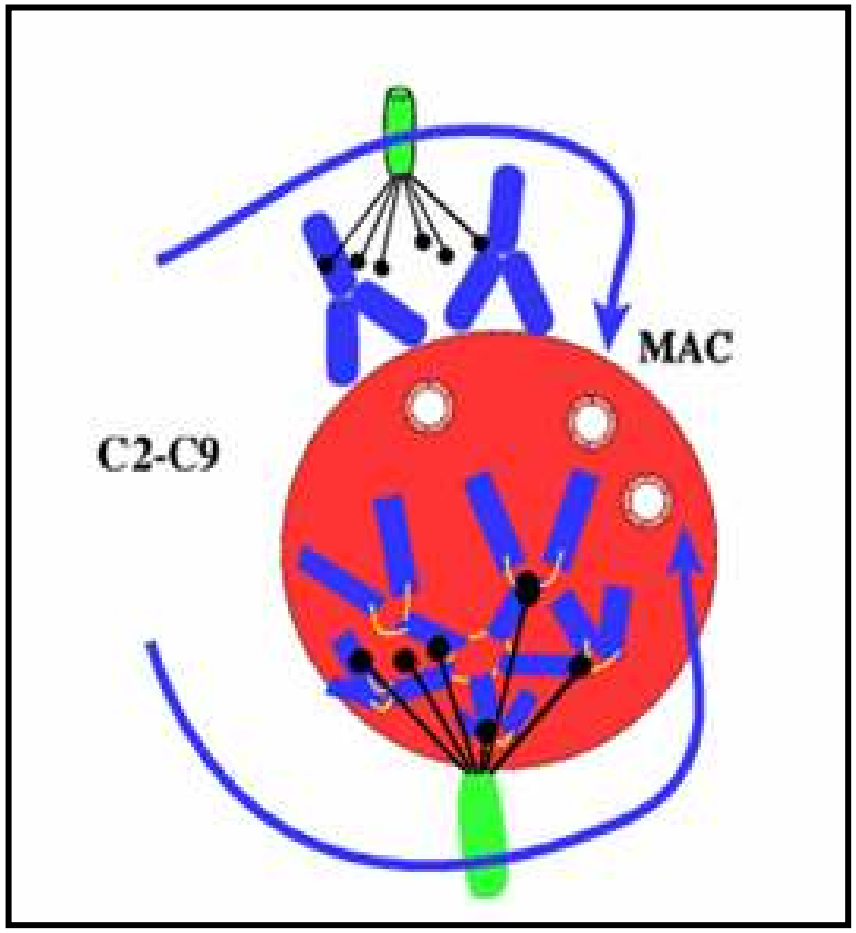
TYPE II & III HYPERSENSITIVITY REACTIONS.

Teaching Objectives:

- Understand the classification of hypersensitivity reactions
- Know the diseases associated with hypersensitivity reactions (**in this case types II & III**)
- Understand the mechanisms of damage in hypersensitivity reactions
- Know the methods for diagnosing conditions due to hypersensitivity
- Know the modes of treating disease due to hypersensitivity and their rationale.

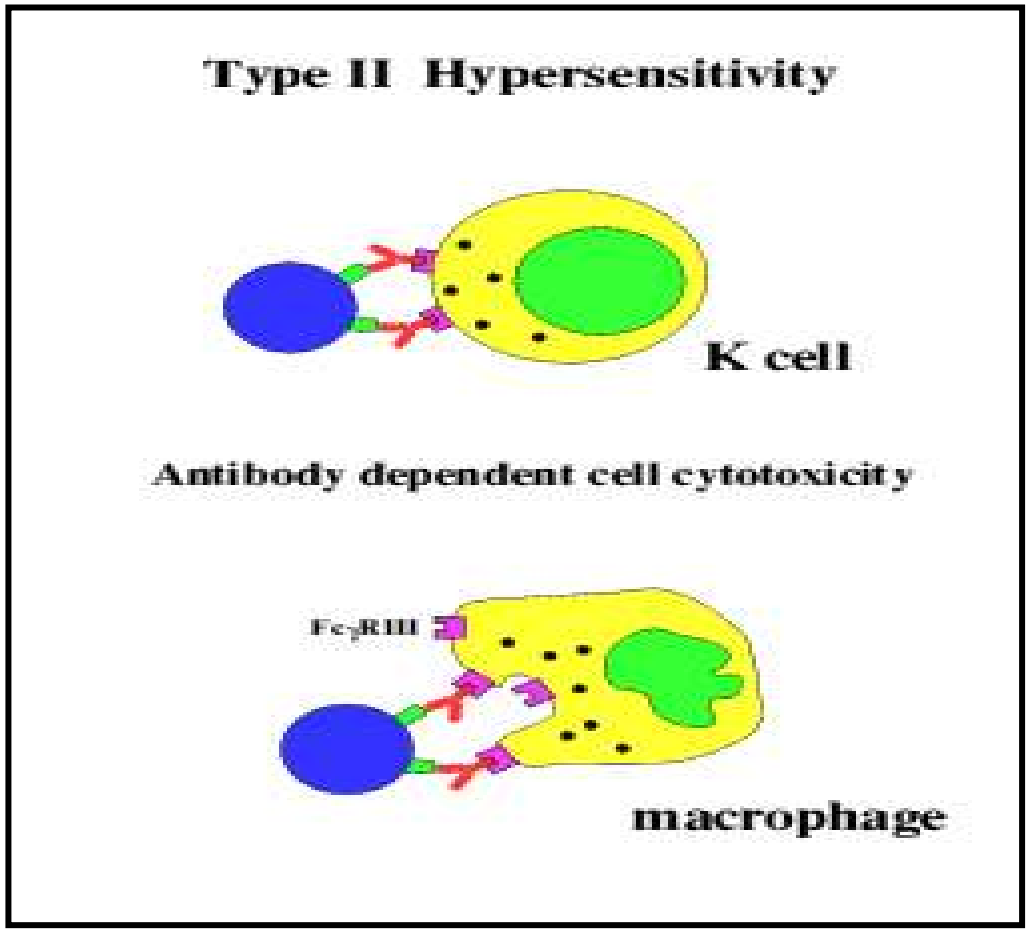
TYPE II HYPERSENSITIVITY (ANTIBODY-MEDIATED CYTOTOXIC) RXN.

