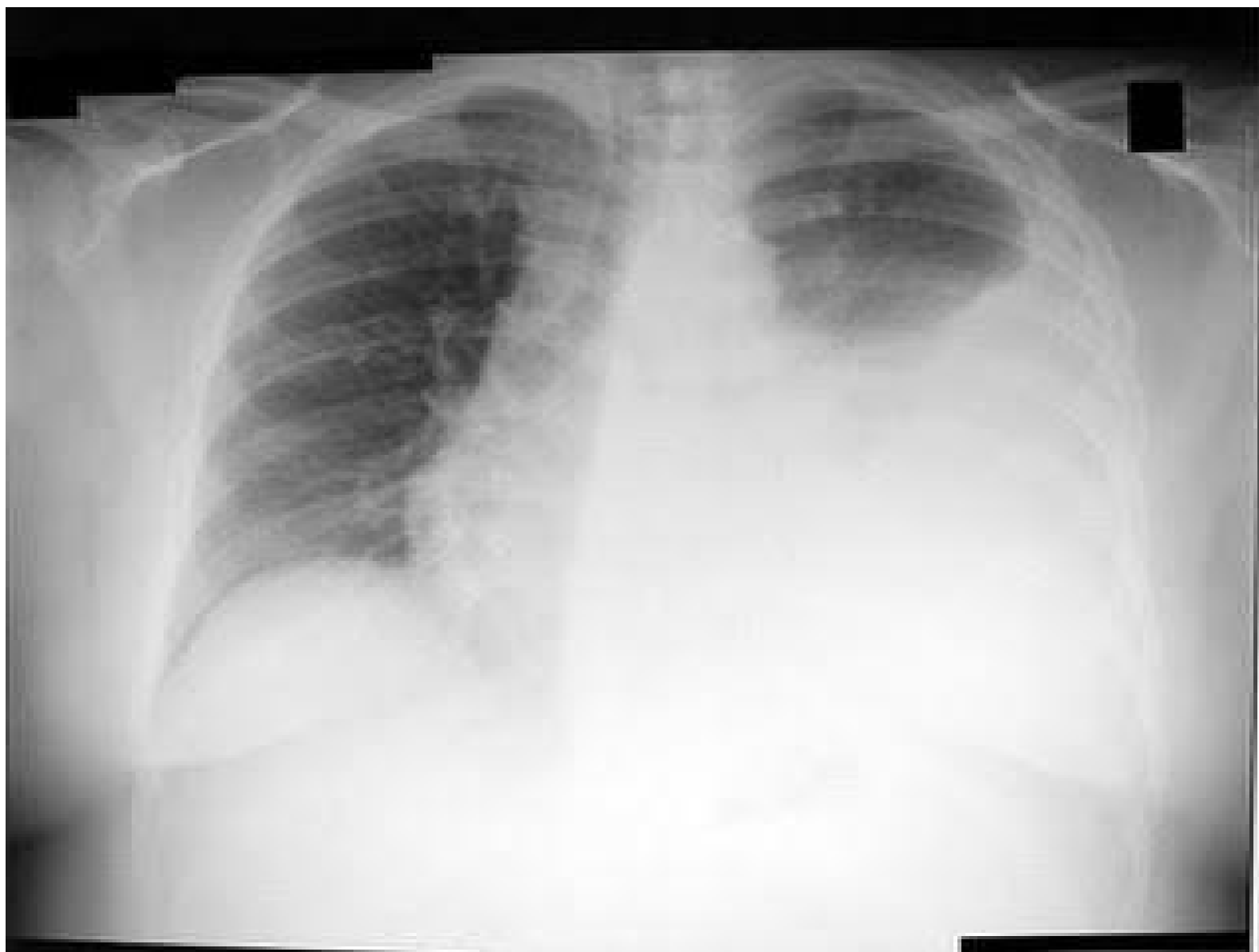
Fibrinous exudate is composed mainly of fibrinogen and fibrin. It is characteristic of **rheumatic carditis**, but is seen in all severe injuries such as strep throat and bacterial pneumonia. Fibrinous inflammation is often difficult to resolve due to the fact that blood vessels grow into the exudate 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 ^l
Specific gravity	< 1.012	> 1.020
Protein content	< 2 g/dL	> 2.9 g/dL
<u>fluid protein</u> serum protein	< 0.5	> 0.5
Difference of albumin content with blood albumin	> 1.2 g/dL	< 1.2 g/dL
<u>fluid LDH</u> upper limit for serum	< 0.6 or < $\frac{2}{3}$	> 0.6 or > $\frac{2}{3}$
<u>fluid glucose</u> serum glucose	< 0.8	> 0.8
Cholesterol content	< 45 mg/dL	> 45 mg/d

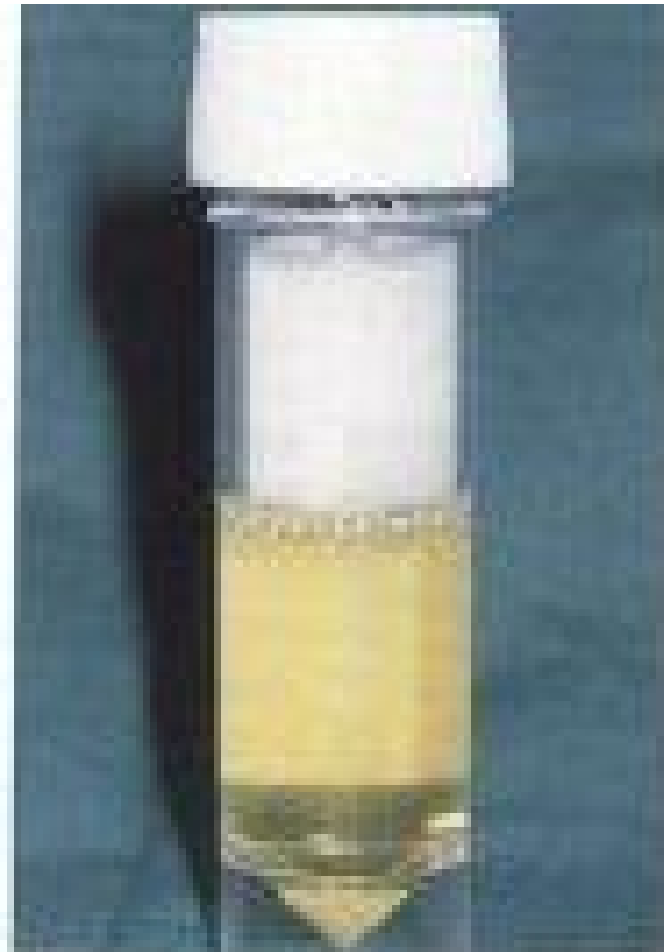




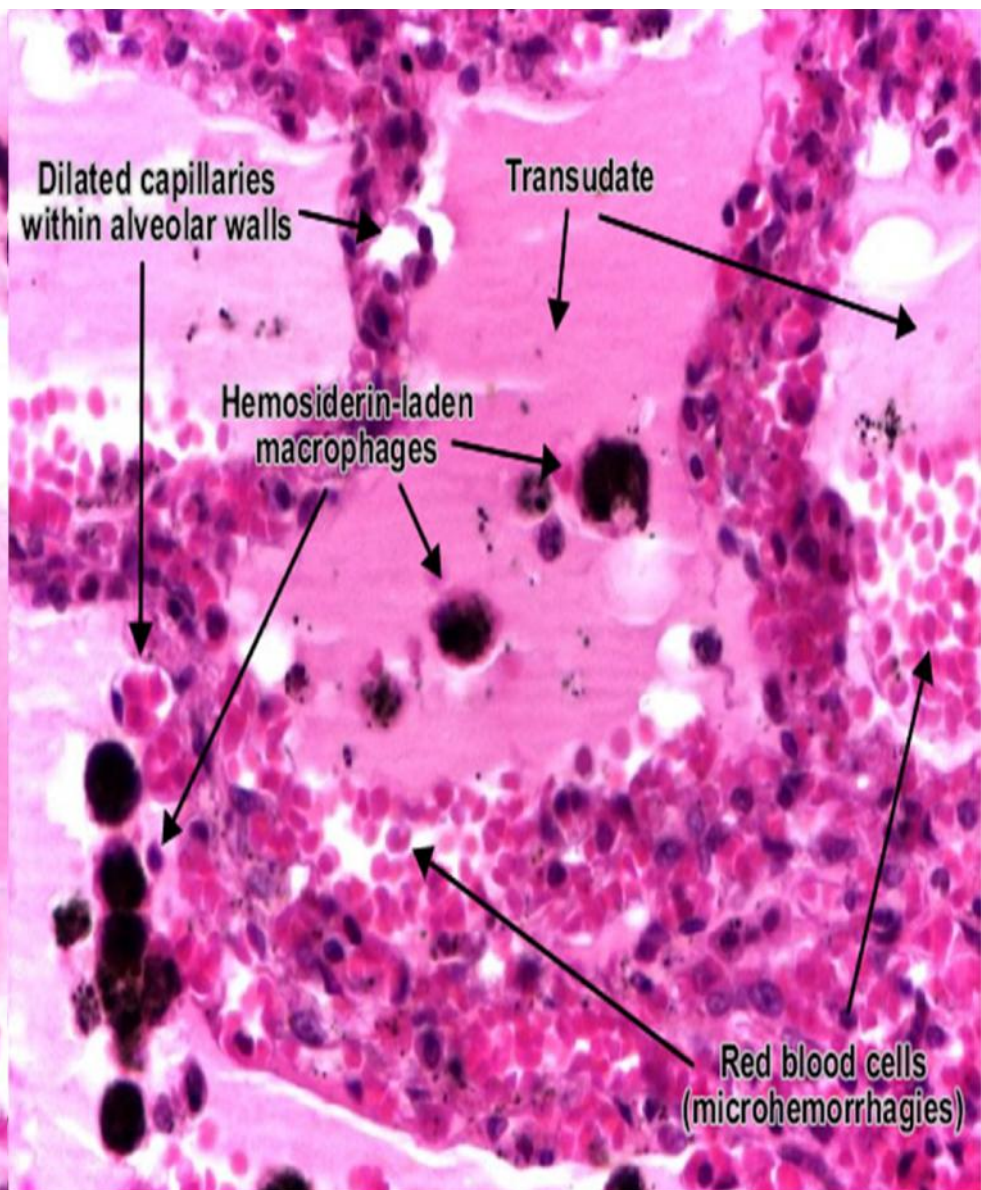
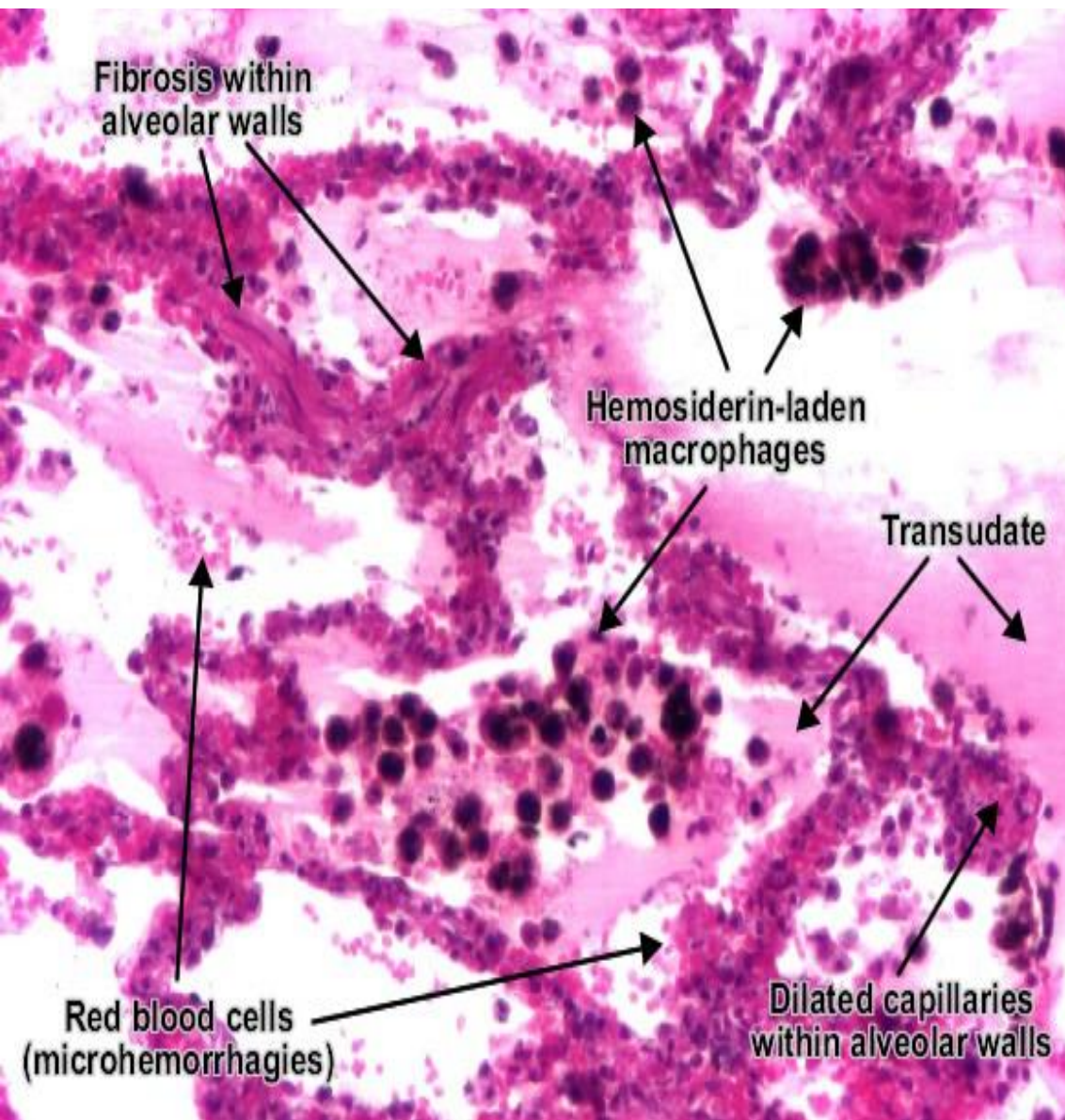
4.56 Blood-stained pleural aspirate. This patient had pleural secondaries from carcinoma of the breast.



