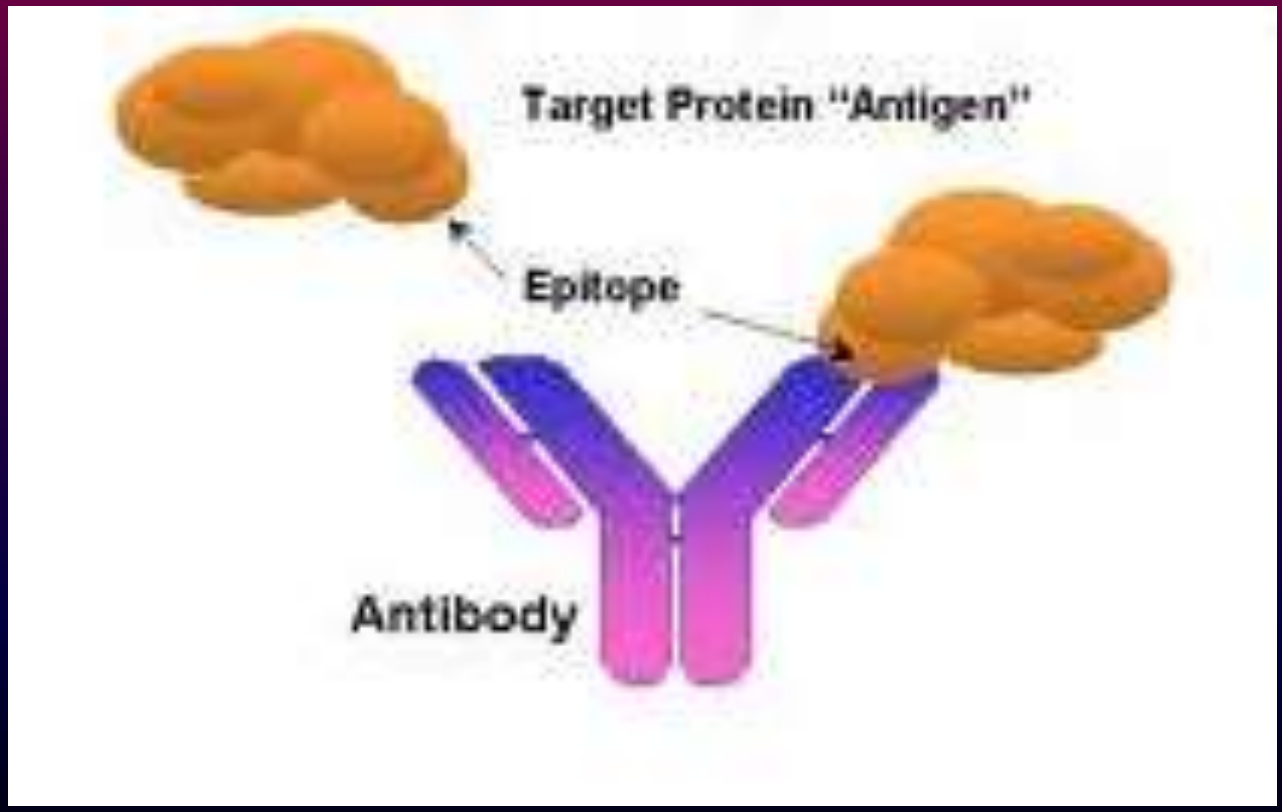
HYPERSENSITIVITY

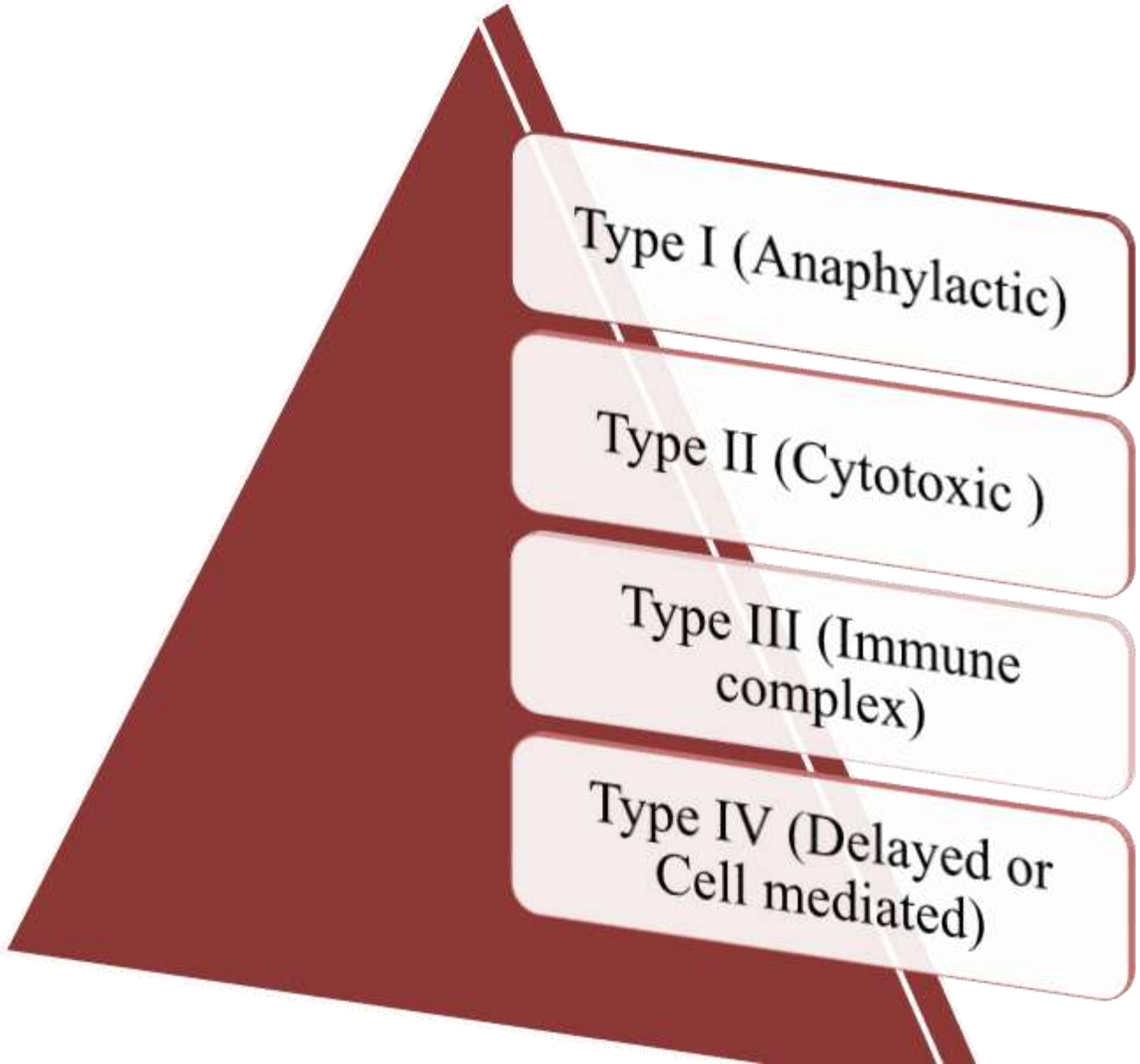


Dr. Amit Makkar, Sudha Rustagi Dental College

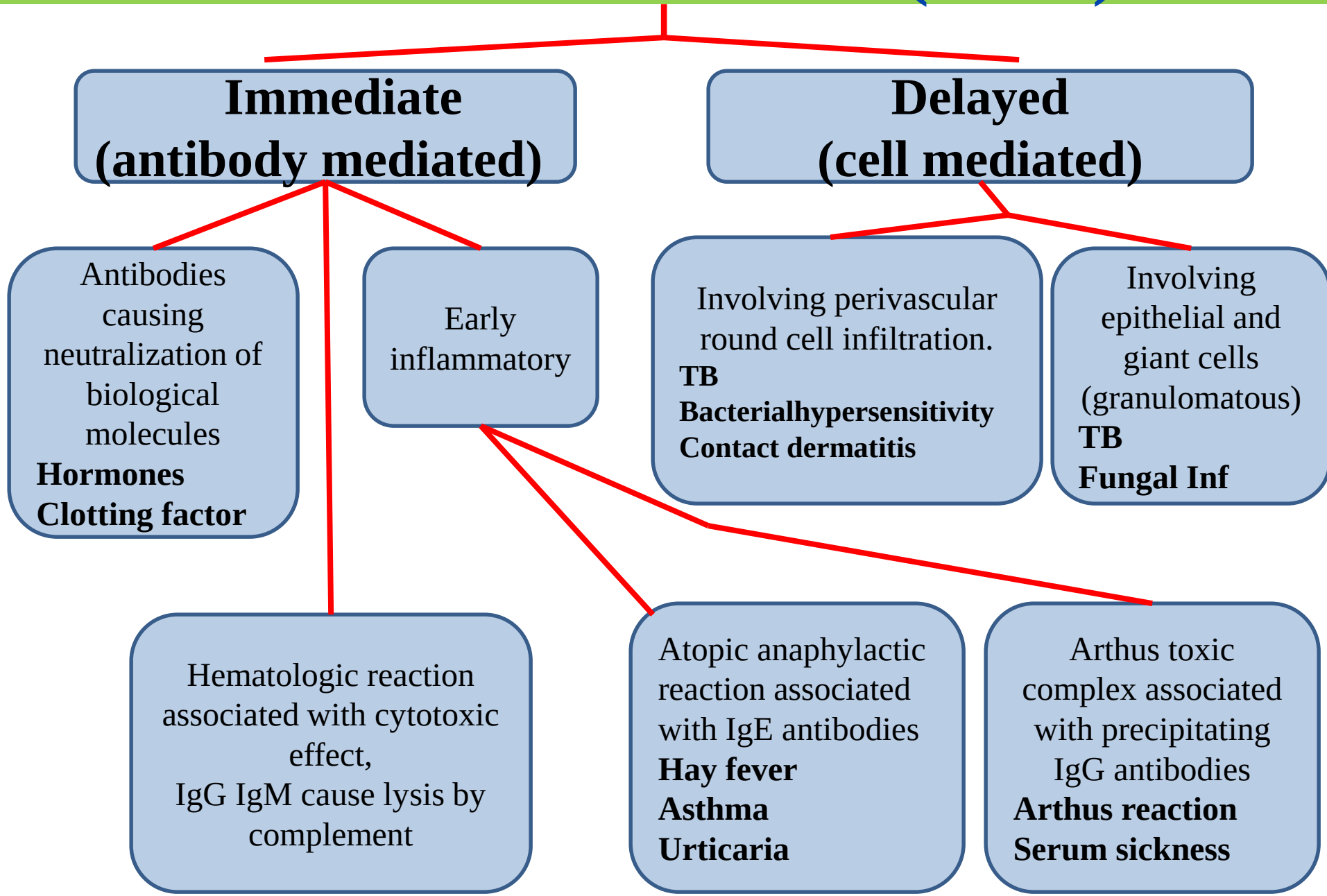
- **Hypersensitivity reactions** are harmful antigen-specific immune responses , occur when an individual who has been primed by an innocuous antigen subsequently encounters the same antigen , produce tissue injury and dysfuntion.

- It is defined as a state of exagerrated immune response to an antigen.

Coombs & Gell Classification (1963)



Sell's Classification (1972)



Chase Classification

IMMEDIATE REACTION	DELAYED REACTION
Appears and recedes rapidly	Appears slowly and lasts longer
Induced by antigen by any route	Indued by infection, antigen injection, skin contact
Circulating antibodies present and responsible for reaction	Cell mediated reaction
Passive transfer possible with serum	Transfer possible by lymphocytes or tranfer factors
Desensitisation is easy but short lived	Desensitisation is difficult but long lasting
Lesions are acute exudation and fatty necrosis	Mononuclear cell collection around blood vessels
Wheal and flare with maximum diameter in ^ hours	Erythema and induration with maximum diameter in 24-48 hours

