



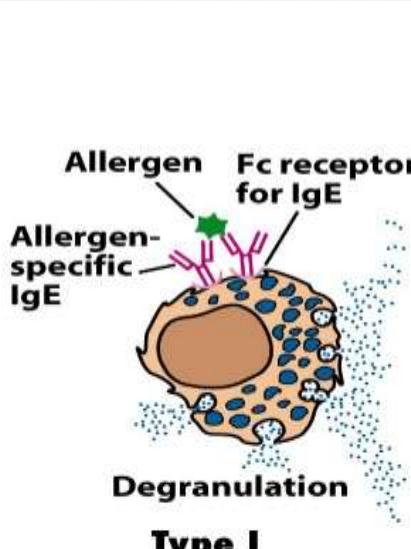
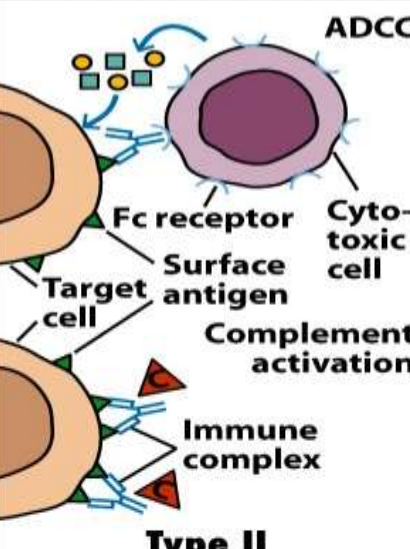
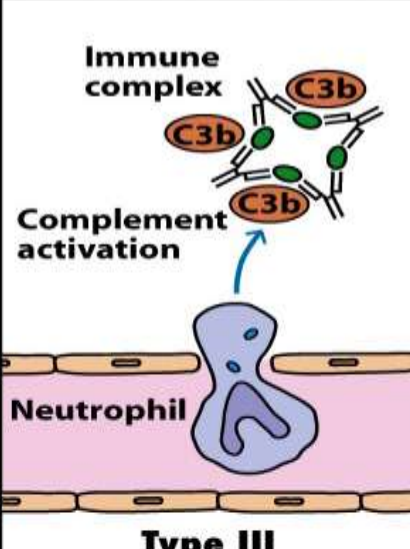
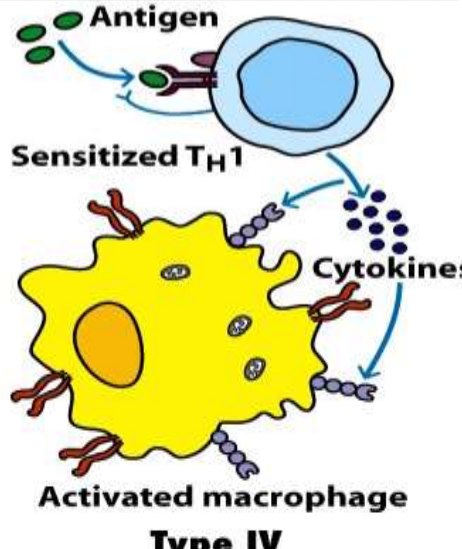
HYPERSENSITIVITY REACTIONS



Introduction

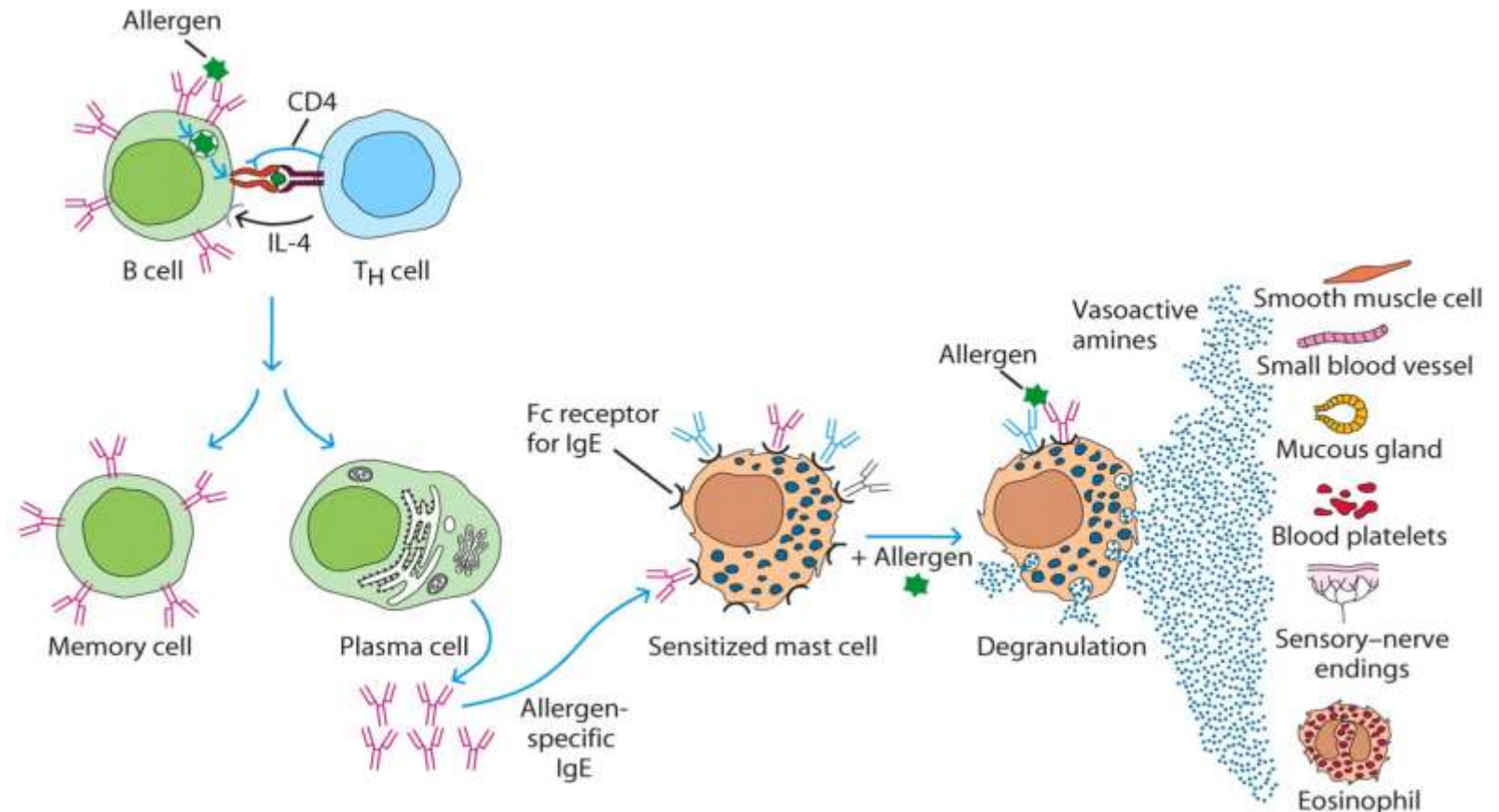
- ▶ Hypersensitivity - this inflammatory response can have deleterious effects, resulting in significant tissue damage or even death. This inappropriate immune response is termed **hypersensitivity** or **allergy**.
- ▶ 1906 – Von Pirquet coined term: hypersensitivity
- ▶ 2 types of hypersensitivity: **immediate hypersensitivity**, because the symptoms are manifest within minutes or hours after a sensitized recipient encounters antigen. **Delayed-type hypersensitivity (DTH)** is so named in recognition of the delay of symptoms until days after exposure.