- Type II hypersensistivity reactions involve antibody-mediated destruction of cells.
  - ➢ Antibody can activate the complement system; Creating pores in the membrane of a foreign cell (see fig), or
  - ➢ It can mediate cell destruction by antibody-dependent cell-mediated cytotoxicity (ADCC).
- In this process, cytotoxic cells with Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells



A. Complement mediated.

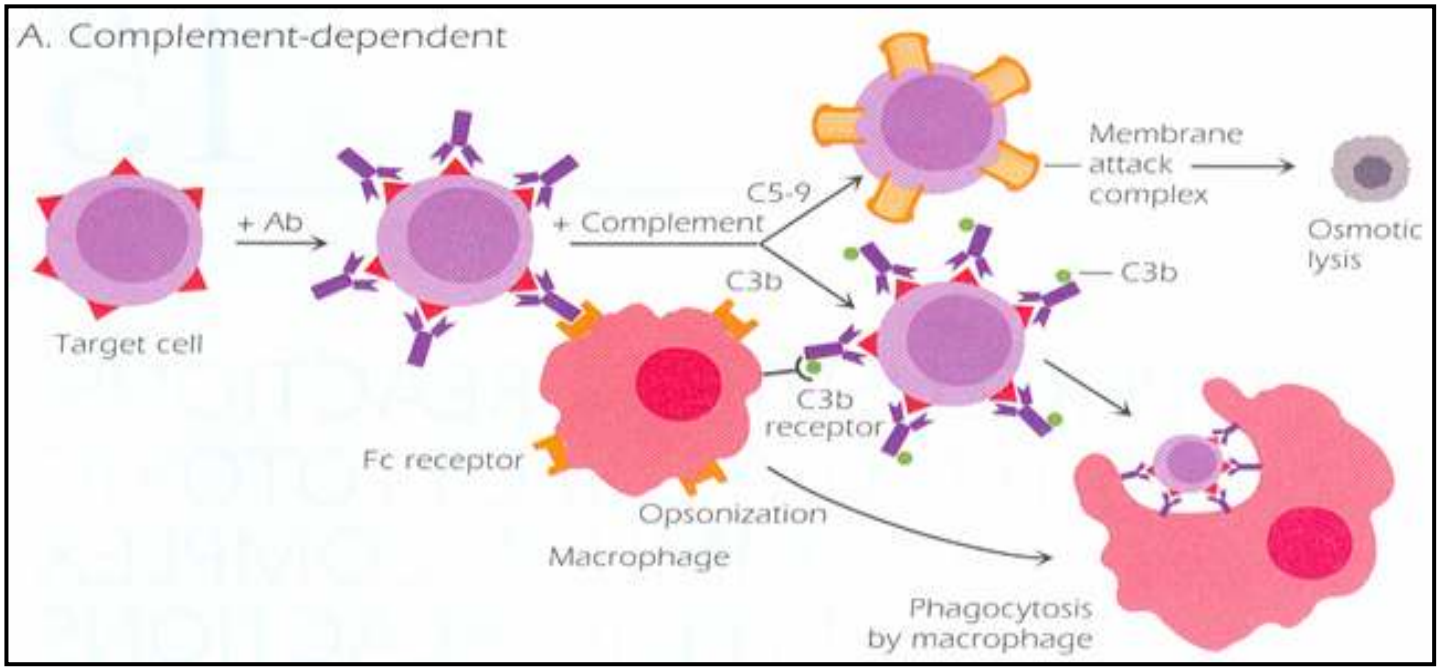
Classical pathway of complement activation.