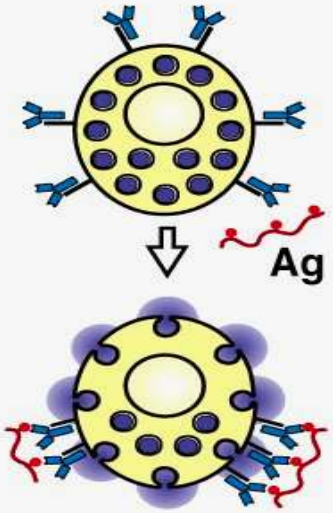
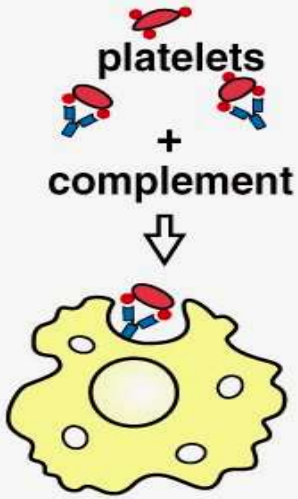
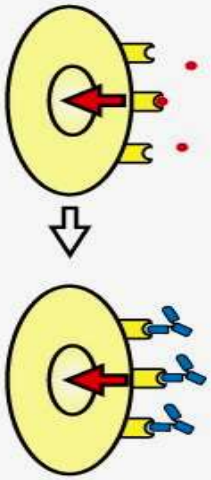
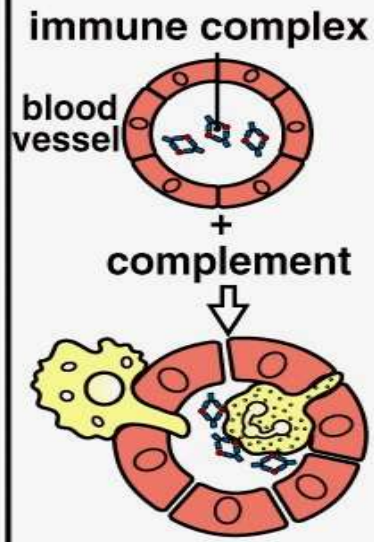
	Type I	Type II		Type III
Immune reactant	IgE	IgG		IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes
				