GELL AND COMBS

| | | | |
|--|---|---|--|
|  <p>Type I</p> |  <p>Type II</p> |  <p>Type III</p> |  <p>Type IV</p> |
| <p>IgE-Mediated Hypersensitivity</p> | <p>IgG- or IgM-Mediated Cytotoxic Hypersensitivity</p> | <p>Immune Complex-Mediated Hypersensitivity</p> | <p>Cell-Mediated Hypersensitivity</p> |
| <p>Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.</p> | <p>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.</p> | <p>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.</p> | <p>Sensitized TH1 cells shown above release cytokines that activate macrophages or TC cells that mediate direct cellular damage. TH2 cells and CTLs mediate similar responses.</p> |
| <p>Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.</p> | <p>Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.</p> | <p>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</p> | <p>Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.</p> |

Type 1 Hypersensitivity

A type I hypersensitive reaction is induced by certain types of antigens referred to as **allergens**, and has all the hallmarks of a normal humoral response. That is, an allergen induces a humoral antibody response by the same mechanisms like for other soluble antigens, resulting in the generation of antibody-secreting plasma cells and memory cells.



Components of type 1 reactions

1. Allergens
2. IgE
3. Mast cells and basophils.

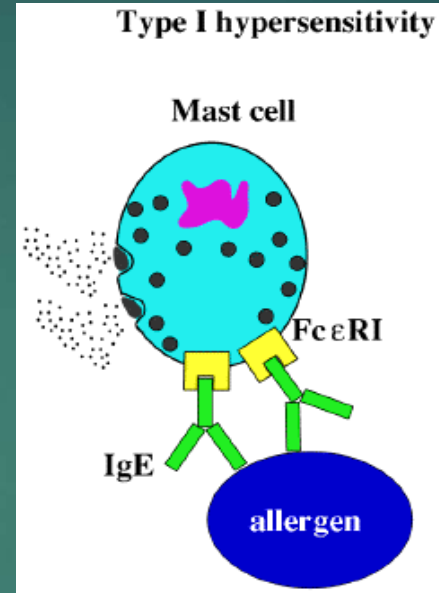


TABLE 16-1 COMMON ALLERGENS ASSOCIATED WITH TYPE I HYPERSENSITIVITY

Proteins

Foreign serum
Vaccines

Plant pollens

Rye grass
Ragweed
Timothy grass
Birch trees

Drugs

Penicillin
Sulfonamides
Local anesthetics
Salicylates

Foods

Nuts
Seafood
Eggs
Peas, beans
Milk

Insect products

Bee venom
Wasp venom
Ant venom
Cockroach calyx
Dust mites

Mold spores

Animal hair and dander

Type 1 reactions

Localized hypersensitivity

In localized anaphylaxis, the reaction is limited to a specific target tissue or organ, often involving epithelial surfaces at the site of allergen entry.

The tendency to manifest localized anaphylactic reactions is inherited and is called *atopy*.

Systemic Anaphylaxis

Systemic anaphylaxis is a shock-like and often fatal state whose onset occurs within minutes of a type I hypersensitive reaction.

Epinephrine is the drug of choice for systemic anaphylactic reactions.

Localized Hypersensitivity Reactions

Allergic rhinitis : the most common atopic disorder , commonly known as hay fever.

Cause: airborne allergens with sensitized mast cells in the conjunctivae and nasal mucosa to induce the release of pharmacologically active mediators from mast cells .

Symptoms : 1. watery exudation of the conjunctivae,
2.nasal mucosa
3.upper respiratory tract
4.sneezing and coughing.

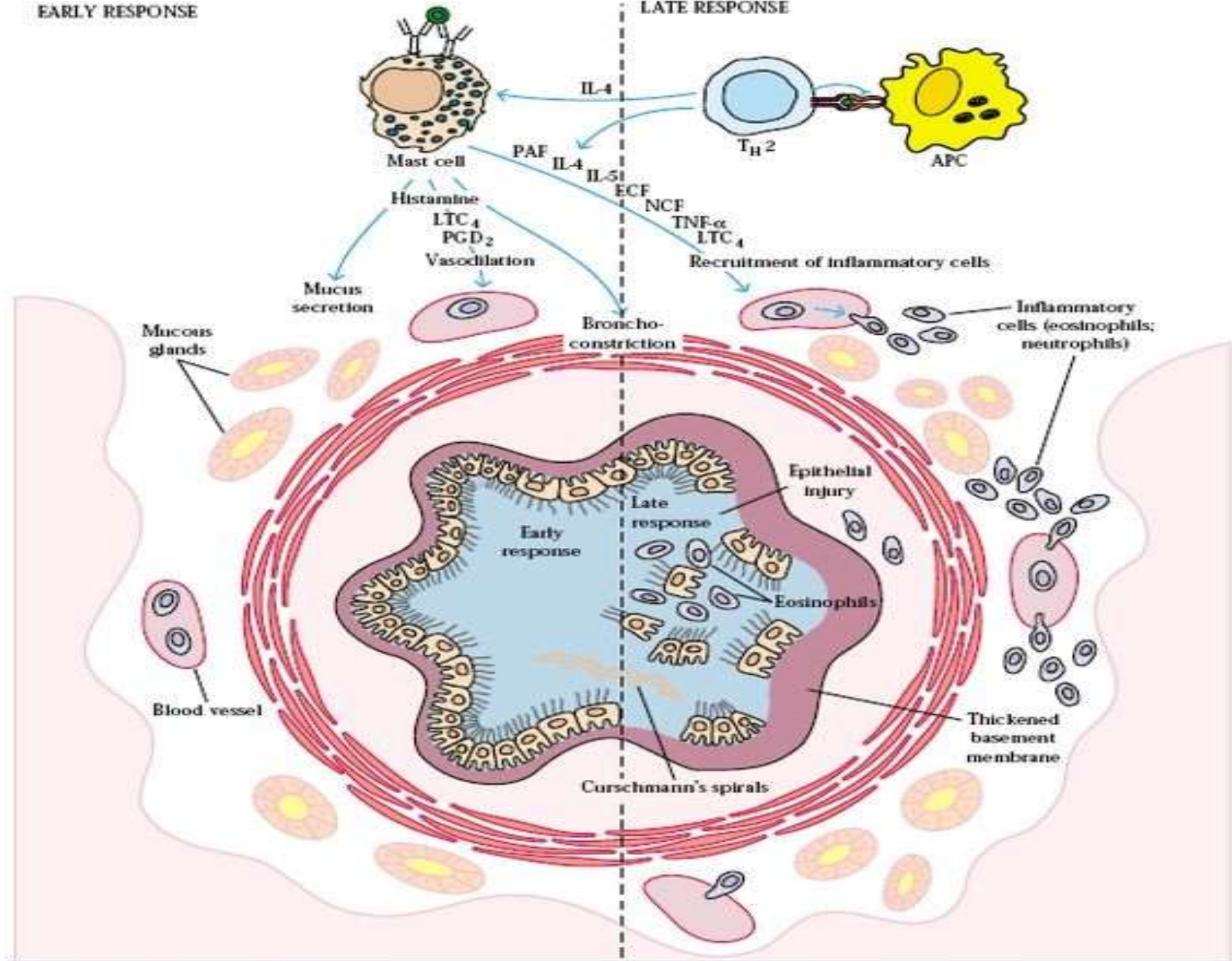
Asthama: A respiratory condition marked by attacks of spasm in the bronchi of the lungs, causing difficulty in breathing. It is usually connected to allergic reaction or other forms of hypersensitivity.