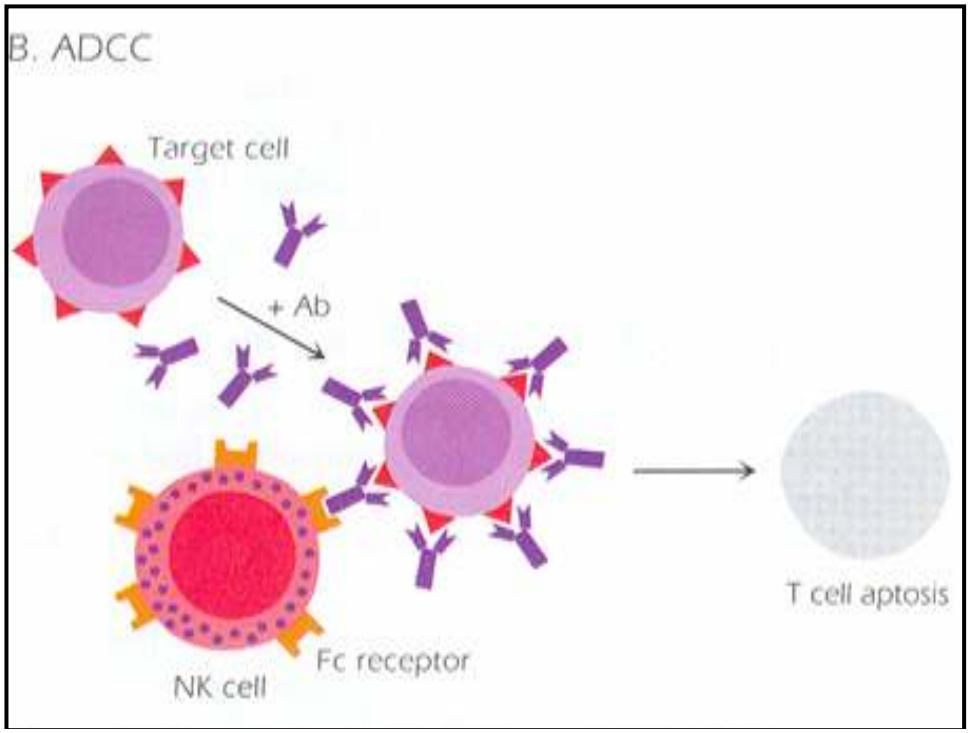


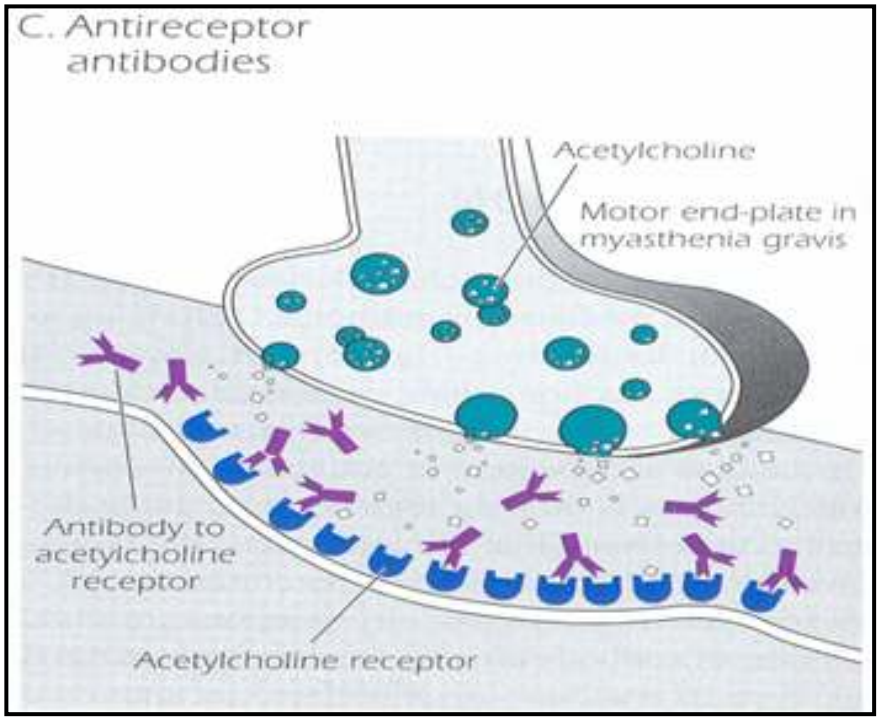
B. Ab-dependent

Mechanism of Ab-mediated injury in type II hypersensitivity Rxn

A. Complement-dependent rxns that leads to lysis of cells or render them susceptible to phagocytosis.
B. In ADCC, IgG-coated cells are killed by cells that bear Fc receptors for IgG (e.g. natural killer (NK) cells and macrophages)
C. Anti-receptor antibodies disturb the normal functions of receptors. In the following example, acetylcholine receptor antibodies impair neuromuscular transmission in myasthenia gravis


A. Complement-dependent
Target cell
+ Ab
+ Complement
C5-9
Membrane attack complex
Osmotic lysis
C3b
C3b
C3b receptor
Fc receptor
Opsonization
Macrophage
Phagocytosis by macrophage


B. ADCC
Target cell
+ Ab
Fc receptor
NK cell
T cell aptosis


C. Antireceptor antibodies
Acetylcholine
Motor end-plate in myasthenia gravis
Antibody to acetylcholine receptor
Acetylcholine receptor

Cytotoxicity in type II hypersensitivity Reactions.

- Cytotoxic reactions occur when IgG or IgM Abs bind to Ag on the surface of cells and activate complement cascade, culminating in destruction of the cells. e.g. **drug-induced auto-Abs, Ab-mediated autoimmunity, cross reactive Abs elicited following infection or modified self-Ags**.
- The targeted cell is either damaged or destroyed.

1- Complement-mediated reactions:

- Ab reacts with cell membrane component, leading to complement fixation. Complement cascade classical pathway is activated.
- Cell may be lysed or opsonization mediated by receptors for Fc or C3b that expressed on M∅ and PMNLs.
- Blood cells are most commonly affected by this mechanism.

2- Antibody-Dependent Cell-Mediated Cytotoxicity "ADCC".

- It uses Fc receptors on many cells "e.g. NK cells, M∅, PMNLs, eosinophils as a means of bringing these cells into contact with Ab-coated target cells.
- **Lysis requires contact but does not include phagocytosis or complement activation**.
- ADCC lysis of target cells is similar to that of T_C cells, perforin and granzymes are released, perforins form pores, granzymes "serine proteases" activate events leading to apoptosis.
- ADCC reactions involve IgG and IgG Fc receptors.
- **IgE can also be involved "the mechanism is similar to type I".**

3- Ab-mediated cellular dysfunction.

Cell surface serve as target Ags when auto-Abs bind to such receptors, they impair function without causing cell injury or inflammation.

Type II hypersensitivity Reactions.

1- Transfusion Reactions.

- Transfusion of ABO-incompatible blood results in complement-mediated cytotoxic reactions.
- Kidney may be damaged because of the large quantities of RBCs membranes and the toxic effects of heme complex.

- Because of cross-matching transfusion reactions are now rare, nevertheless sometimes IgG can exist for minor blood group antigens at a level sufficient to cause destruction of the transfused cells but too low to detect *in vitro*.

- **2- Drug-induced Reactions.**
- Certain antibiotics (e.g. penicillin, cephalosporin, and streptomycin) can adsorb nonspecifically to proteins on RBC membranes, forming a complex similar to a hapten-carrier complex.
- In some patients, such drug-protein complexes induce formation of antibodies, which then bind to the adsorbed drug on red blood cells, inducing complement-mediated lysis and thus progressive anemia.
- Some drugs bind to platelets, causing them to become immunogenic, Ab responses cause lysis of platelets resulting in thrombocytopenia.

3- Rh incompatibility (hemolytic disease of the new born).

- Rhesus disease (or haemolytic disease of the newborn) is a special example since the IgG antibodies which cause destruction of foetal red blood cells by antibody dependent cellular cytotoxicity (ADCC) are passively acquired by the host via the placenta.

4- Autoimmune Reactions involving cell Membrane Receptors.