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

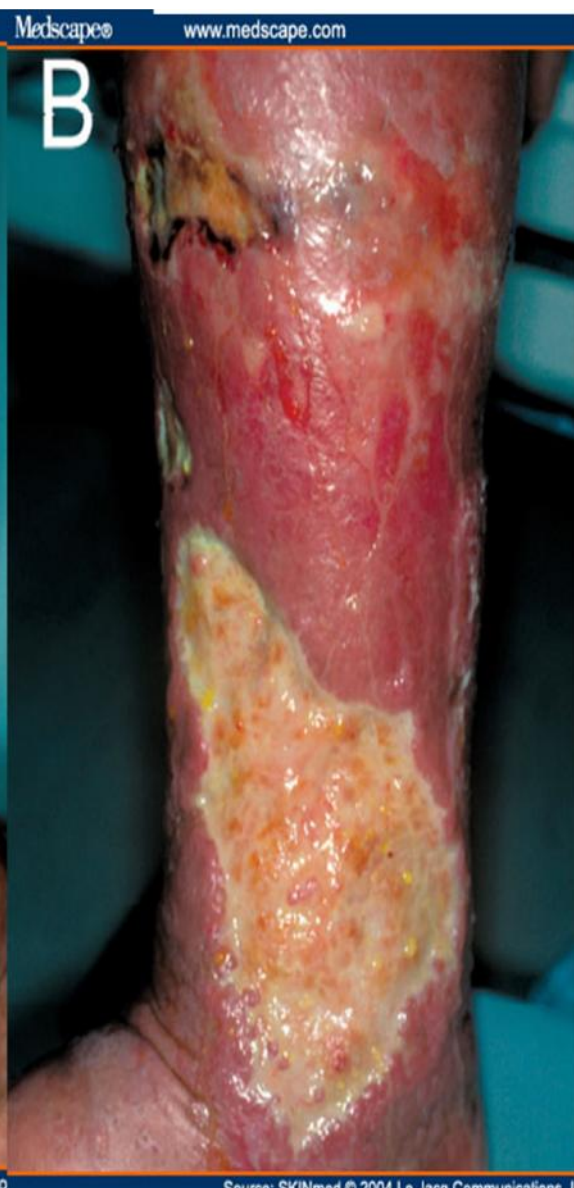


4.58 Pleural transudate. This pale effusion is typically found in patients with heart failure or other causes of generalized oedema.