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction

Figure 12-2 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

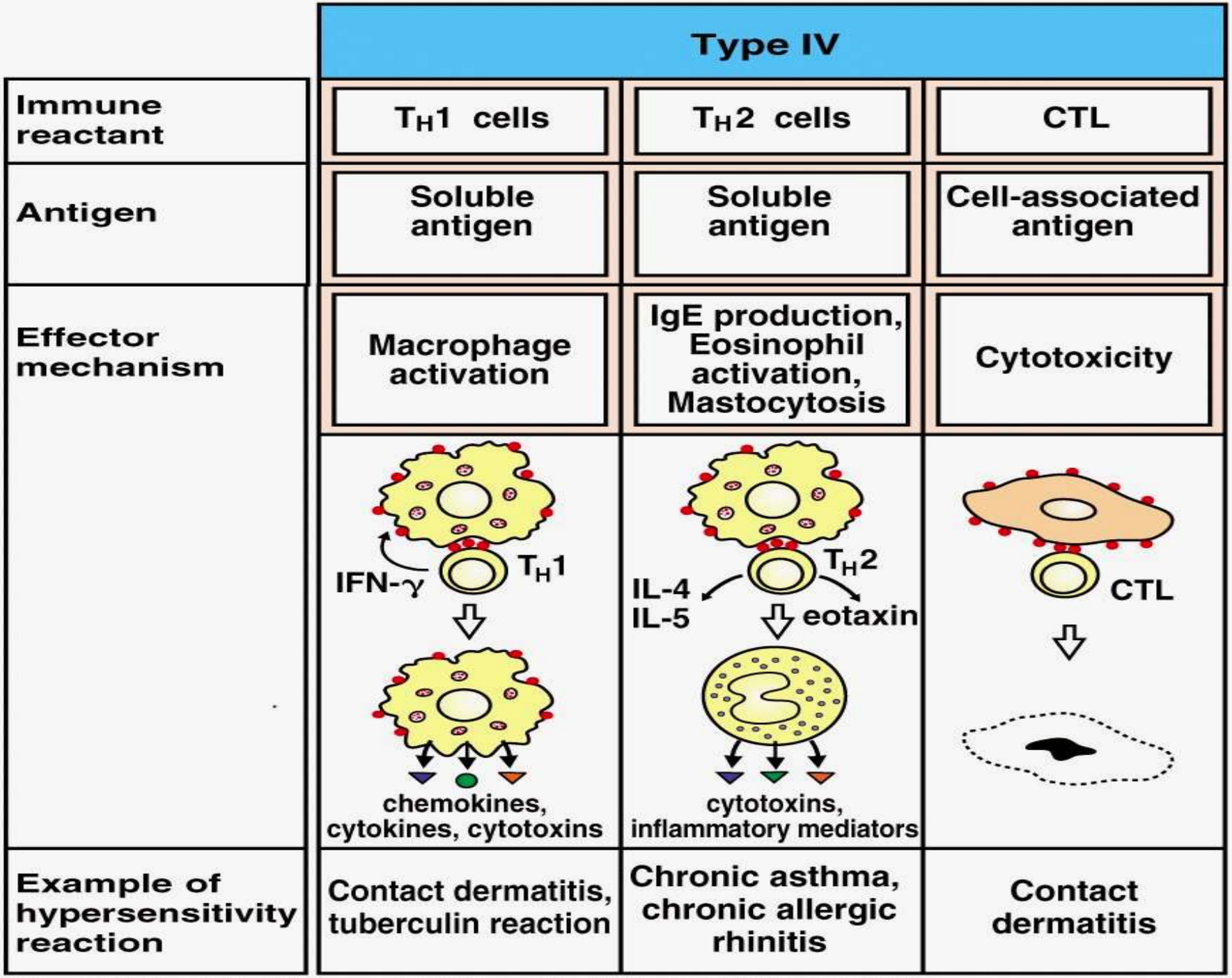
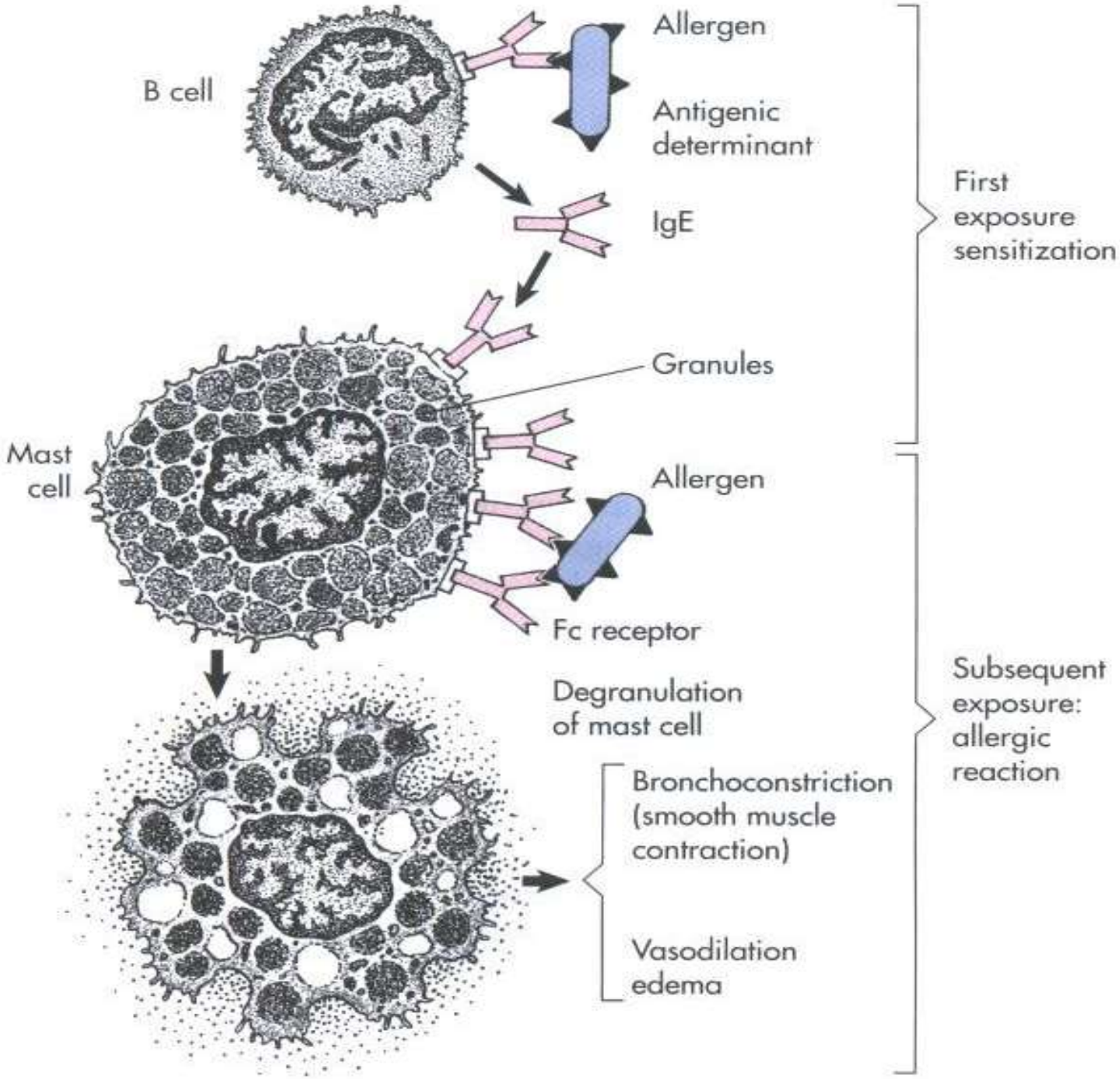