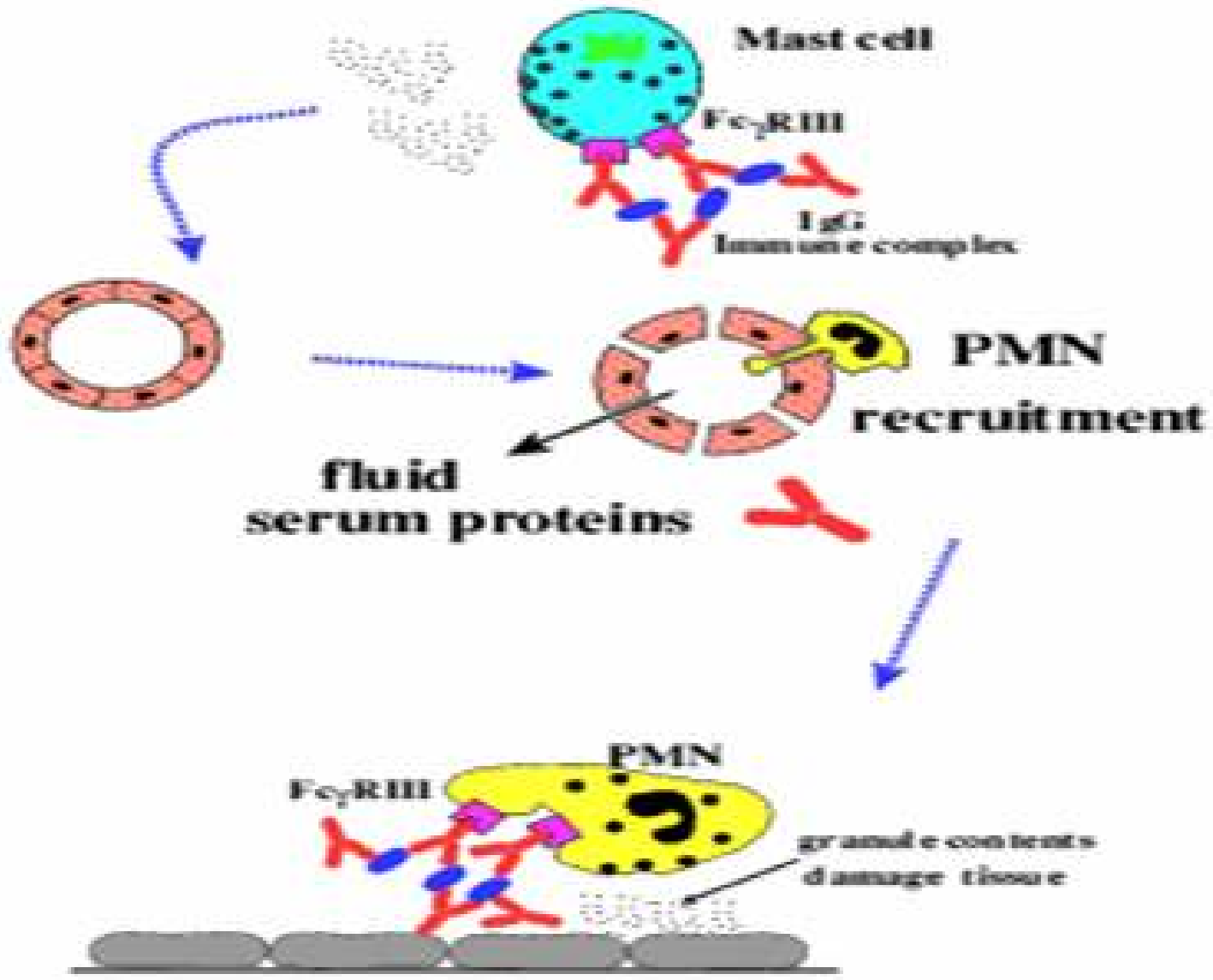
- Myasthenia gravis , Grave's disease, auto-Abs serve as agonists, causing stimulation of target cells, resulting in hyperthyroidism.
- "autoimmune hemolytic, Some people produce Abs reactive against their own blood cells", destroys them by mechanisms that involve hemolysis or phagocytosis via receptors for FC and C3b.

TYPE III HYPERSENSITIVITY (Immune Complex) REACTIONS.

- Usually, **immune complex reactions occur when complexes of Ag and IgM or IgG accumulate in the circulation or in tissue and activate the complement cascade**.
- Normally small amounts of complexes are removed by phagocytic cells.
- Complexes bind IgG Fc receptors on phagocytic cells.
- RBCs with C3b receptors may bind complexes which are removed in the liver by kupffer cells.

- When large amounts of complexes are deposited in tissues, they trigger a variety of systemic symptoms known as type III hypersensitivity reactions (**Generalized**).
- Complexes may be deposited in kidneys, skin, joints, choroids plexus and ciliary artery of the eye causing tissue damage.
- C3a, C5a generated by complement activation induce mast cell degranulation.
- M∅ are stimulated to release TNF-∝ and IL-1, platelets form microthrombi and release platelet derived growth factor-PDGF.

Type III Hypersensitivity



Phases of Systemic Immune Complex Disease.

- Ag-Ab immune complexes form in the circulation.
- Deposition of immune complexes in various tissues.
- Occurrence of inflammatory reactions in various tissues.