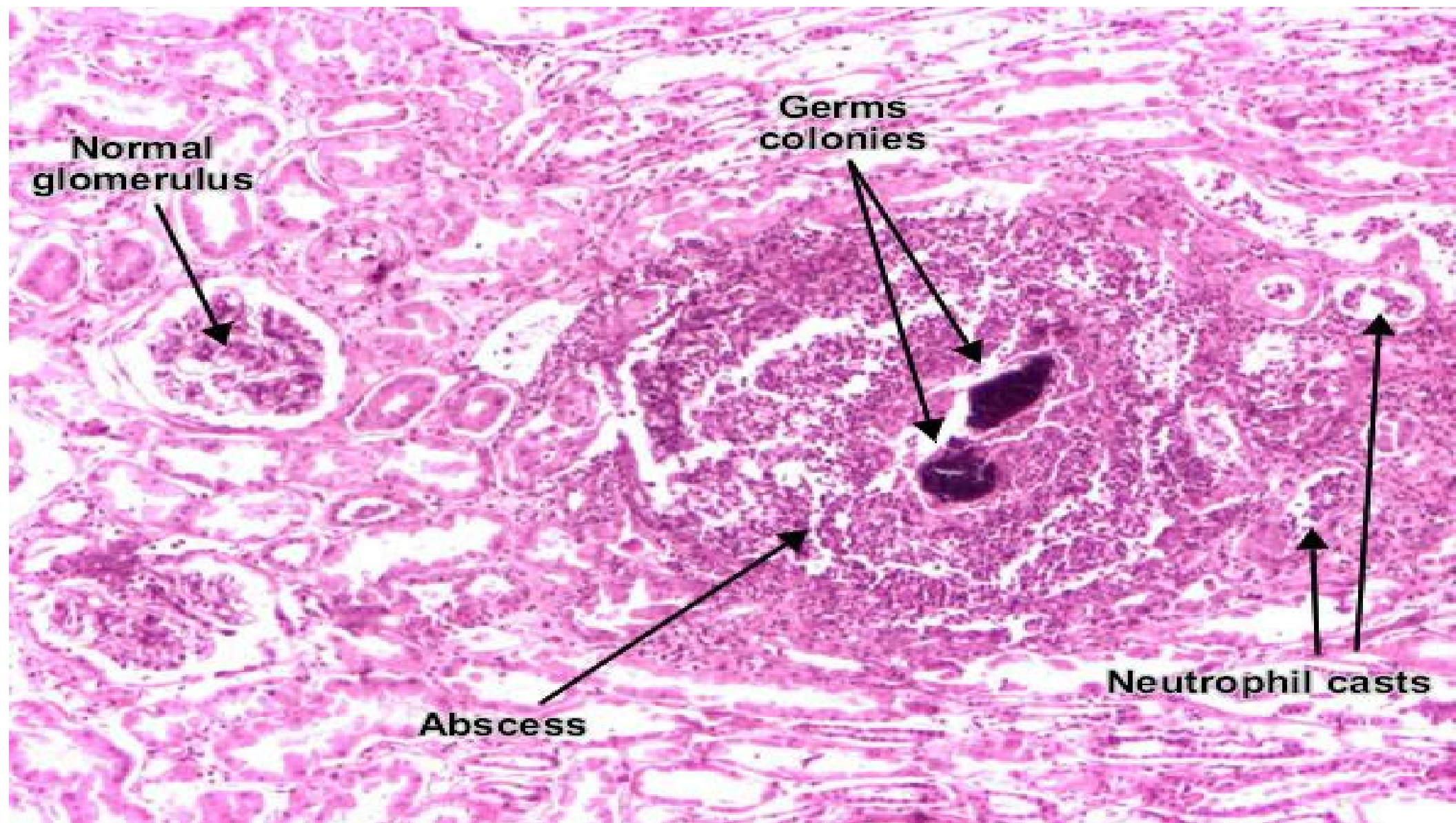


Exudate



Source: SKINmed © 2004 Le Jacq Co

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Information only

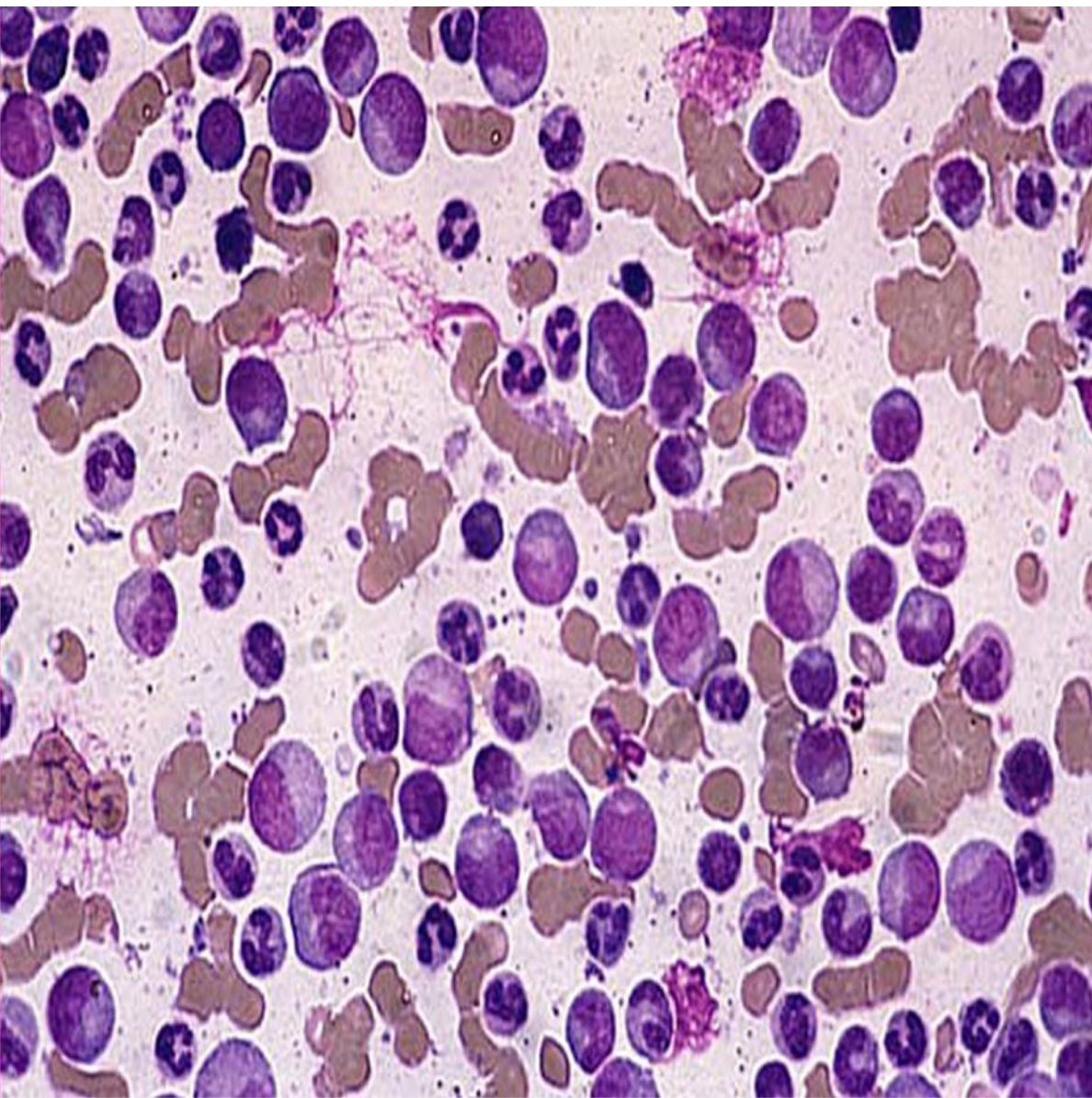
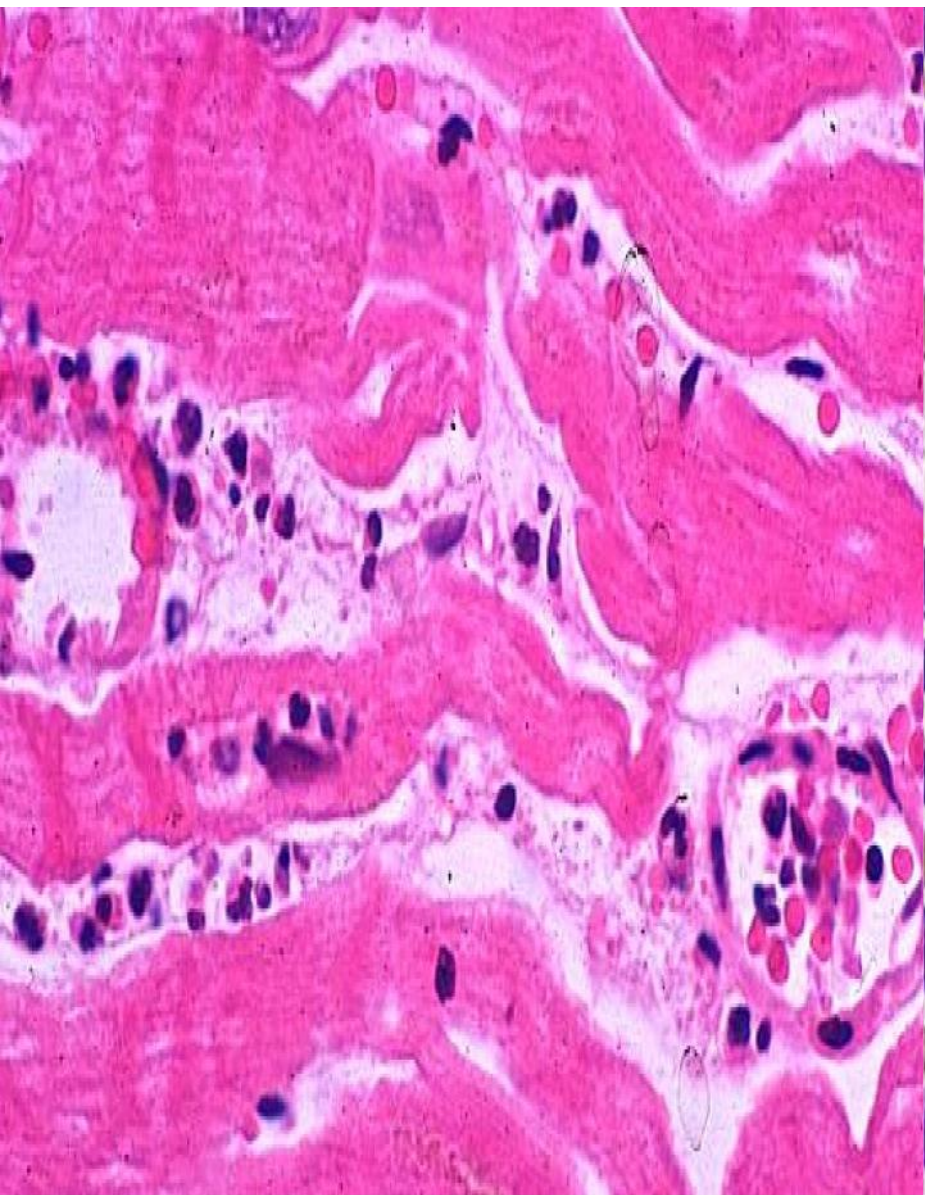
Rivalta test is used in order to differentiate a transudate from an exudate^[1]. A test tube is filled with distilled water and acetic acid is added. To this mixture one drop of the effusion to be tested is added. If the drop dissipates, the test is negative, indicating a transudate. If the drop precipitate, 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, Rullièrè 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) <ul style="list-style-type: none">▪ Alpha (α) and beta (β)▪ Gamma (γ)	Secreted by leukocytes, fibroblasts, and other cells; antiviral effects; activate macrophages and NK cells 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 _H 1
Interleukins (ILs) <ul style="list-style-type: none">▪ IL-1▪ IL-2▪ IL-3	Secreted by activated macrophages; promotes inflammation and T cell activation; causes fever (a pyrogen that resets the thermostat of the hypothalamus) Secreted by T cells; stimulates proliferation of T cells; activates NK cells Stimulates production of leukocytes and mast cells

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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 _H 2; 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 secrete 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 _H 1 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