Causes : airborne or blood-borne allergens, such as pollens, dust, fumes, insect products, or viral antigens, trigger an asthmatic attack (allergic asthma)

Symptoms : 1.Coughing especially at night
2. Wheezing
3.Shortness of breath
4.Chest tightness, pain, or pressure

EARLY RESPONSE

LATE RESPONSE



| EARLY RESPONSE (minutes) | | LATE RESPONSE (hours) | |
|--------------------------|---------------------|--|-------------------------------------|
| Histamine | Vasodilation | IL-4, TNF- α , LTC ₄ | Increased endothelial cell adhesion |
| PGD ₂ | Bronchoconstriction | PAF, IL-5, ECF | Leukocyte migration |
| LTC ₄ | Mucus secretion | IL-4, IL-5 | Leukocyte activation |

Clinical Methods

- ▶ Allergen -specific IgE blood testing : this is testing that is used to help diagnose allergies. The test measures the amount of allergen-specific IgE antibodies in the blood in order to detect an allergy to a particular substance. It involves taking a blood sample and checking for each allergen suspected.
- ▶ Skin prick tests : involve pricking the skin where diagnostic allergen has been placed. It provides evidence for sensitization and can help to confirm the diagnosis of a suspected type I allergy.
- ▶ intradermal skin tests : are more sensitive but less specific than SPT . They are more labor-intensive and require more precise techniques Intradermal (ID) tests involve injecting environmental allergen into the superficial dermis. ID tests have many more false positive reactions.
- ▶ Another method of assessing type I hypersensitivity is to determine the serum level of total IgE antibody by the radioimmunosorbent test (RIST). This highly sensitive technique, based on the radioimmunoassay, can detect nanomolar levels of total IgE.
- ▶ The similar radioallergosorbent test (RAST) detects the serum level of IgE specific for a given allergen.

Interdermal Test



Figure 15-10
Kuby IMMUNOLOGY, Sixth Edition
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Food Allergy Skin Prick (Scratch) Test

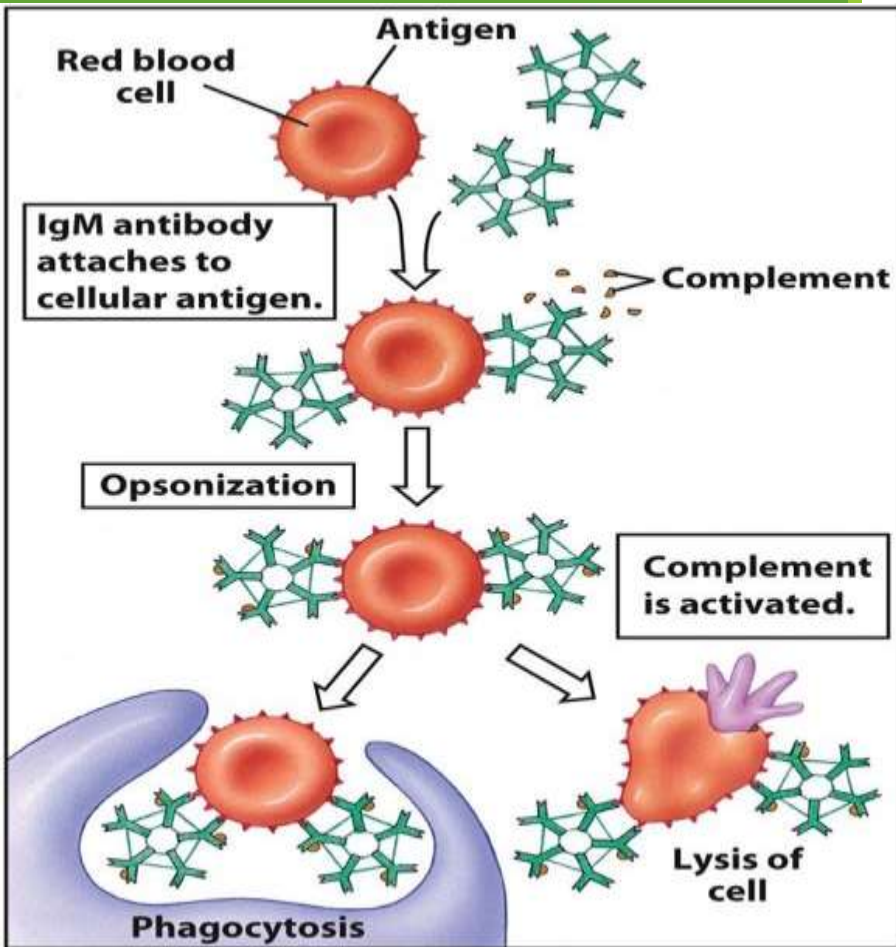
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TABLE 15-4**Mechanism of action of some drugs used to treat type I hypersensitivity**

| Drug | Action |
|---------------------------------|---|
| Antihistamines | Block H₁ and H₂ receptors on target cells |
| Cromolyn sodium | Blocks Ca²⁺ influx into mast cells |
| Theophylline | Prolongs high cAMP levels in mast cells by inhibiting phosphodiesterase, which cleaves cAMP to 5'-AMP* |
| Epinephrine (adrenaline) | Stimulates cAMP production by binding to β-adrenergic receptors on mast cells* |
| Cortisone | Reduces histamine levels by blocking conversion of histidine to histamine and stimulates mast-cell production of cAMP* |

*** Although cAMP rises transiently during mast-cell activation, degranulation is prevented if cAMP levels remain high.**

HYPERSENSITIVITY TYPE 2



Type 2 hypersensitivity reactions involve antibody mediated destruction of cells .

The antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.

The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen).

These cells are recognized by macrophages or dendritic cells, which act as antigen-presenting cells.

EXAMPLES OF TYPE 2 HYPERSENSITIVITY REACTIONS

1. CLASSICAL 'ABO' BLOOD GROUP

RELATIONSHIPS BETWEEN BLOOD TYPES AND ANTIBODIES

| Blood Type | Antigens on Red Blood Cell | Can Donate Blood To | Antibodies in Serum | Can Receive Blood From |
|------------|----------------------------|---------------------|---------------------|------------------------|
| A | A | A,AB | Anti-A | A,O |
| B | B | B,AB | Anti-B | B,O |
| AB | A and B | AB | None | AB,O |
| O | None | A,B,AB and O | Anti-A and Anti-B | O |

Antibodies to the A,B,O antigen called isohemagglutinins are usually of Ig M CLASS.

If type A individual is transfused with blood type B then a TRANSFUSION REACTION occurs .