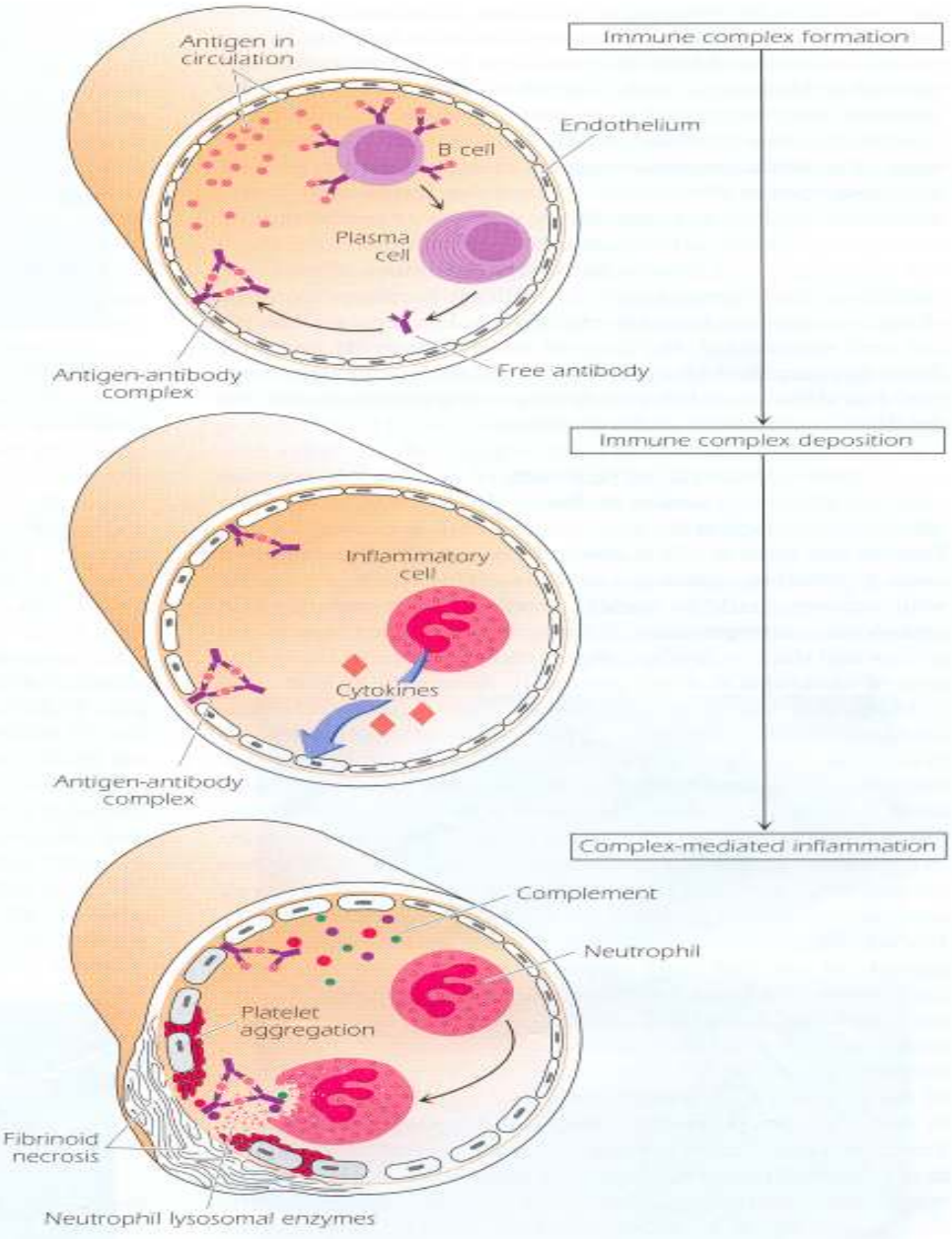
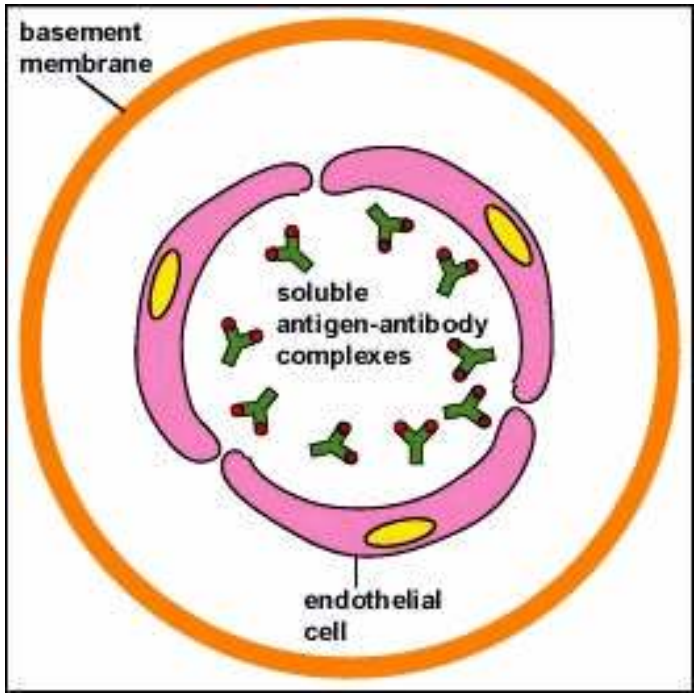
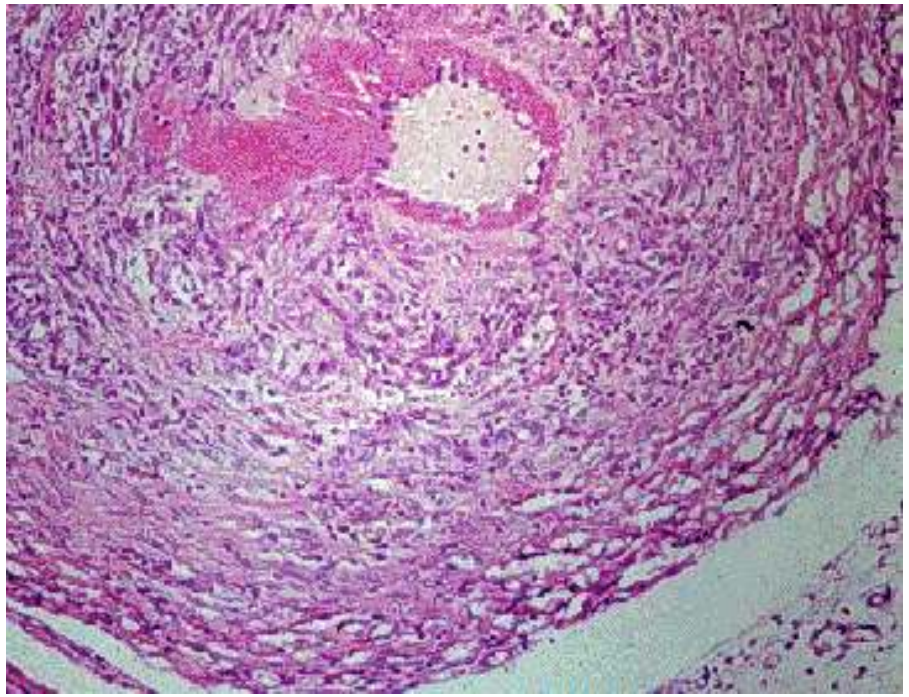


Figure 15.2. The three sequential phases in the induction of systemic type III (immune complex) hypersensitivity.