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Table 21.4.3

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

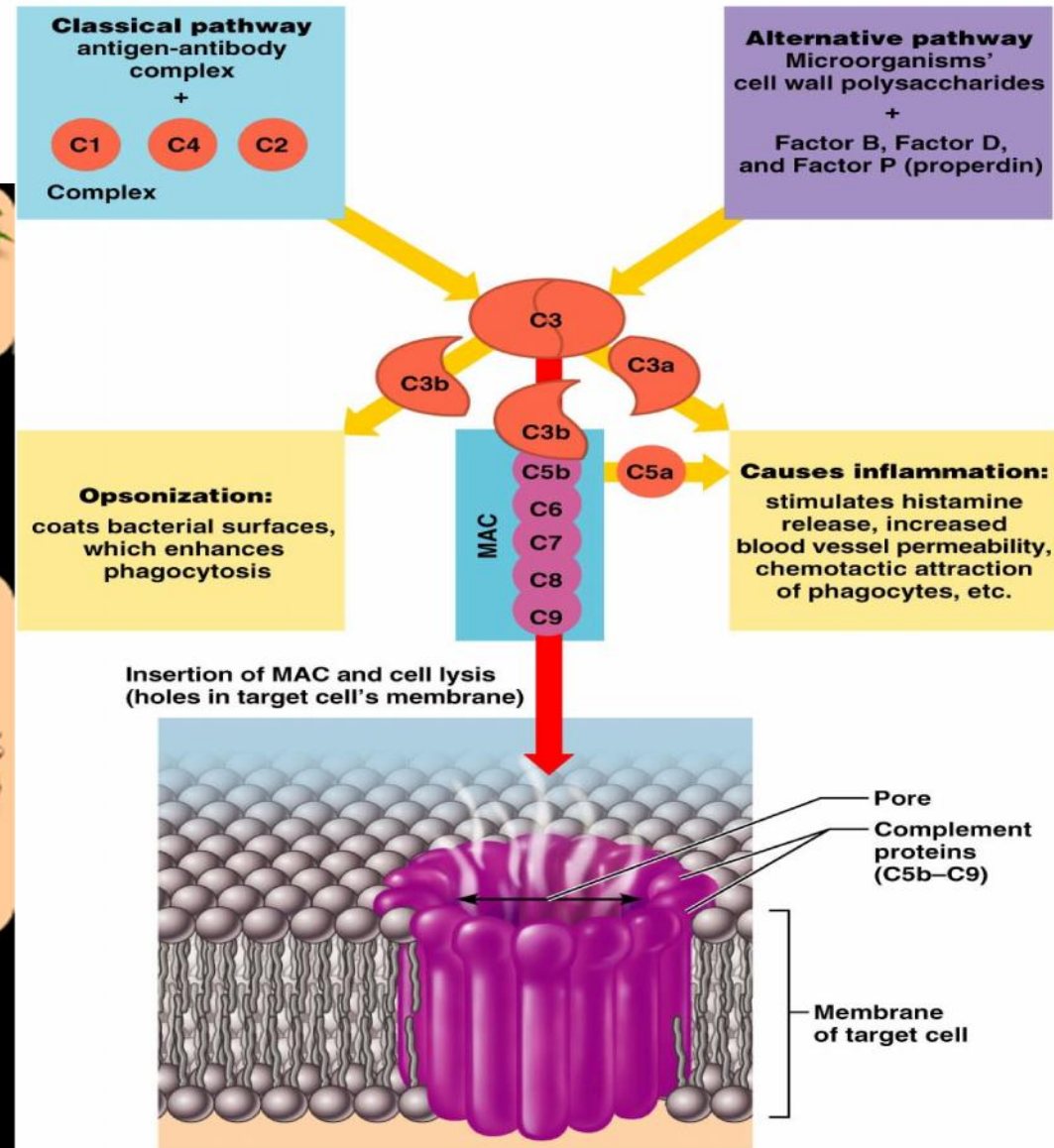
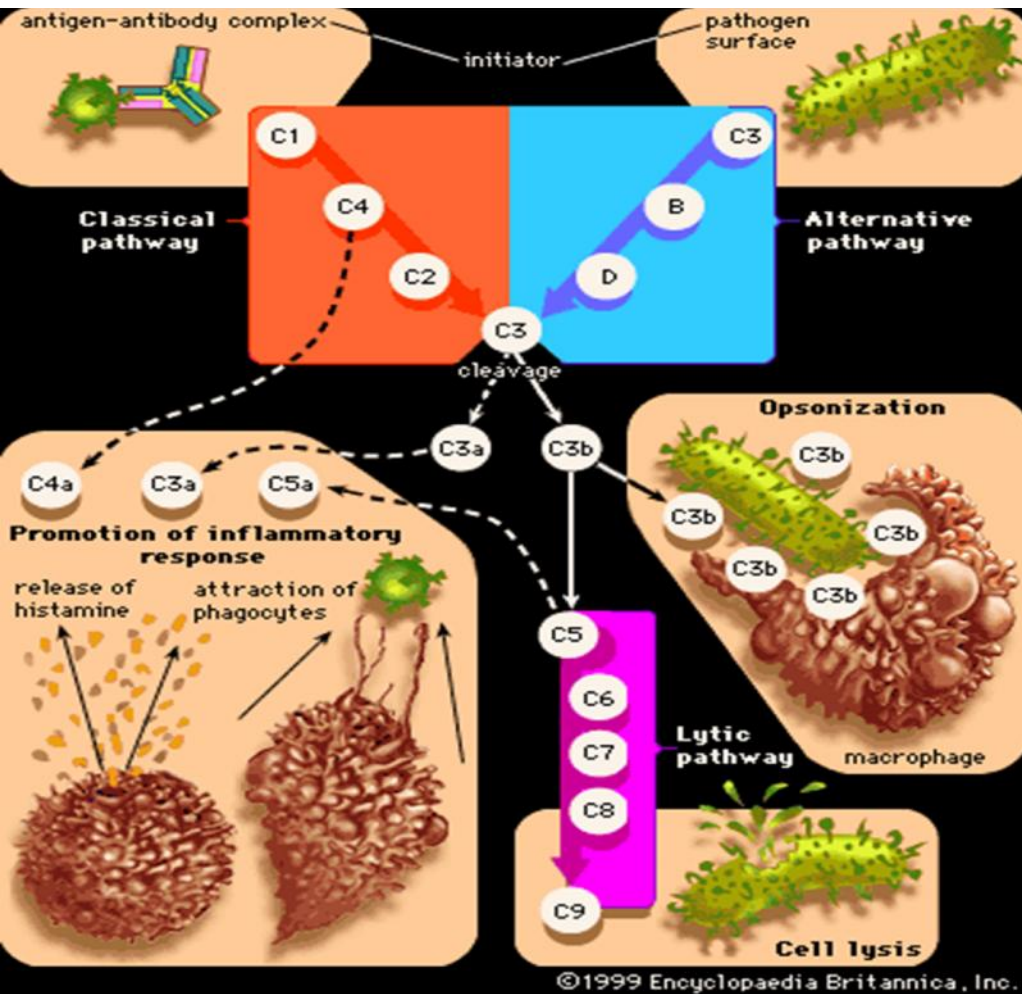
Complement

- 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



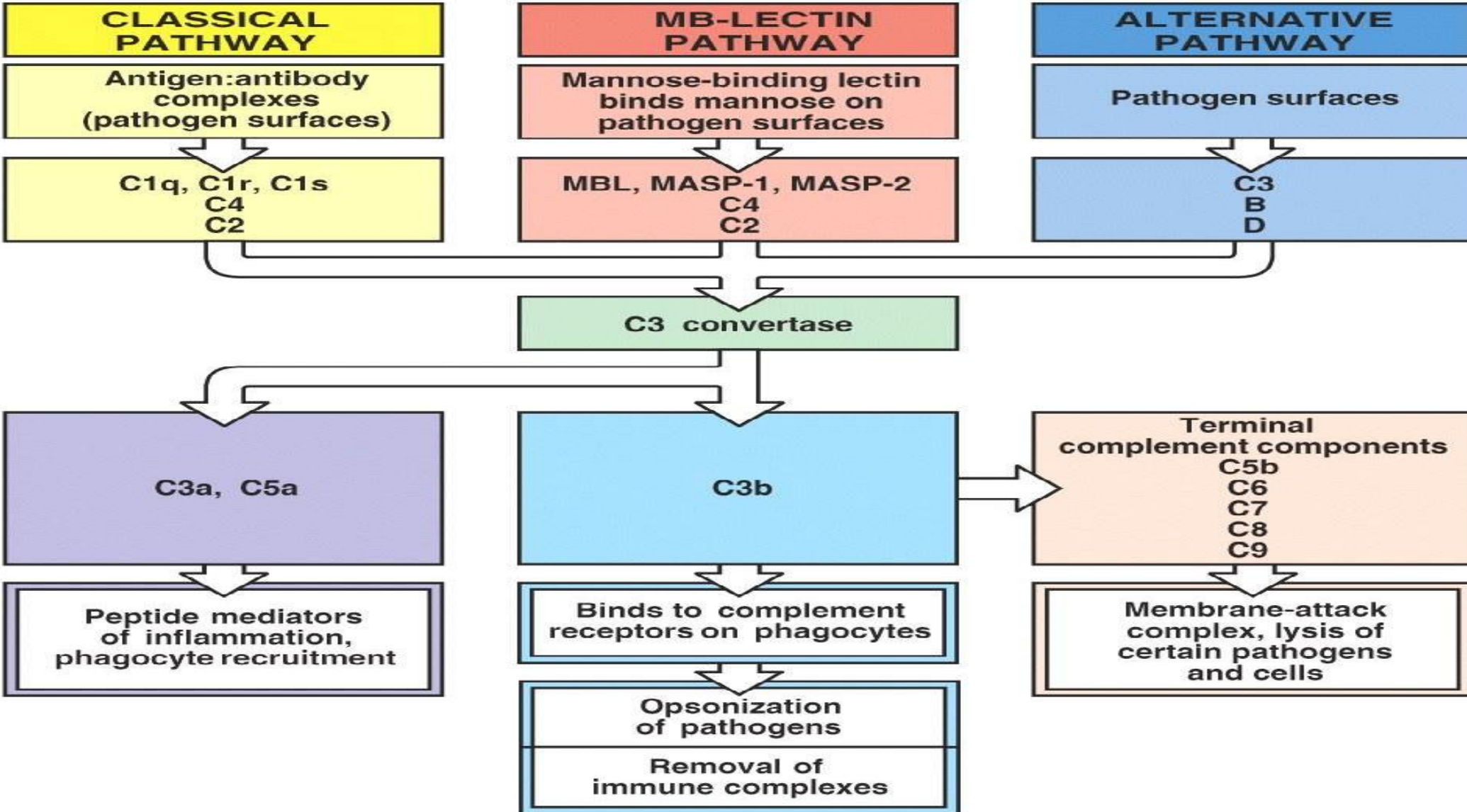


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

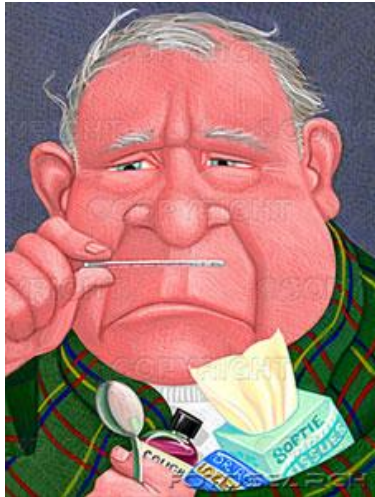
Part v : Fever

Fever = pyrexia ← IL1

- 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 HELPER cells)**
- **Speed up metabolism for tissue repair**
- **Increases the antiviral effect of interferons**

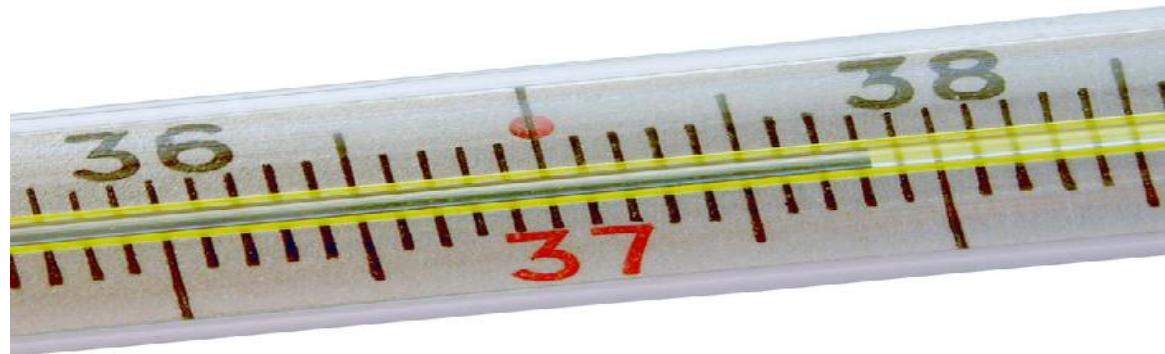


- IFNs are a class of anti-viral proteins that disrupt viral multiplication
- Not very effective (short-lived and no effect for infected cells)
- Nonspecific to viral types

Fever can be classified as low (oral reading of 99° to 100.4° F [37.2° to 38° C]), moderate (100.5° to 104°