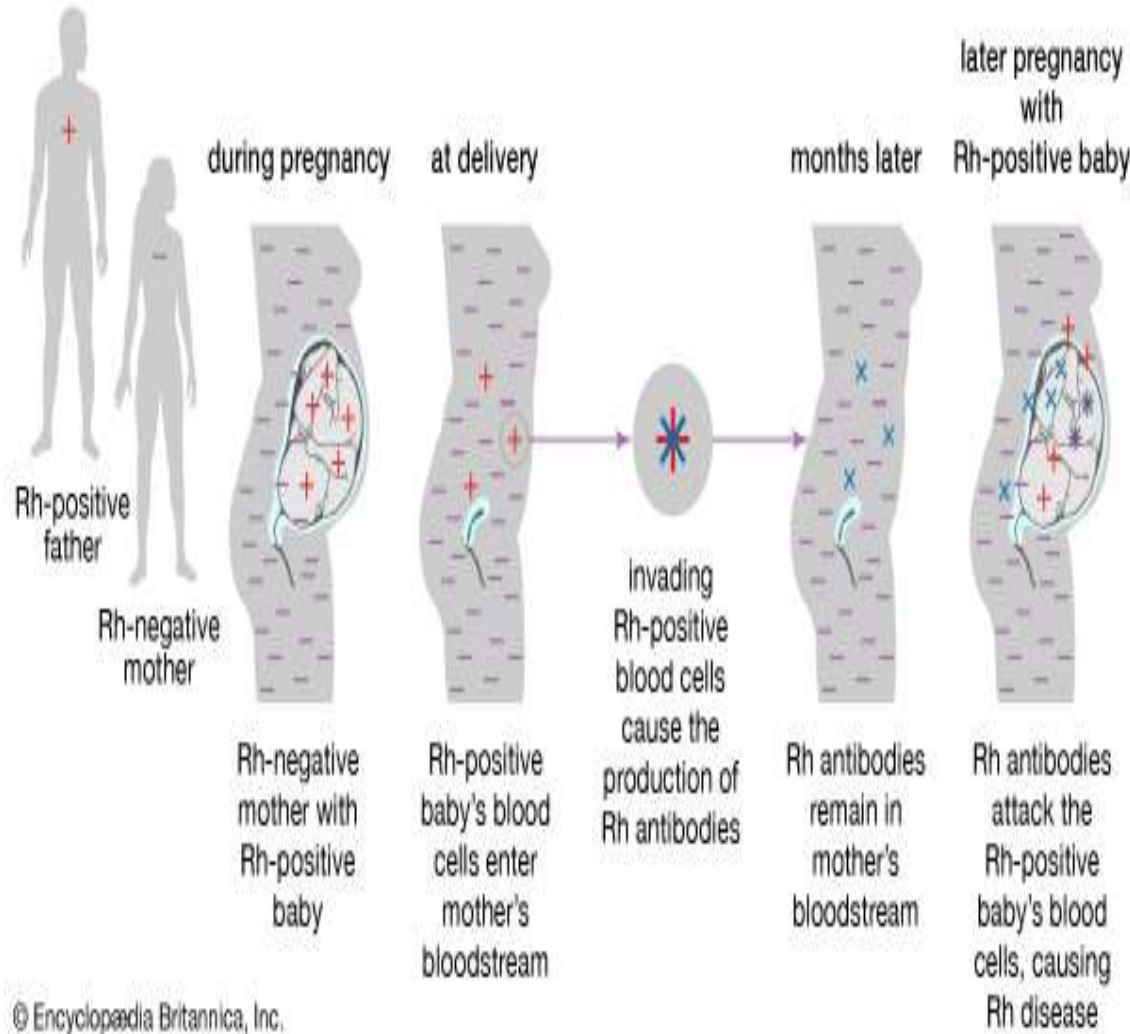
In this anti B isohemagglutinins bind to B cells and mediate their destruction.

HEMOLYTIC DISEASE OF NEWBORN

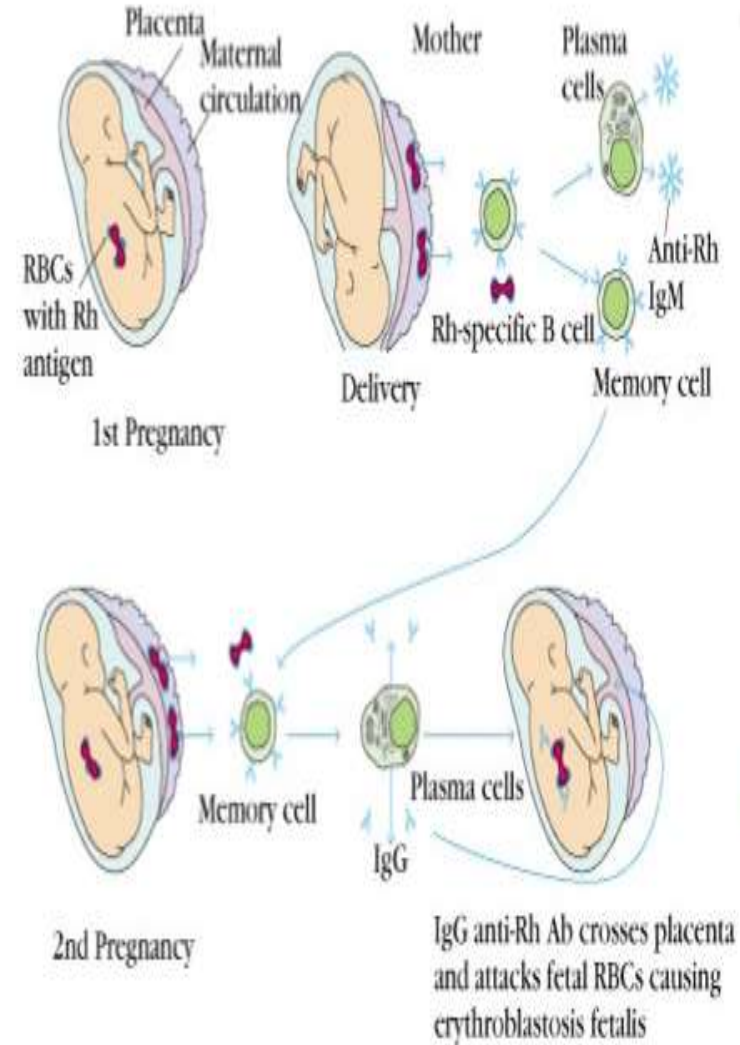
It develops when maternal IgG antibodies specific for fetal blood group antigens cross the placenta and destroy fetal RBC.

Severe hemolytic disease of new born called ERYTHROBLASTOSIS FETALIS develop when RH + FETUS express an Rh antigen on its blood cells that the Rh- mother does not express.

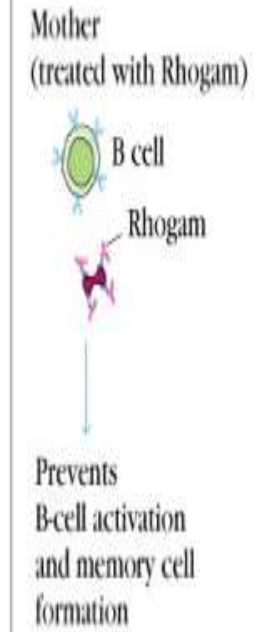
How Rh hemolytic disease develops



DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)



PREVENTION (WITH RHOGAM)



Human anti-Rh IgG antibodies

DETECTION

The hemolytic disease of newborn caused by Rh incompatibility can be detected by testing maternal serum at intervals during pregnancy for antibodies to the Rh antigen.

A rise in titer of these antibodies as pregnancy progress indicates that mother has been exposed to Rh antigens and is producing increasing amounts of antibody.

The presence of maternal IgG on fetal rbc can be detected by coombs test.

TREATMENT

Treatment depend upon severity of the reaction.

For severe reaction , fetus can be given intrauterine blood exchange transfusion to replace fetal Rh+ blood cells with Rh- cells (10-21 days untill delivery)

In less severe cases , blood transfusion not given untill after birth , primarily to remove bilirubin ; infant is exposed to low levels of UV to break down the bilirubin.

Mother can be treated during pregnancy by plasmapheresis.

DRUG INDUCED HEMOLYTIC ANEMIA

In some cases, a drug can cause the immune system to mistakenly think the body's own red blood cells are dangerous, foreign substances.

Antibodies then develop against the red blood cells.

The antibodies attach to red blood cells and cause them to break down too early and thus progressive anemia.