Type-III Hypersensitivity: Immune Complex



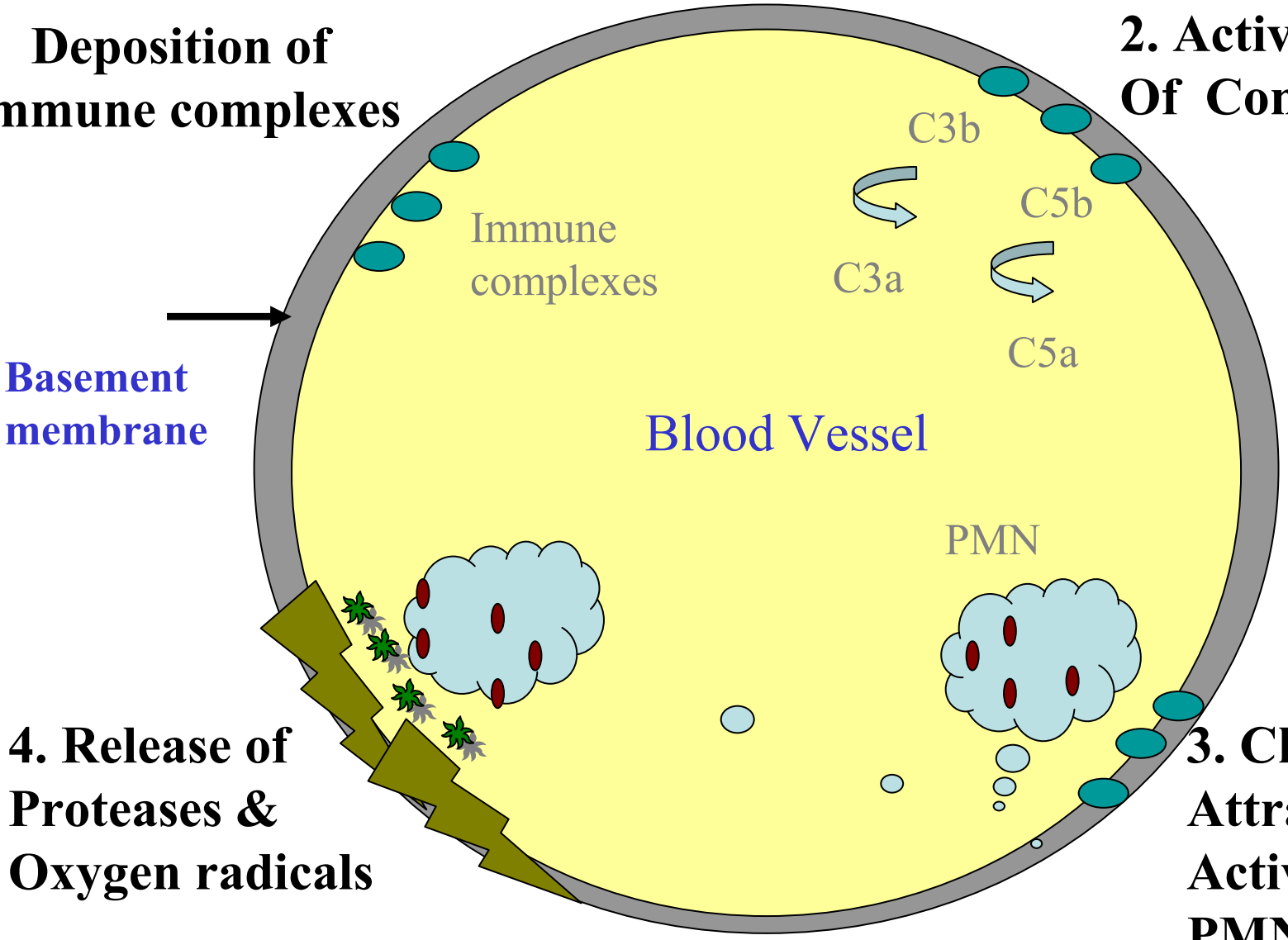


Large quantities of soluble antigen-antibody complexes form in the blood and are not completely removed by macrophages. These antigen-antibody complexes lodge in the capillaries between the endothelial cells and the basement membrane. The antigen-antibody complexes activate the classical complement pathway and complement proteins and antigen-antibody complexes attract leukocytes to the area. The leukocytes then discharge their killing agents and promote massive inflammation. This leads to tissue death and hemorrhage

Hypersensitivity type III

1. Deposition of Immune complexes

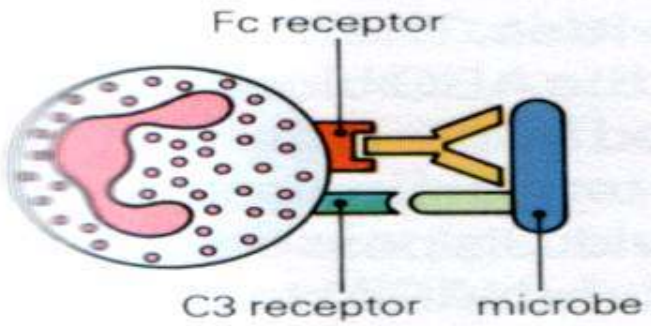
2. Activation Of Complement



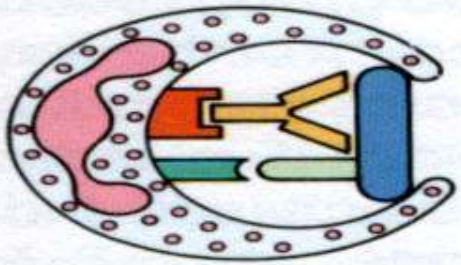
4. Release of Proteases & Oxygen radicals