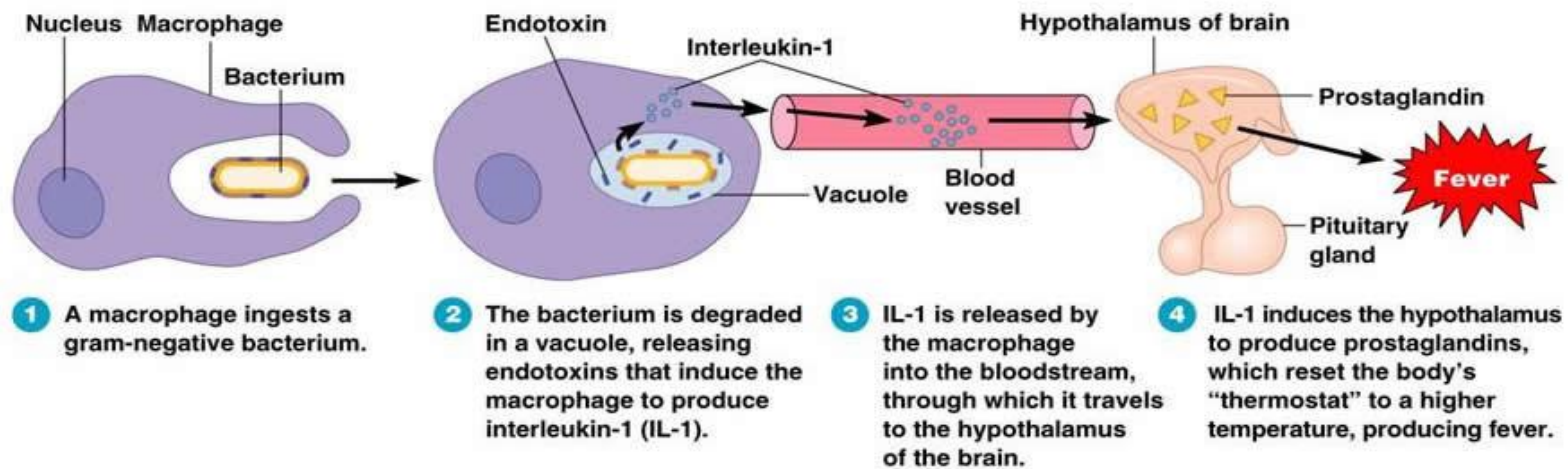
Fever

- 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, HEART BLOCK.



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.



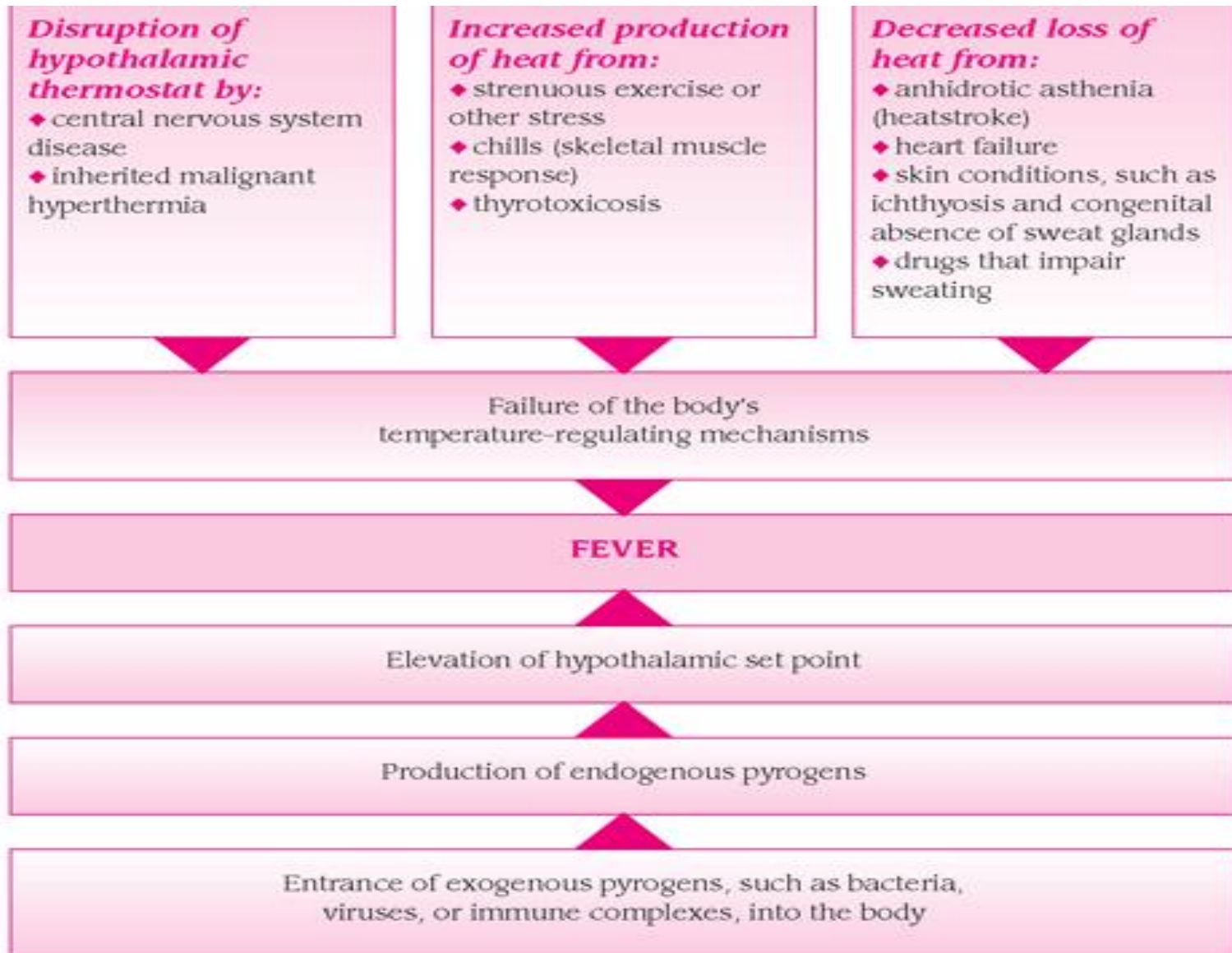
Fever

- 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**
 - **INCREASE IGA**



LOW GRADE FEVER LET IT BE

SECRETION OF IGA , KEEP YOU
HEALTHIER.

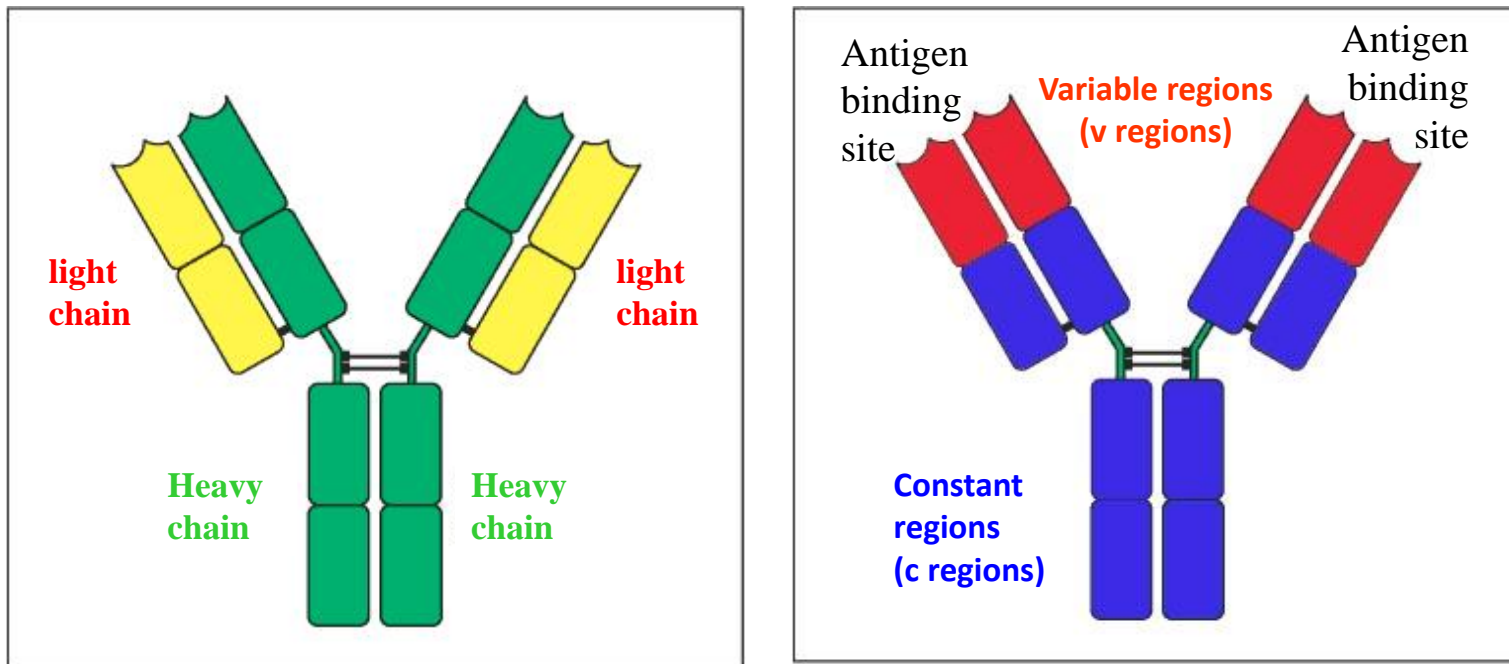


Immunoglobulins

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

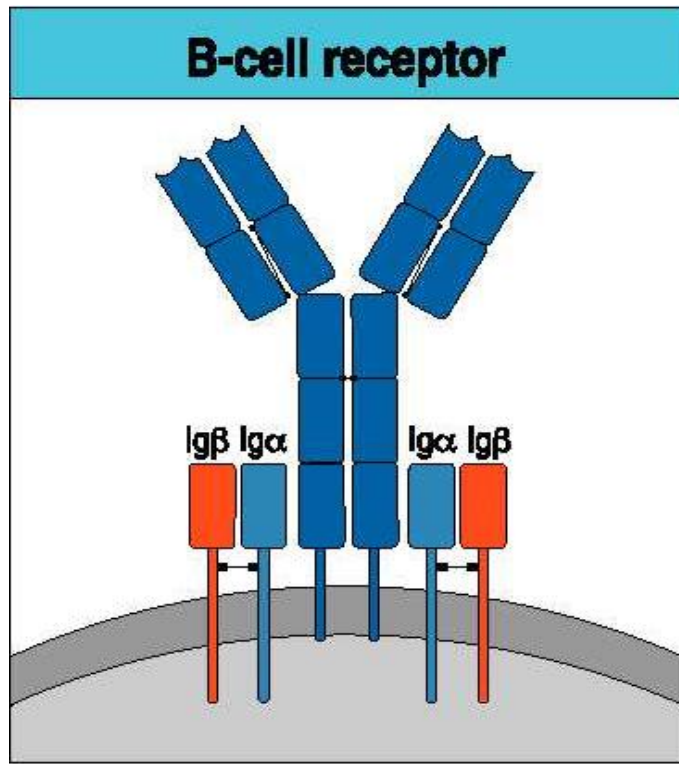
Immunoglobulins (i.e., antibodies)