Drugs that can cause this type of hemolytic anemia include:

Cephalosporins

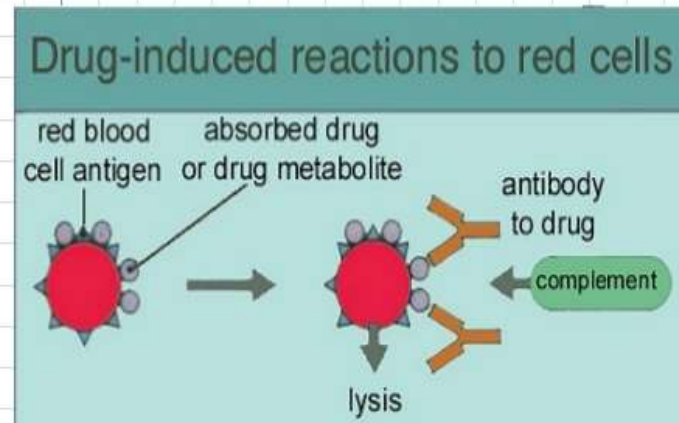
Dapsone

Levodopa

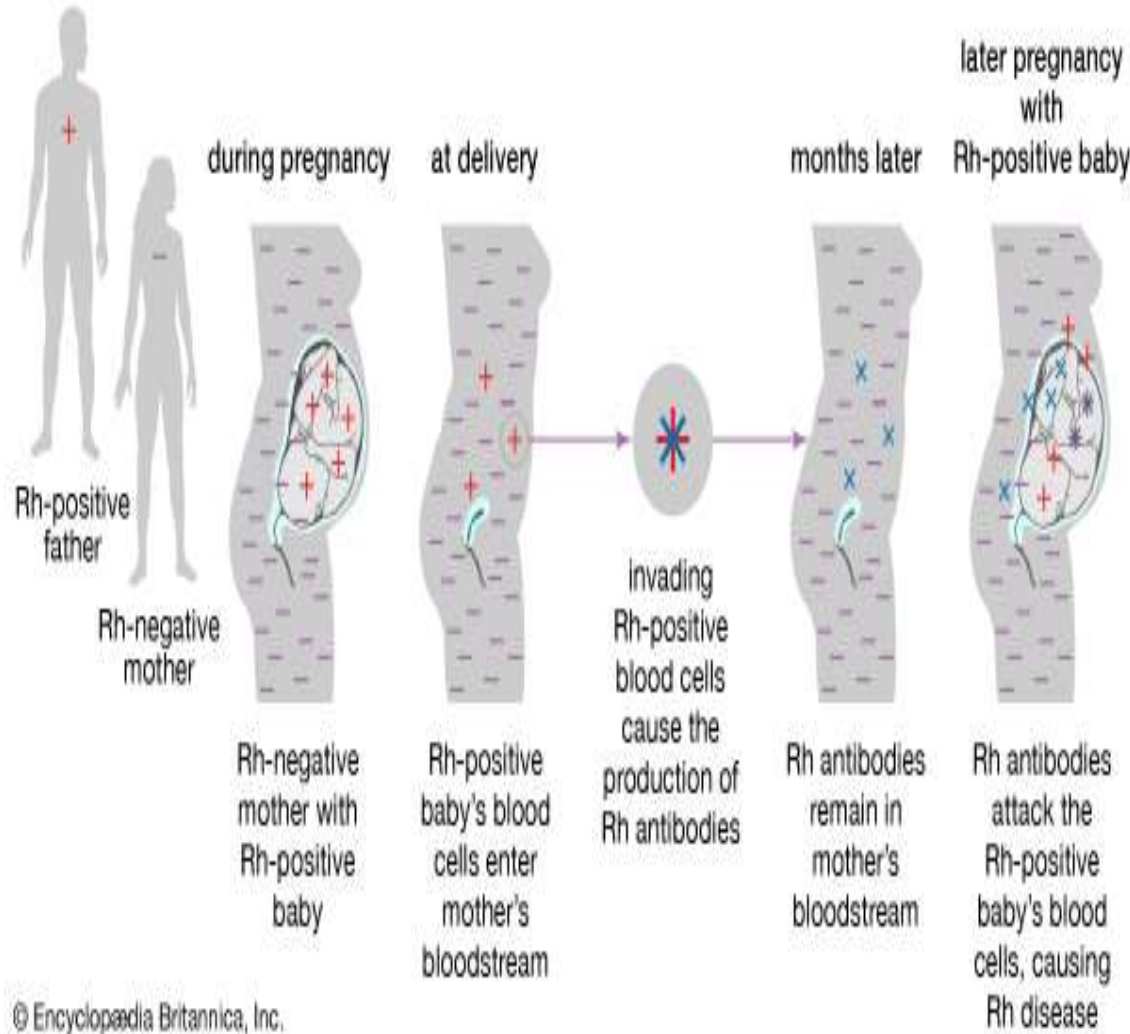
When drug is withdrawn, the hemolytic anemia disappears.

Drug-induced hemolytic anemia

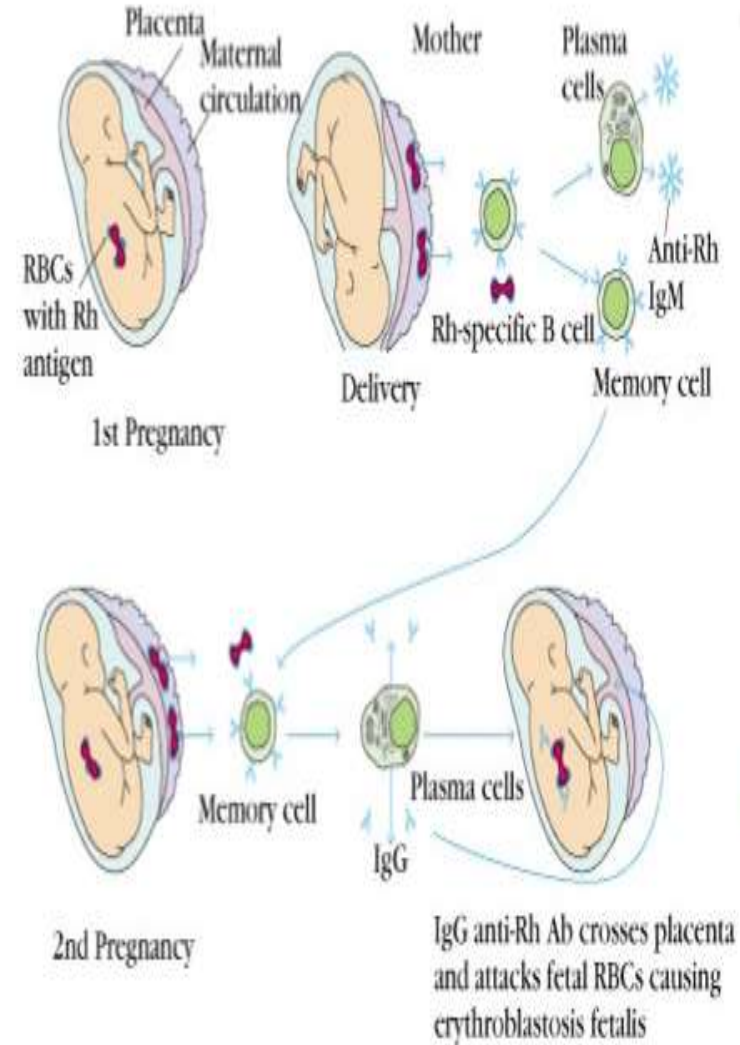
- ◆ Drug adsorb RBC proteins → Anti-RBC IgG/IgM → complement, opsonization, ADCC → RBC lysis, anemia



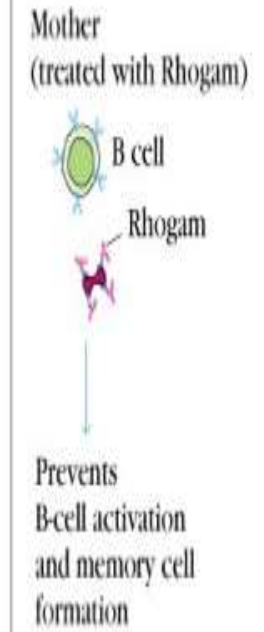
How Rh hemolytic disease develops



DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)