3. Chemotactic Attraction & Activation of PMNs

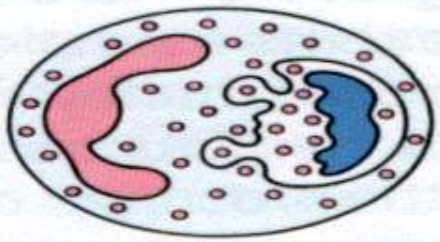
normal antimicrobial action



1. neutrophil

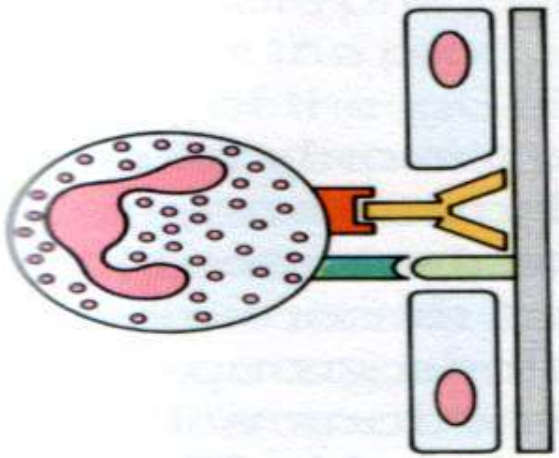


2. phagocytosis

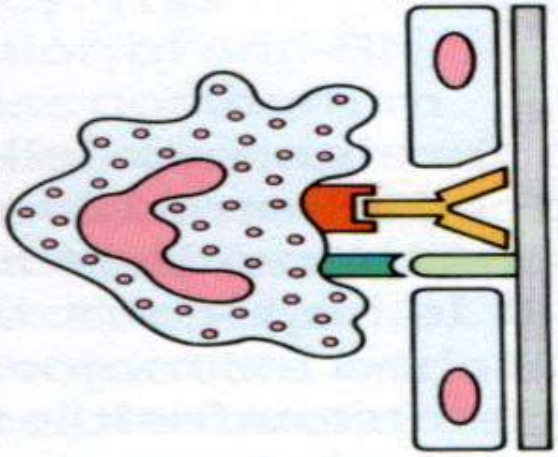


3. lysosome fusion

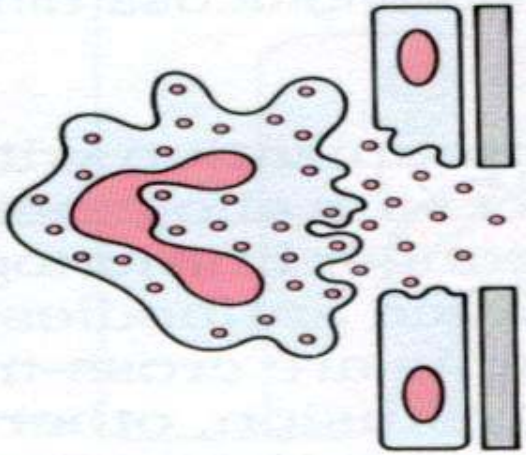
hypersensitivity reaction



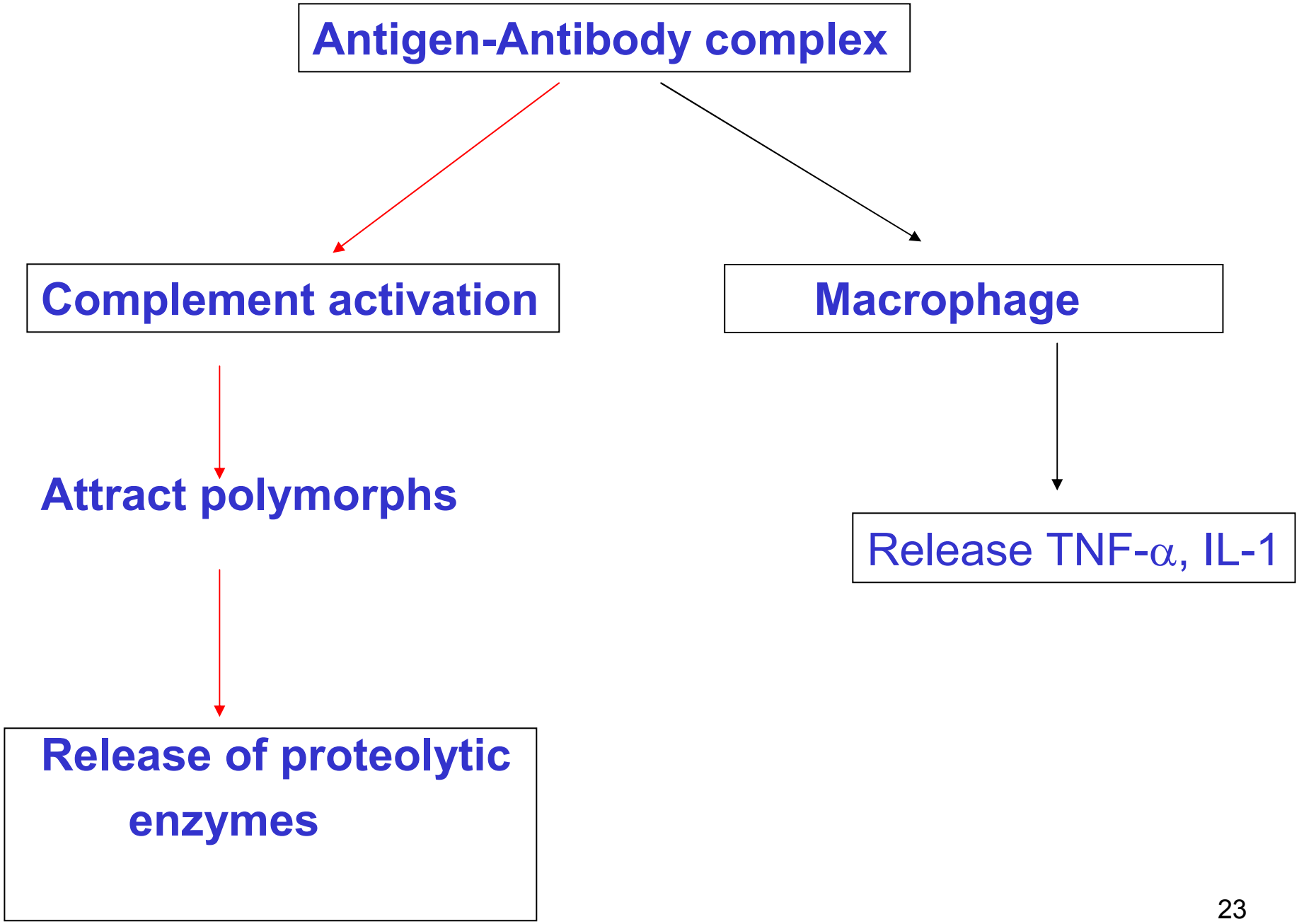
4. neutrophil



5. 'frustrated phagocytosis'



6. extracellular enzyme release


Antigen-Antibody complex
Complement activation
Macrophage
Attract polymorphs
Release TNF-α, IL-1
Release of proteolytic enzymes

- **Deposition of immune complexes is influenced by the size** e.g. small or intermediate immune complexes which circulate for longer time tend to be deposited, while larger complexes are rapidly removed by phagocytic cells.

while

- **The integrity of the mononuclear** phagocytic system influence the development of systemic immune complexes.

Factors that determine the tissue damage.

- Size of immune complexes
- Quantity of immune complexes
- Site of deposition (local or systemic)

Type III Hypersensitivity Rxns.

- ***Systemic reactions***
- Circulating immune complexes deposit in blood vessels, synovial membrane of joints, glomerular basement membrane of kidney, brain and cause tissue damage

Examples of systemic rxns.