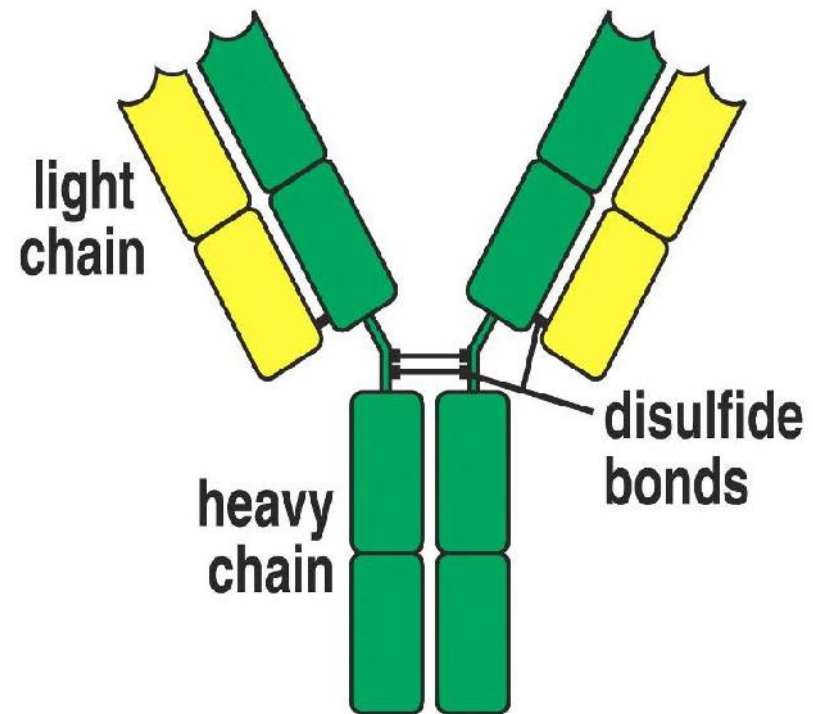
Antibodies with different specificities differ in the amino acid sequence of the variable regions of the heavy and light chains

The two heavy chains are identical and the two light chains are identical so the **two antigen binding sites are identical**

Two Forms of Immunoglobulin



Membrane-bound receptor



Soluble antibody

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

Immunoglobulin Classes

I. IgG

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

Immunoglobulin Classes

II. IgM

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

Immunoglobulin Classes

III. IgA

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

Immunoglobulin Classes

IV. IgD

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

Immunoglobulin Classes

V. IgE

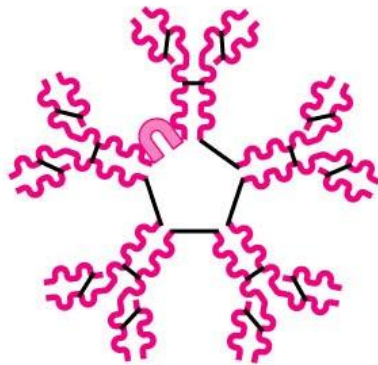
- u Structure: Monomer**
- u Percentage serum antibodies: 0.002%**
- u Location: Bound to mast cells and basophils throughout body. Blood.**
- u Half-life in serum: 2 days**
- u Complement Fixation: No**
- u Placental Transfer: No**
- u Known Functions: Allergic reactions. Possibly lysis of worms.**

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.



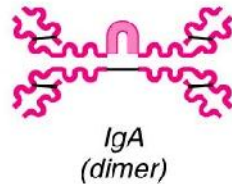
IgM
(pentamer)

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.

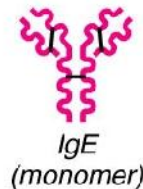
TABLE 21.3 Immunoglobulin Classes *(continued)*



IgG 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.



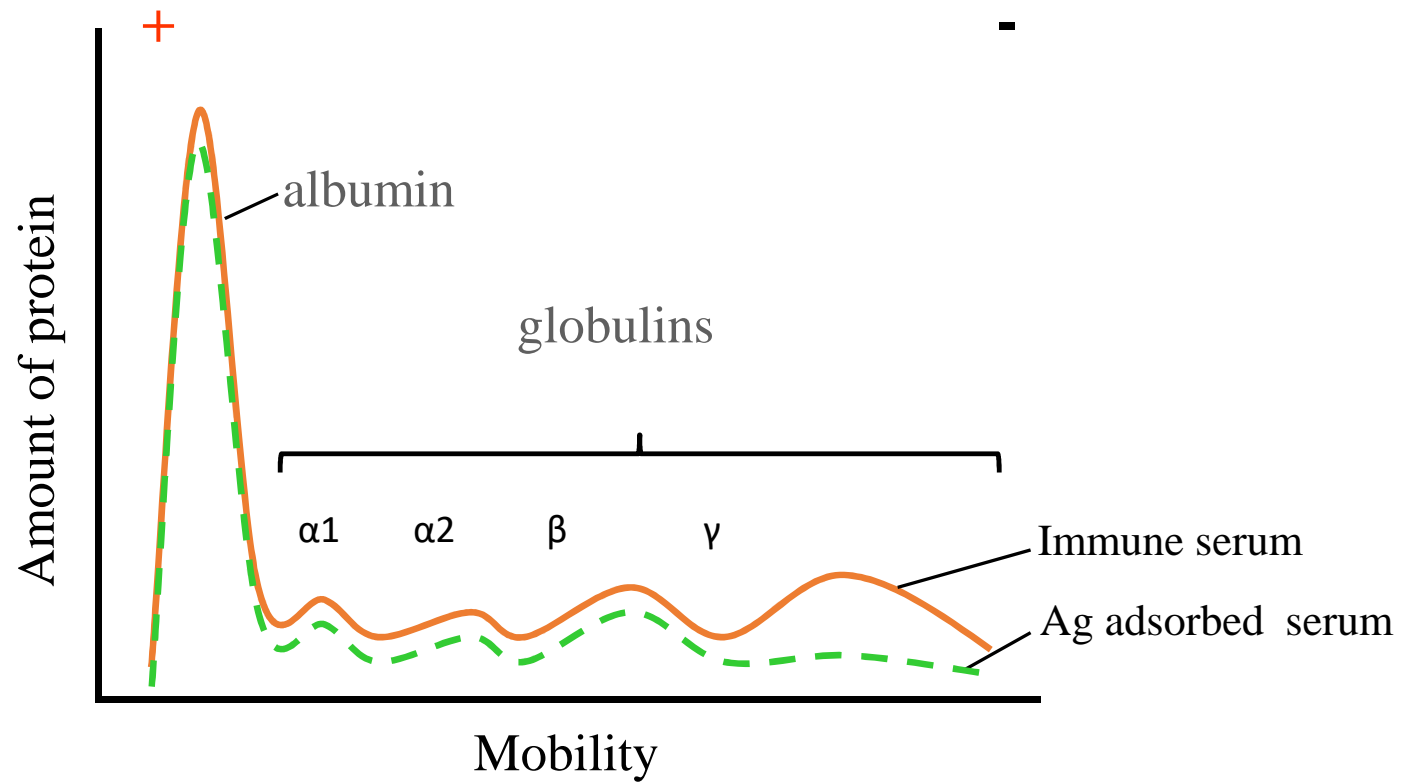
IgA monomer exists in limited amounts in plasma. The dimer (illustrated), referred to as secretory IgA, is found in body secretions such as saliva, sweat, intestinal juice, and milk, and helps prevent attachment of pathogens to epithelial cell surfaces (including mucous membranes and the epidermis).

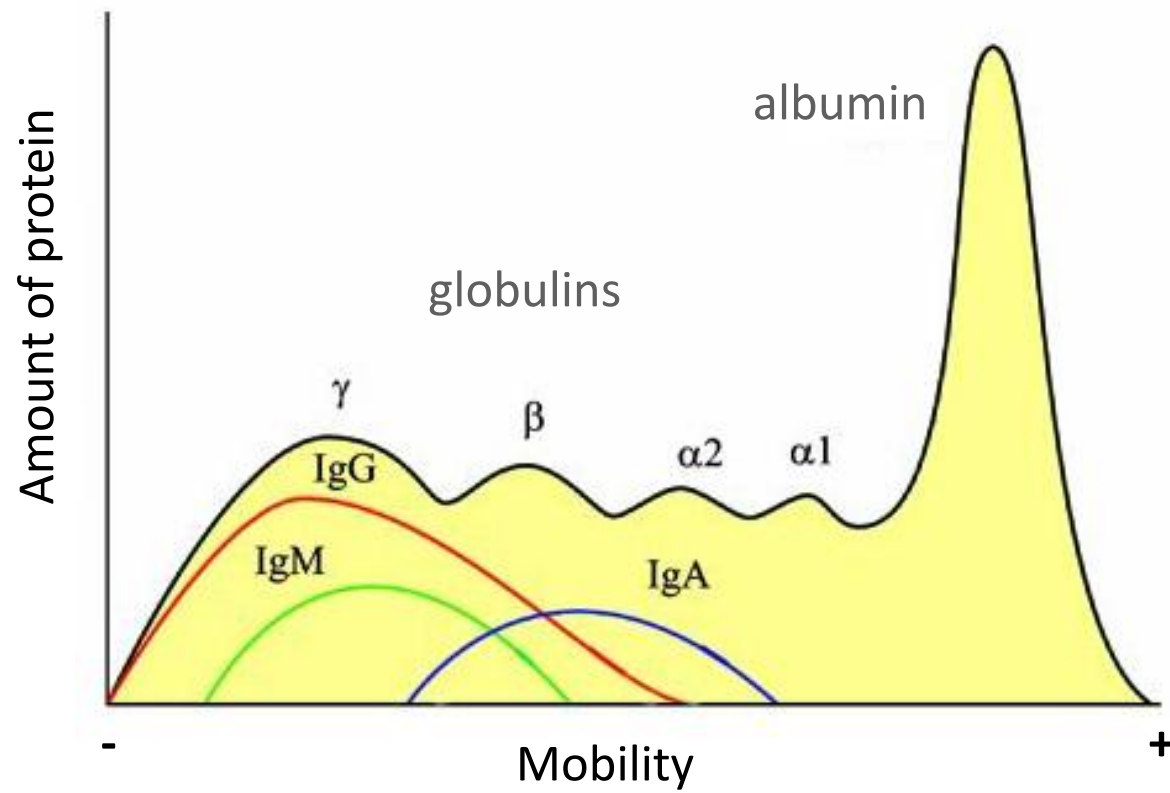


IgE is slightly larger than the IgG antibody. It is secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. Its stem region becomes bound to mast cells and basophils, and when its receptor ends are triggered by an antigen, it causes the cells to release 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.