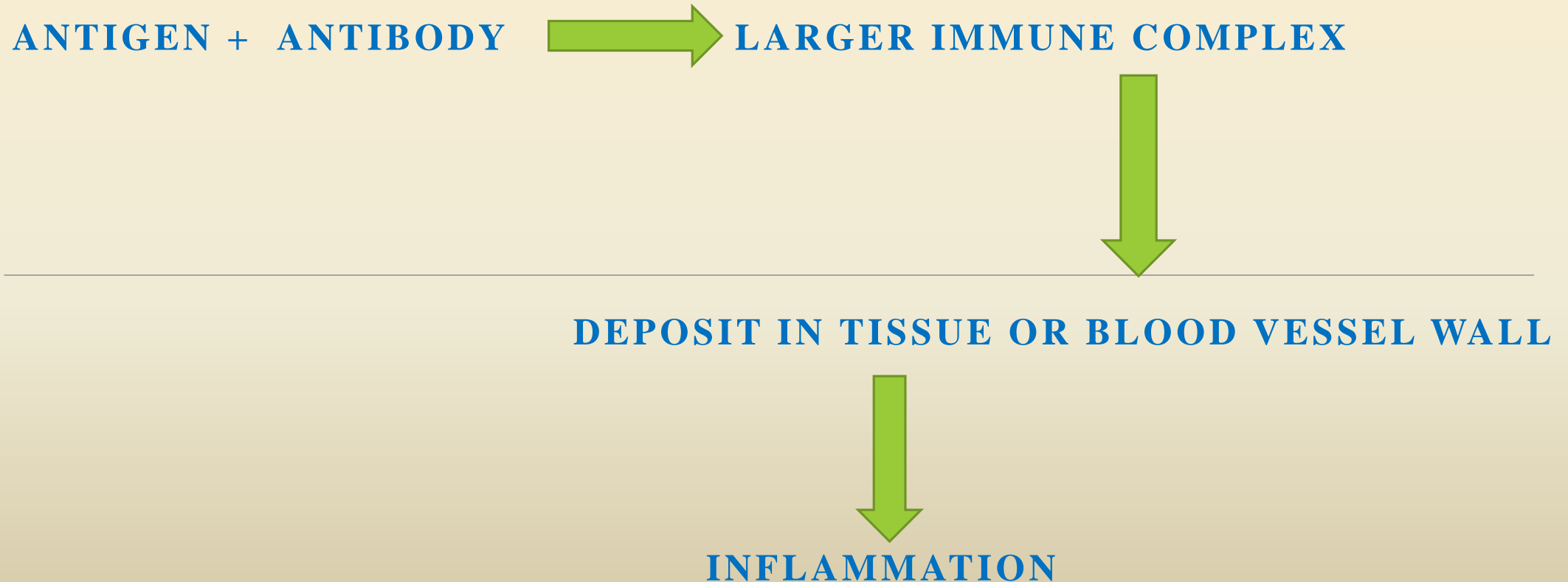
PREVENTION (WITH RHOGAM)



Human anti-Rh IgG antibodies

Hypersensitivity type III (Immune Complex mediated)

*TYPE III HYPERSENSITIVITY IS CAUSED BY GENERATION OF ANTIBODY-ANTIGEN COMPLEXES, TERMED "**IMMUNE COMPLEXES**", WHICH INDUCE INJURIOUS INFLAMMATION FOLLOWING DEPOSITION IN HOST TISSUE.*



Formation of Immune Complexes

Antigens which induce complex formation can be of endogenous or exogenous origin.

Exogenous

- Infectious agent (bacteria, viruses etc.)
- Certain drugs and chemicals

Endogenous

- Blood components (Ig , tumor antigens)

Deposition of Immune Complexes

Normally, large immune complexes are cleared by tissue macrophages in the spleen and lymph nodes; however, if the complexes are smaller or macrophages become burdened, the complexes can precipitate out of circulation and deposit in a variety of tissues.

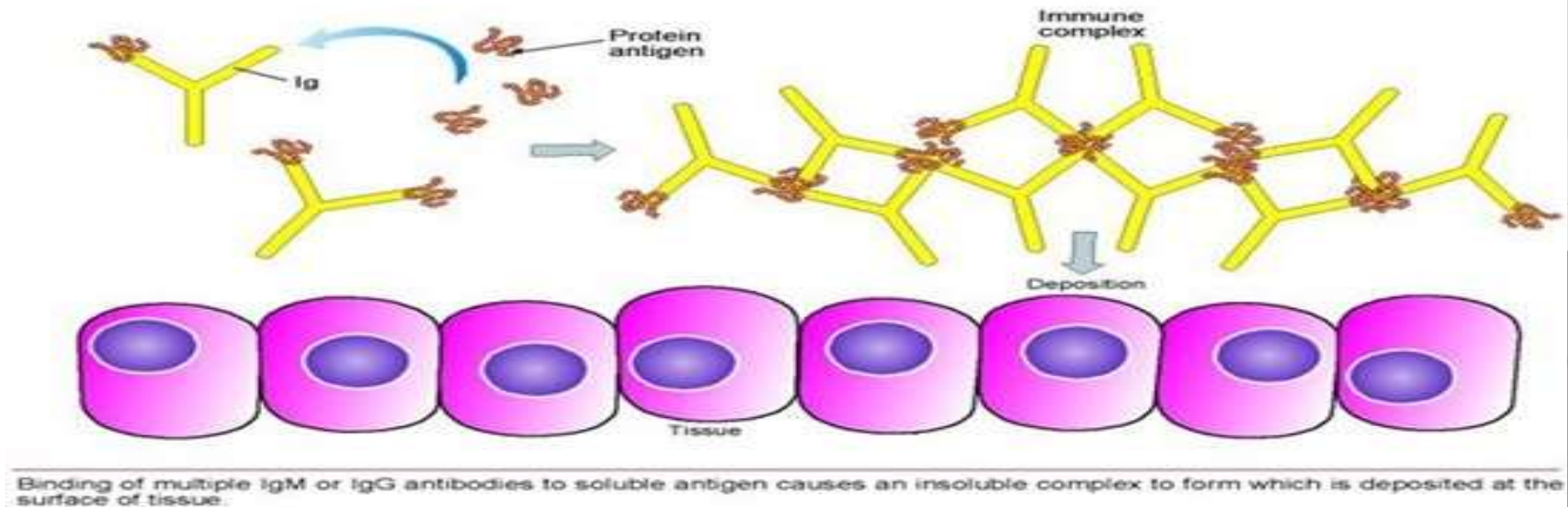
Preferred sites of deposition:

- small blood vessels
- synovial membrane of joints
- glomerular basement membrane of kidney

Inflammatory Reaction

Deposited complexes can activate the Classical Pathway of the complement cascade, resulting in the release of C3a and C5a which recruit of **neutrophils and macrophages**. Additionally, the Fc Region of antibodies within the complex can directly recruit neutrophils and macrophages that in turn cause potent inflammatory damage to the tissue.