- **Serum Sickness:**
- The prototype of systemic immune complex disease.
- Treatment with horse serum containing Abs to some bacterial toxins.
- 2nd injection of horse serum "foreign for human body" may develop serum sickness **"allergic manifestations".**
- **Rheumatic fever as sequale of group A streptococcal infection:**
- It involves inflammation and damage to heart, joints and kidneys.
- Ags in the cell wall and membrane of streptococci cross react with human Ags found in heart muscle, cartilage, glomerular basement membrane.
- Abs to streptococcal Ags bind to these components and induce inflammatory reactions.

Other Examples

1. Infections : persistent infections (e.g. streptococcal & staphylococcal infections, malaria, viral hepatitis) lead to chronic Ab production

2. Auto-immune diseases:

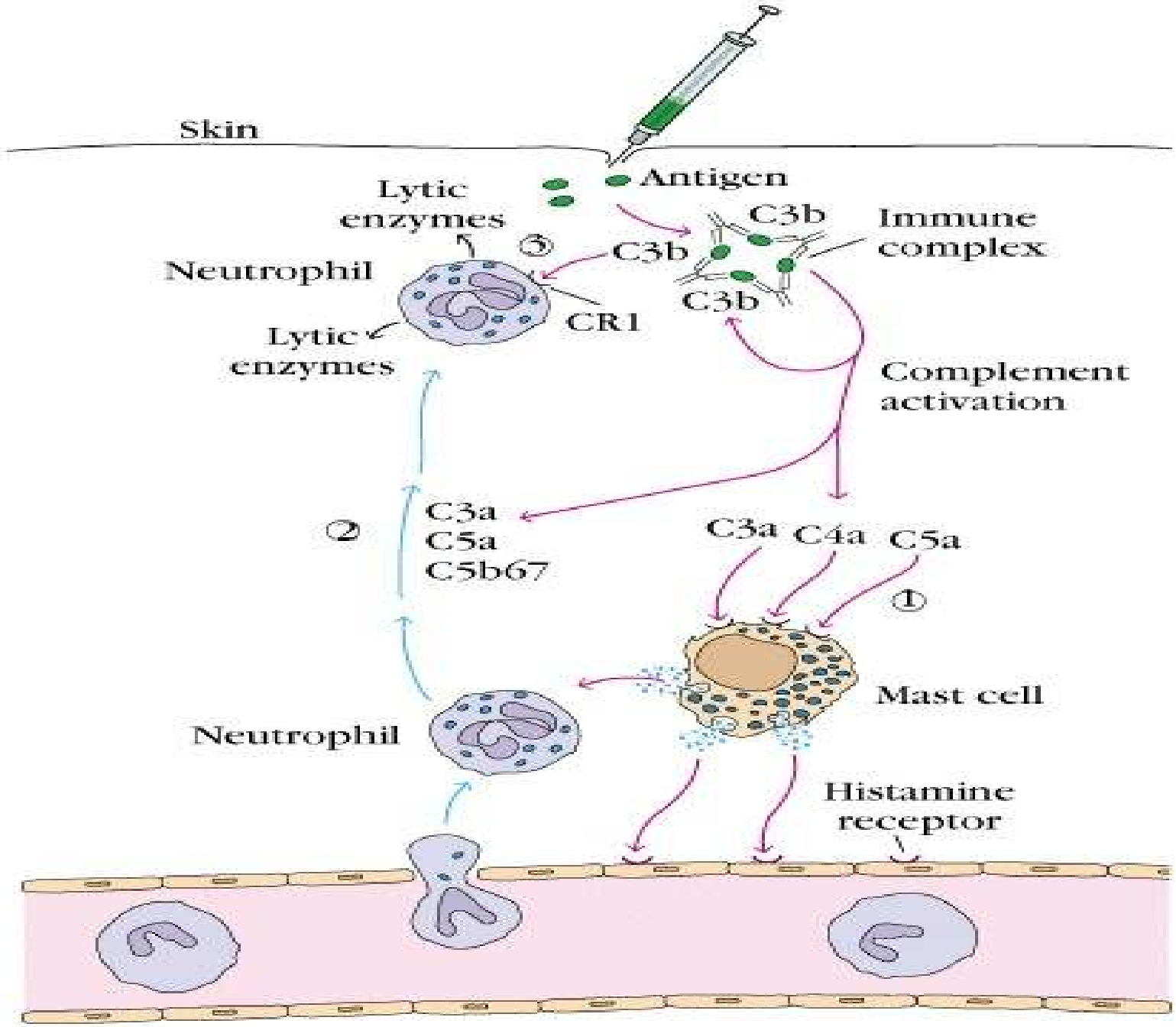
Continuous auto-Ab production to soluble self-Ag,

MØ & Complement responsible for removal of I.C. become overloaded & deposition takes place e.g. SLE (anti- DNA, anti- nuclear Ab), Rheumatoid arthritis (Rheumatoid Factor).

3. Tumors: continuously shed Ag

Local Reactions.

- Arthus reactions:
- It is the prototype of localized (type III) immune complex reactions.
- Local inflammatory response generated after reactivity of Ag with already formed Ag-specific IgG. Ag-Ab reactions near vessel walls, complexes form and accumulate ending with the rupture of the vessel wall and hemorrhage, accompanied by necrosis of local tissue.


Skin
Antigen
Lytic enzymes
③
Neutrophil
C3b
C3b
Immune complex
C3b
CR1
Lytic enzymes
Complement activation
②
C3a
C5a
C5b67
C3a
C4a
C5a
①
Mast cell
Neutrophil
Histamine receptor

Examples in man

Local reactions

Intra-pulmonary reaction (pneumonitis, alveolitis) induced by bacterial spores, fungi

1. Farmer's lung disease due to inhalation of fungi & bacterial spores

2. 'Pigeon fancier's lung' disease due to repeated exposure to dried pigeon droppings containing pigeon proteins

Tests for type III hypersensitivity.

1. Immunofluorescence tests for the detection of antigens, antibodies, Complement and immune complexes in tissues.

2. Detection of antibodies to suspected antigens such as horse serum proteins, spores, pigeon dropping antigens etc.

3. Tests for immune complexes in the serum

Summary.

- Hypersensitivity reaction is an undesirable excessive immune reaction to antigens that ends up destroying host tissue.
- Can be managed by eliminating the trigger (pathogen or stimuli)
- Type II= antibody-mediated cytotoxic reaction.
- Type III= immune complex mediated reaction.