ADAPTIVE IMMUNE SYSTEM

T-lymphocytes

T-cytotoxic → Cytotoxic

B-lymphocytes

Plasma cells → Antibodies

Response takes 7 to 10 days

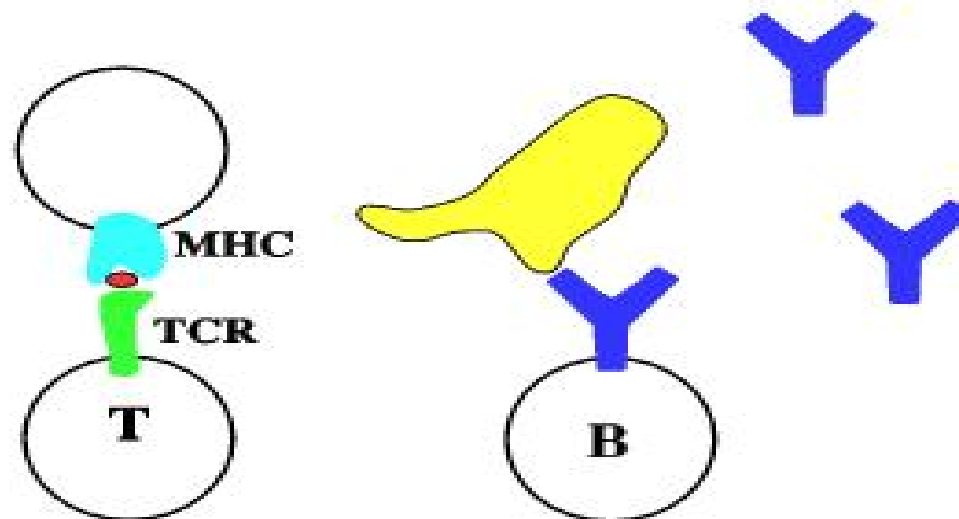
Adaptive Immune System

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

T versus B cell Response

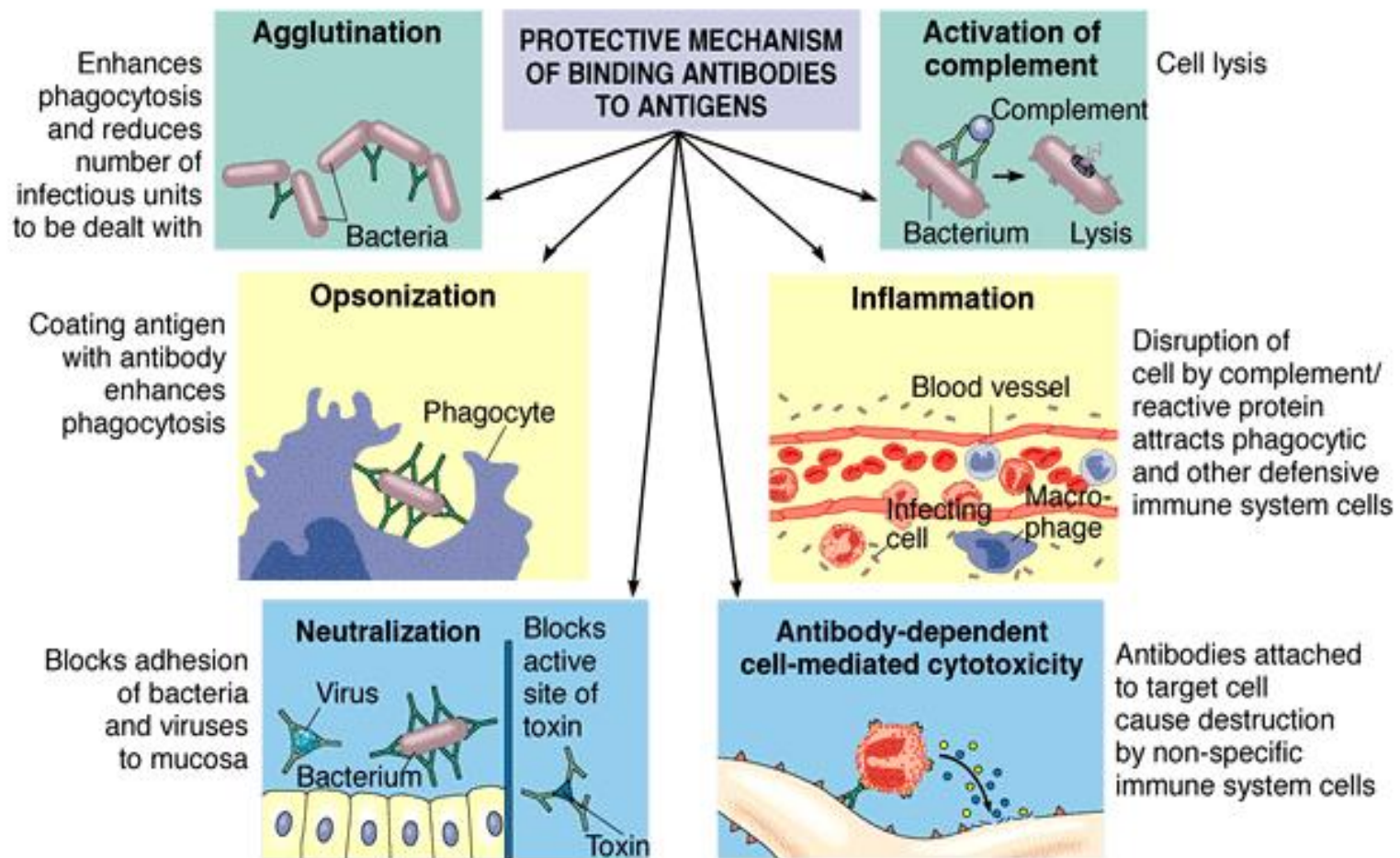
B cells recognise native antigen

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.

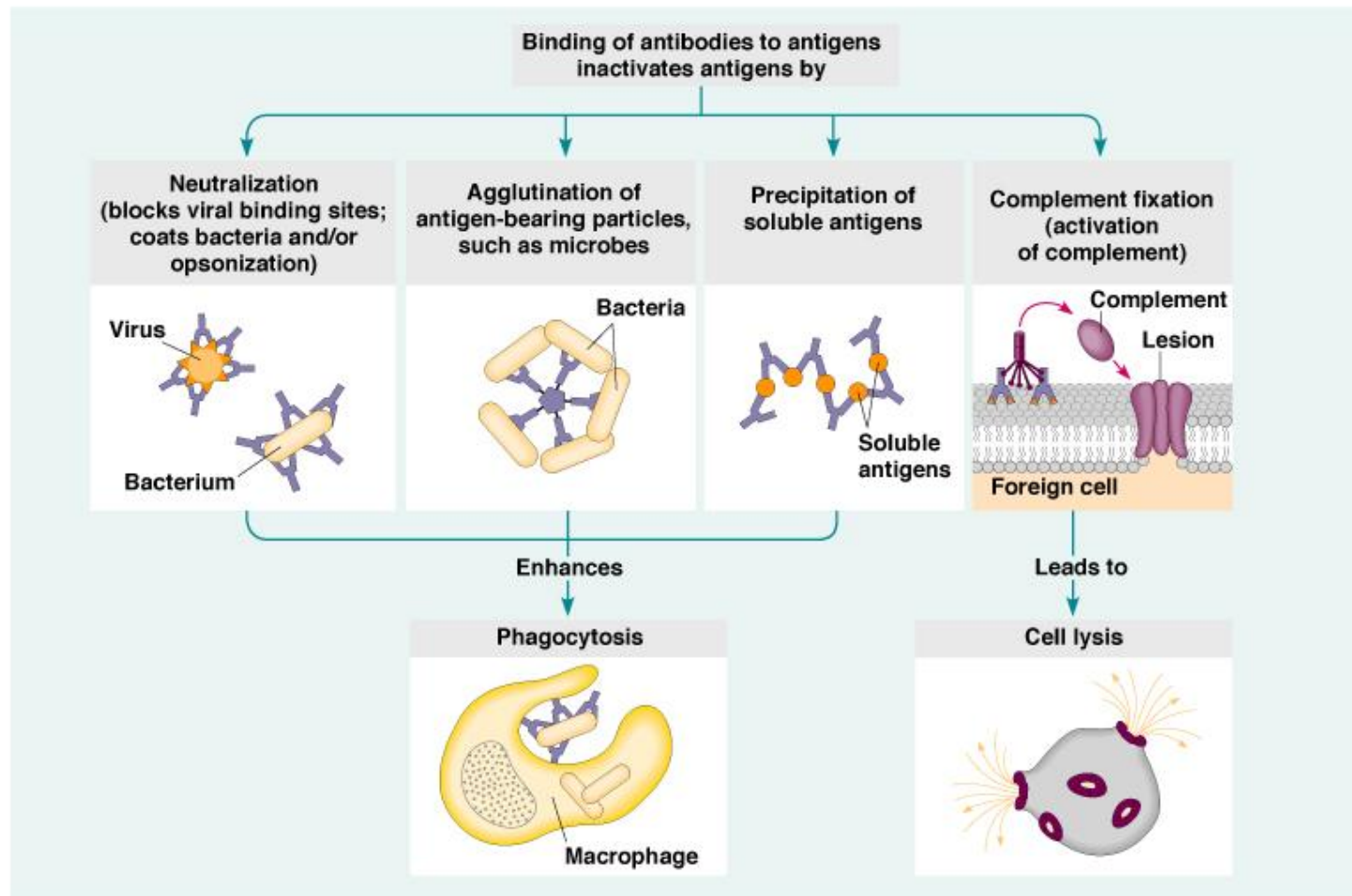
- IgM (decavalent) is more effective than IgG (bivalent).
- **Hemagglutination:** Agglutination of red blood cells. Used to determine ABO blood types and to detect influenza and measles viruses.