Type 3 - immune complex hypersensitivity



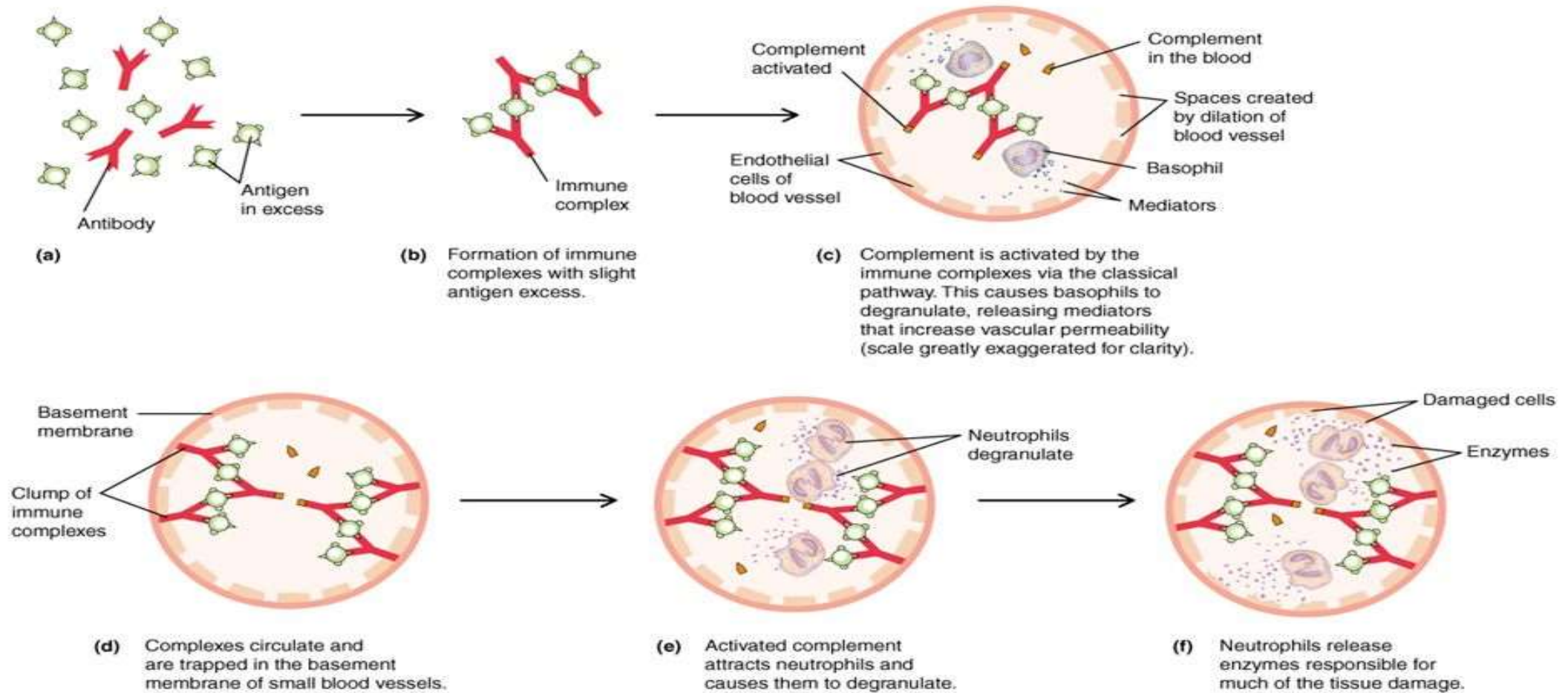
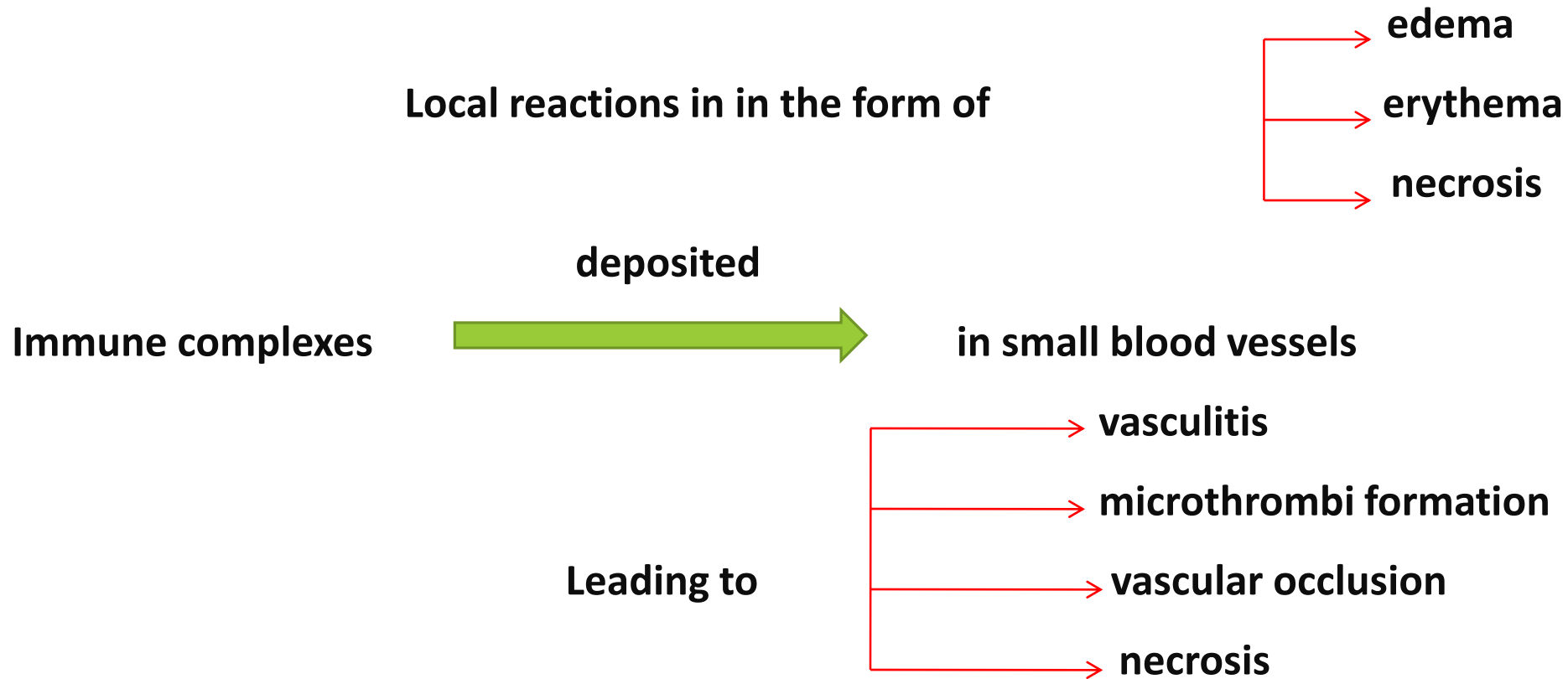


Figure 18.5 Immune complex - mediated

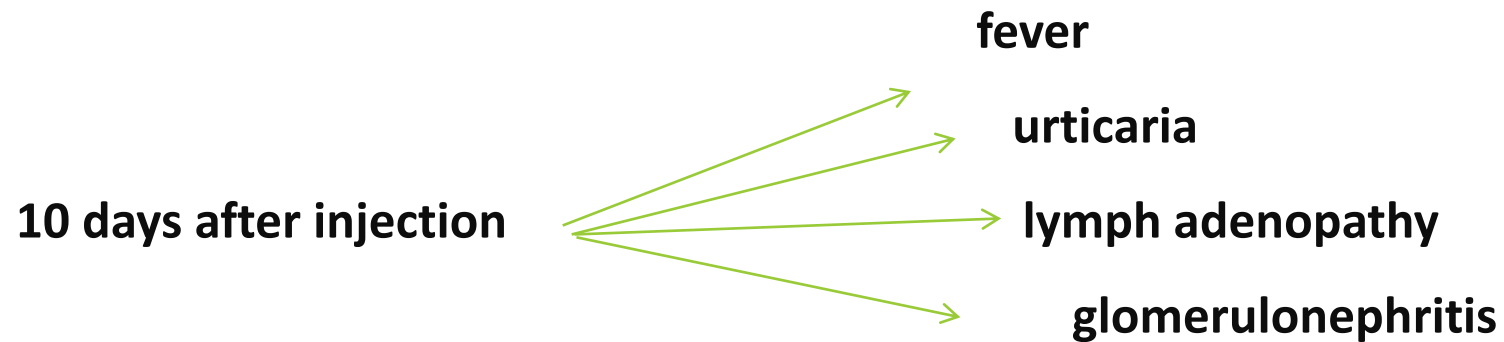
Arthus Reaction

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



Serum Sickness

- A systemic immune complex phenomenon
- Injection of large doses of foreign serum e.g. Antitoxin
- Anti-antitoxin antibodies react with the antitoxin forming immune complexes that deposit in tissues, walls of the blood vessels, skin, joints, kidney



IMMUNE COMPLEX DISEASES

- ❖ **Glomerulonephritis**
- ❖ **Rheumatoid Arthritis**
- ❖ **Systemic Lupus Erythematosus**

Glomerulonephritis



- Immune complexes in the blood are deposited in glomeruli
- Damage to the glomerular cells impedes blood filtration
- Kidney failure and, ultimately, death result
- Treated with corticosteroids (reduce swelling and suppress immune system).