Figure 12-2 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

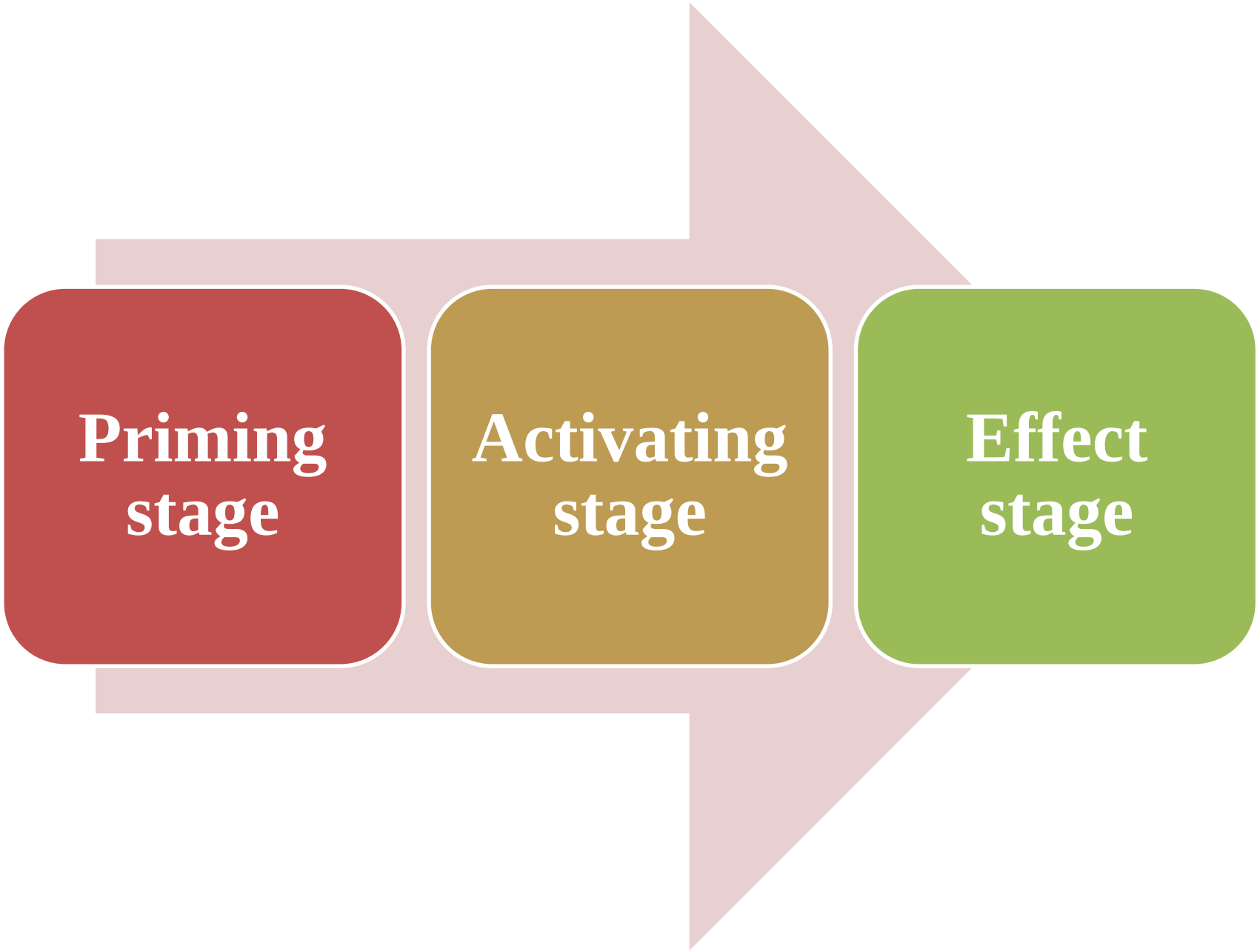
I)Type I Hypersensitivity (Anaphylactic, Atopic)

- It is defined as a state of rapidly developing immune response to an antigen to which the individual is previously sensitised.