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- **Therapeutic** (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 to help it 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 1 st dose given at age <12 mos 8 wks (as final dose): if 1 st dose given at age 12–24 mos No further doses needed: if 1 st 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 2 nd 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 1 st dose given at age <12 mos and current age <24 mos 8 wks (as final dose): if 1 st dose given at age ≥12 mos or current age 24–59 mos No further doses needed: for healthy children if 1 st 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 1 st dose given at age <12 mos and current age <11 yrs 5 yrs: if 1 st dose given at age ≥12 mos and 3 rd dose given at age <7 yrs and current age ≥11 yrs 10 yrs: if 3 rd 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 1 st 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 schedule¹ — United States, 2003

Vaccine	Range of recommended ages				Catch-up vaccination ²				Preadolescent assessment			
	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	24 mos	4–6 yrs	11–12 yrs	13–18 yrs
Hepatitis B²	HepB #1	only if mother HBsAg (+)										
			HepB #2									
				HepB #3								
Diphtheria, Tetanus, Pertussis³			DTaP	DTaP	DTaP		DTaP			DTaP		Td
<i>Haemophilus influenzae</i> Type b⁴			Hib	Hib	Hib		Hib					
Inactivated Polio			IPV	IPV			IPV			IPV		
Measles, Mumps, Rubella⁵						MMR #1				MMR #2		MMR #2
Varicella⁶							Varicella			Varicella		
Pneumococcal⁷			PCV	PCV	PCV	PCV			PCV	PPV		
Hepatitis A⁸											HepA series	
Influenza⁹												Influenza (yearly)

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. **2.** 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:

1) 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

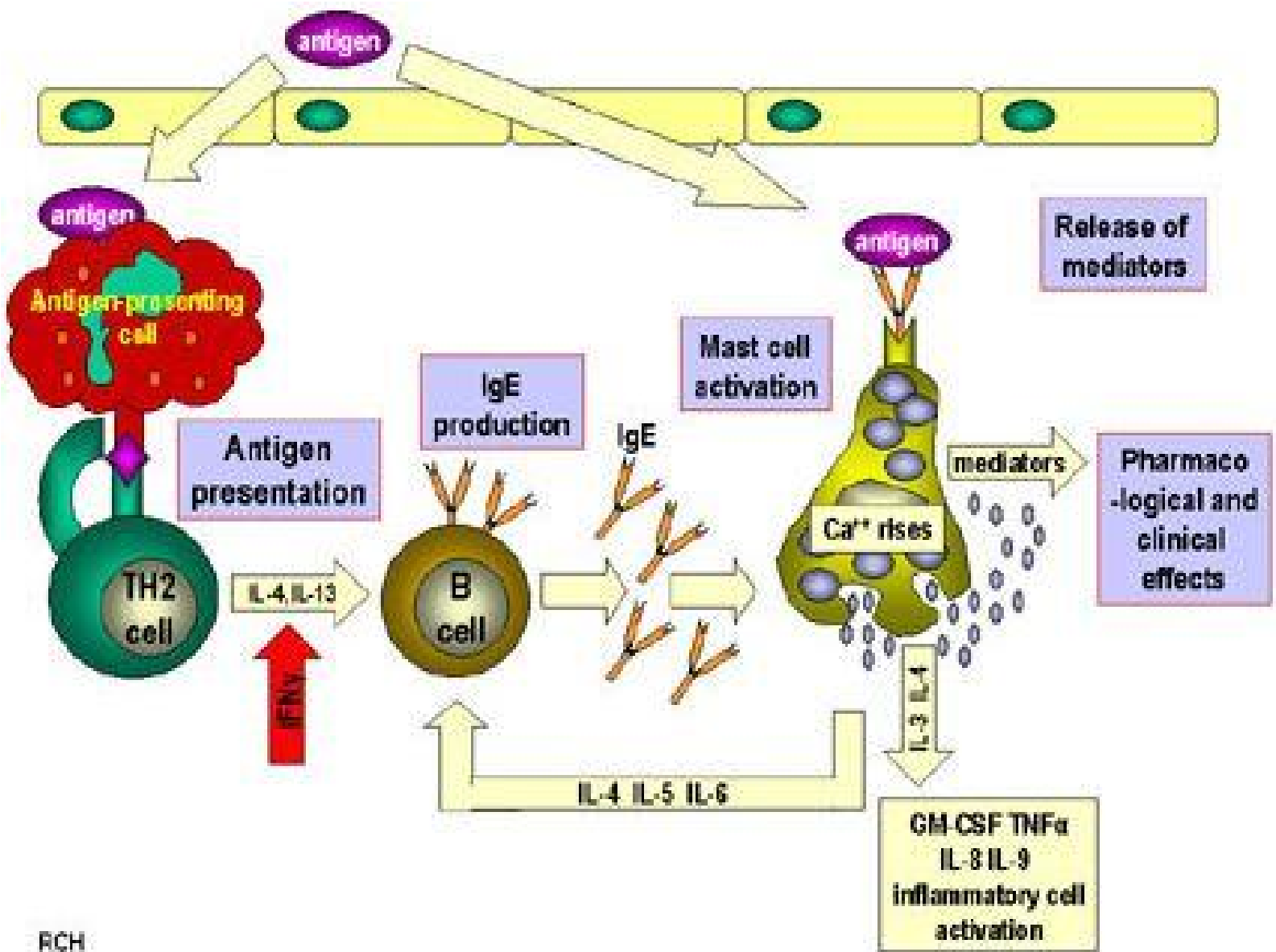
- * Systemic form of Type I hypersensitivity
- * Exposure to allergen to which a person is previously sensitized
- * Allergens:
 - Drugs: penicillin
 - Serum injection : anti-diphtheritic or ant-tetanic serum
 - anesthesia or insect venom
- * Clinical picture:
 - Shock due to sudden decrease of blood 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



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 disease

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

This leads 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

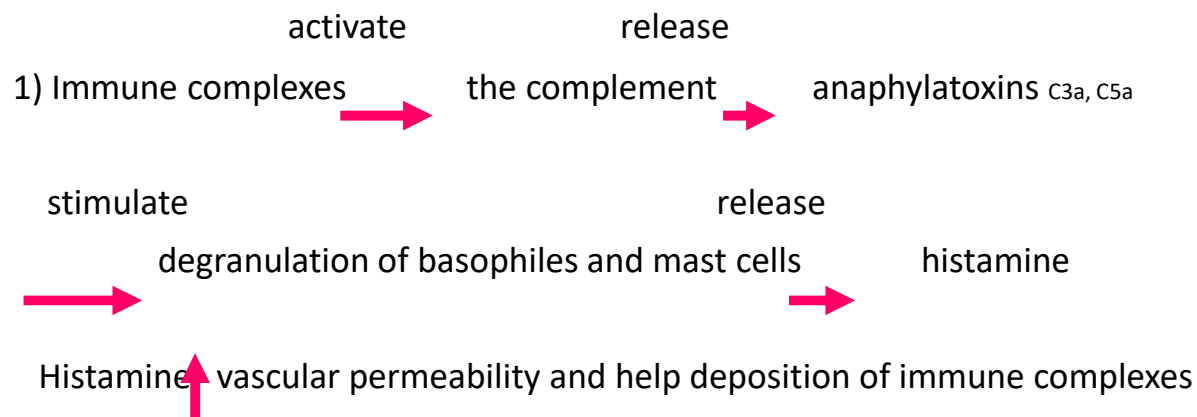
Immune Complex Mediated Reaction

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:



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

3) Platelets are aggregated with two consequences

- a- release of histamine
- b- formation 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:

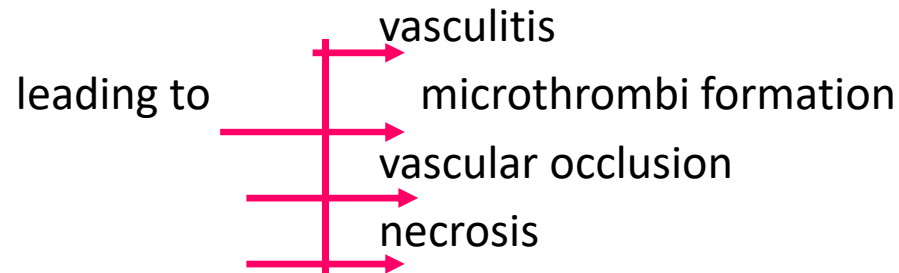
- a- Repeated exposure to extrinsic antigen
- b- injection of large amounts of antigens
- c- Persistent infections
- d- Autoimmunity to self components

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

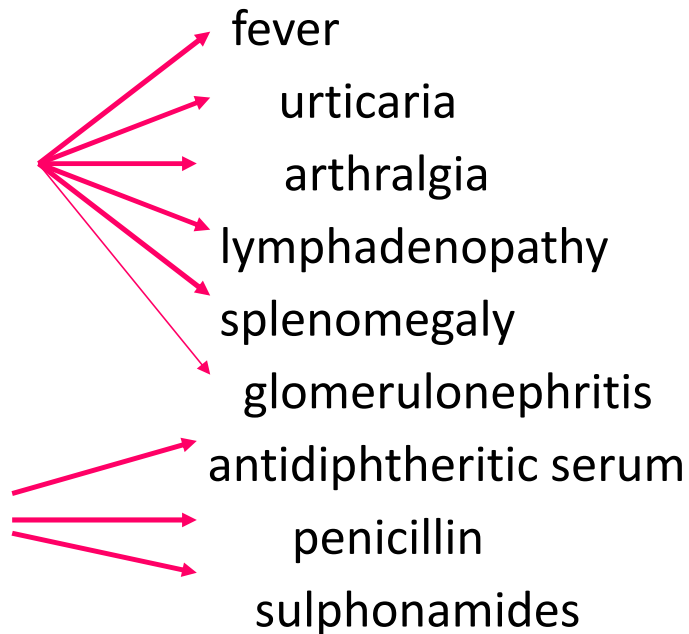


2- Serum Sickness

- * 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

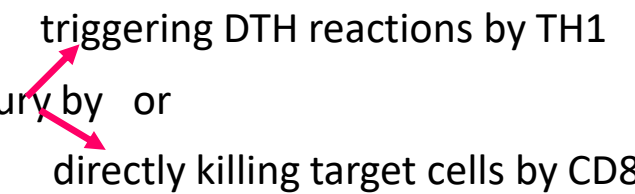
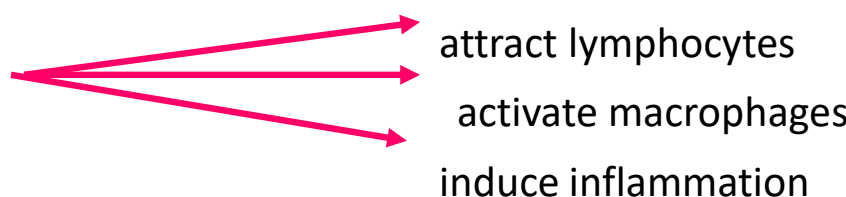
* 10 days after injection

e.g. treatment with



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

NOT REQUIRED TO KNOW UNLESS
MEDSCHOOLER

T CELLS IMMUNODEFICIENCY= DIE FROM VIRAL INFECTION = CMV

- DIGEORGE SYNDROME [THE ONLY IMMUNODEFICIENCY WITH HYPOCALCEMIA]
- CHRONIC MUCOCUTANEOUS CANDIDIASIS
- STEROIDS
- CYCLOSPORINE
- HAIRY CELL LEUKEMIA
- SCID
- WISKOTT-ALDRIDGE SYNDROME
- HIV

Steroids

- Anti-inflammatory action:
 - Kills T cells and eosinophils
 - Inhibit macrophages migration
 - Stabilizes mast cells membranes
 - Stabilizes endothelium
 - Inhibits phospholipase a

The end

- Stop complaining, it has been resumed



It can be worst