Rheumatoid arthritis

- ❖ Immune complexes deposited in the joint

- ❖ Rheumatoid factor (RF) defined as an antibody against the Fc portion of IgG.
- ❖ Results in release of inflammatory chemicals
- ❖ The joints begin to break down and become distorted
- ❖ Trigger not well understood
- ❖ Treated with anti-inflammatory drugs.



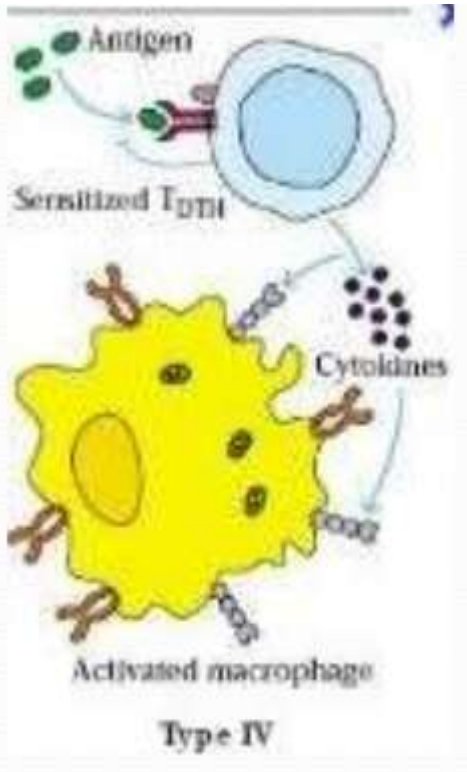
Systemic lupus erythematosus

- **Autoantibodies against DNA ,histone result in immune complex formation**
- **Many other autoantibodies can also occur against:**
 - ✓ **red blood cells**
 - ✓ **Platelets**
 - ✓ **lymphocytes**
 - ✓ **muscle cells**
- **Immunosuppressive drugs reduce autoantibody formation**
- **Glucocorticoids reduce inflammation**

The characteristic facial and hand rash of systemic lupus erythematosus



Hypersensitivity Type IV



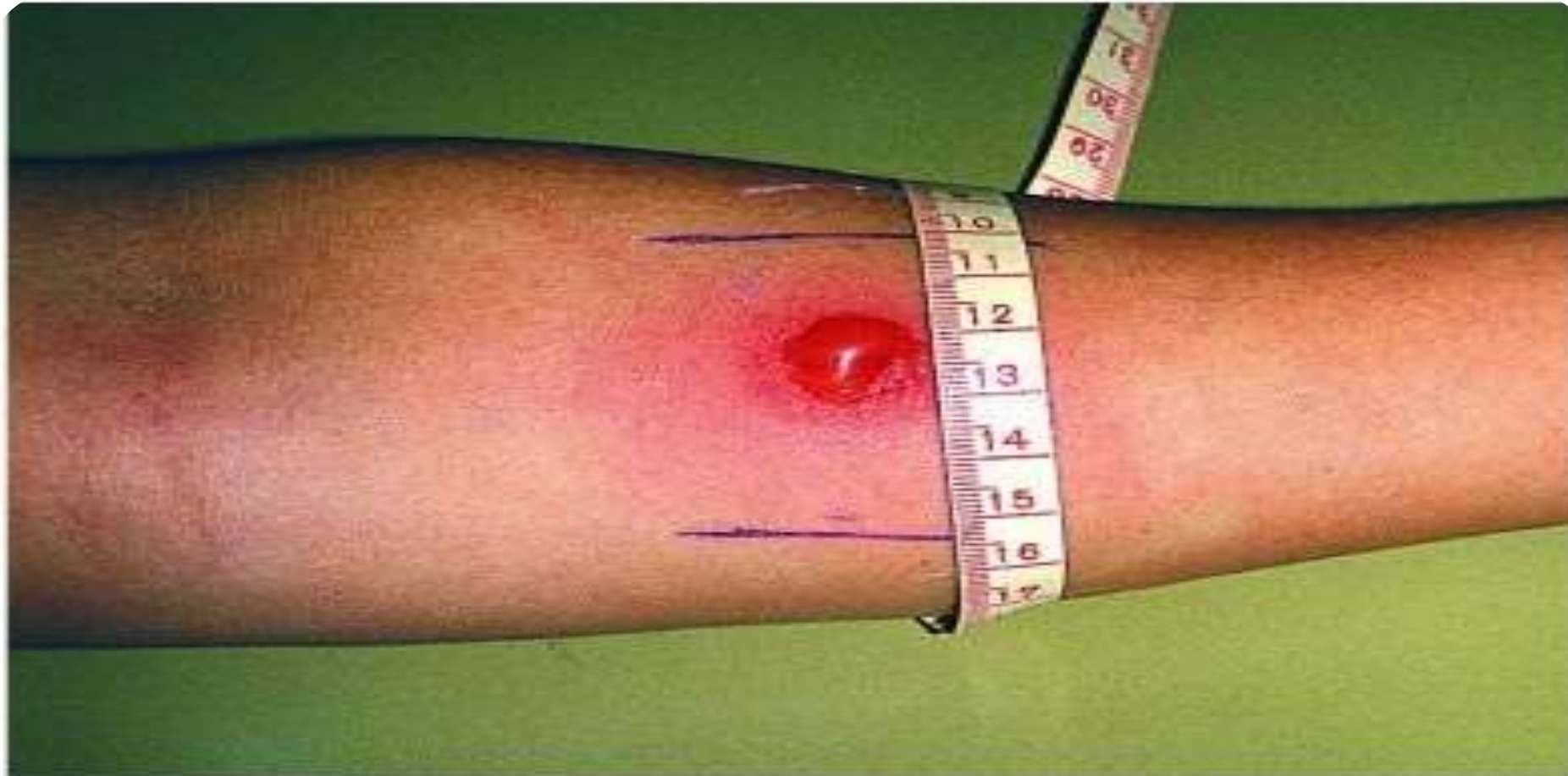
Type IV hypersensitivity reaction is also called delayed type hypersensitivity reaction because it takes 2 to 3 days for the reaction to develop after exposure to the particular substance.

Initiated by specifically sensitized T lymphocytes which respond to an antigen by producing and releasing certain cytokines and they recruit, retain and activate macrophages to destroy the antigen

Tuberculin-type hypersensitivity

- An injection of tuberculin beneath the skin causes reaction in individual exposed to tuberculosis or tuberculosis vaccine
- Used to diagnose contact with antigens of **M. tuberculosis**
 - ✓ No response when individual not infected or vaccinated
 - ✓ Red, hard swelling develops in individuals previously infected or immunized.

Positive tuberculin test



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Allergic contact dermatitis

- ❖ Cell-mediated immune response
- ❖ Results in an intensely irritating skin rash
- ❖ Triggered by chemically modified skin proteins that the body regards as foreign
- ❖ fluid-filled blisters develop in severe cases
- ❖ Can be treated with glucocorticoids



THANK YOU !!!!!

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