- The response is mediated by humoral antibodies of IgE type or reagin antibodies.


B cell
Allergen
Antigenic determinant
IgE
Granules
Mast cell
Allergen
Fc receptor
Degranulation of mast cell
Bronchoconstriction (smooth muscle contraction)
Vasodilation edema
First exposure sensitization
Subsequent exposure: allergic reaction

The process and mechanism of Type I hypersensitivity



1) **Priming stage**：last more than half a year

2) **Activating stage**：

Cross-linkage → Enzyme reaction

↓

De-granulation of mast cell , basophil

3) Effect stage

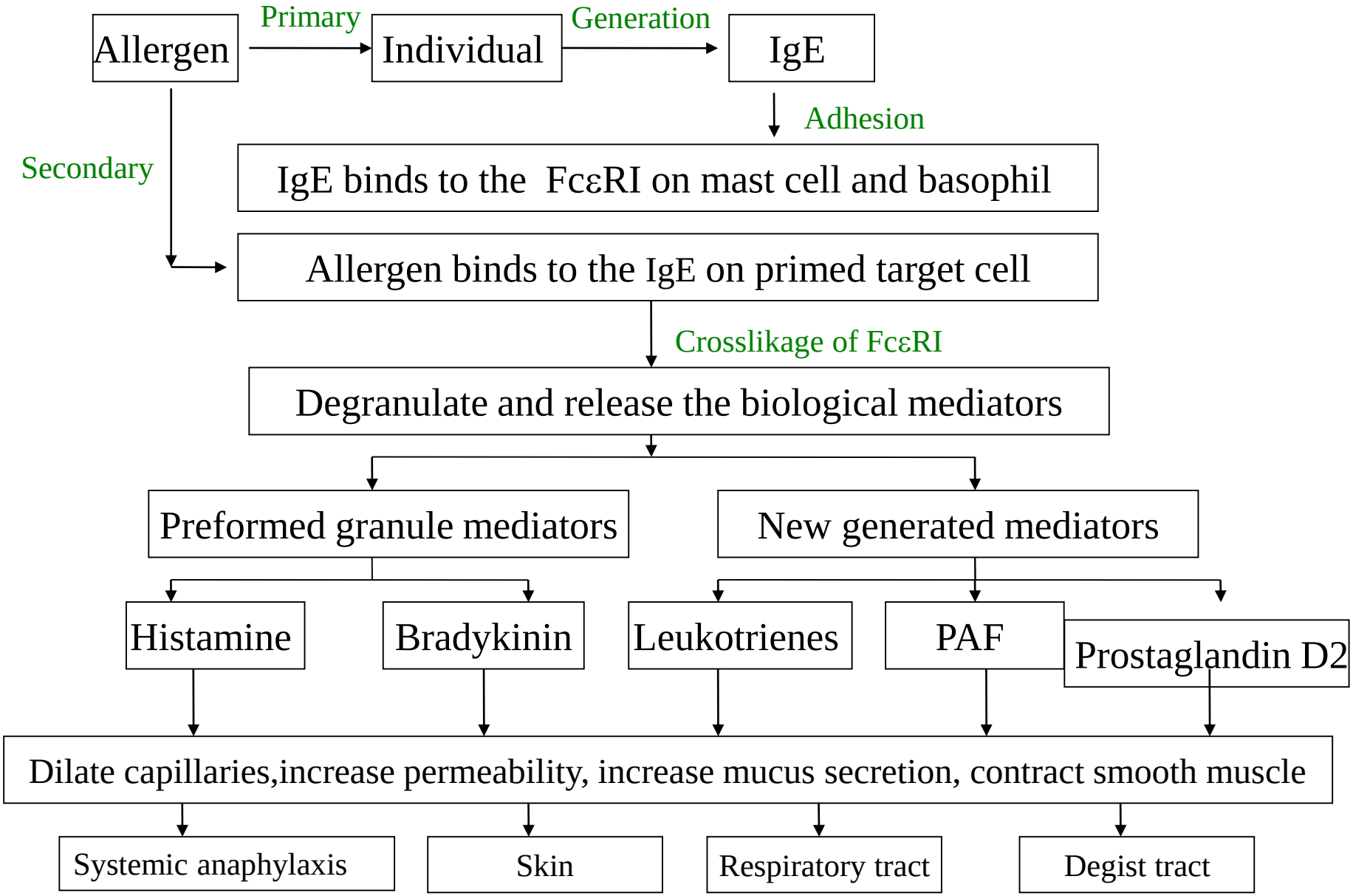
Immediate/early phase response

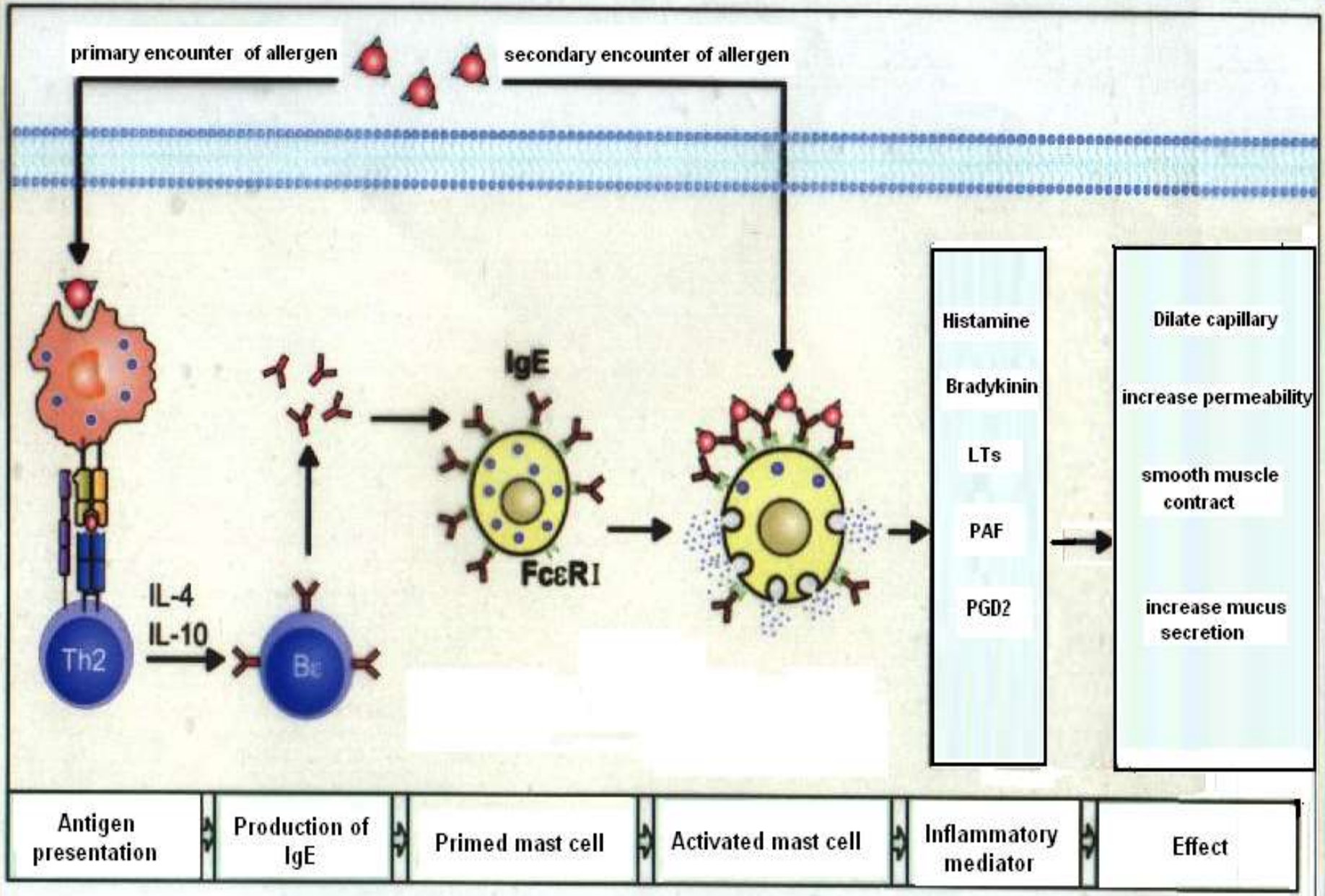
- Mediated by histamine
- Start within seconds
- Last several hours

Late-phase response

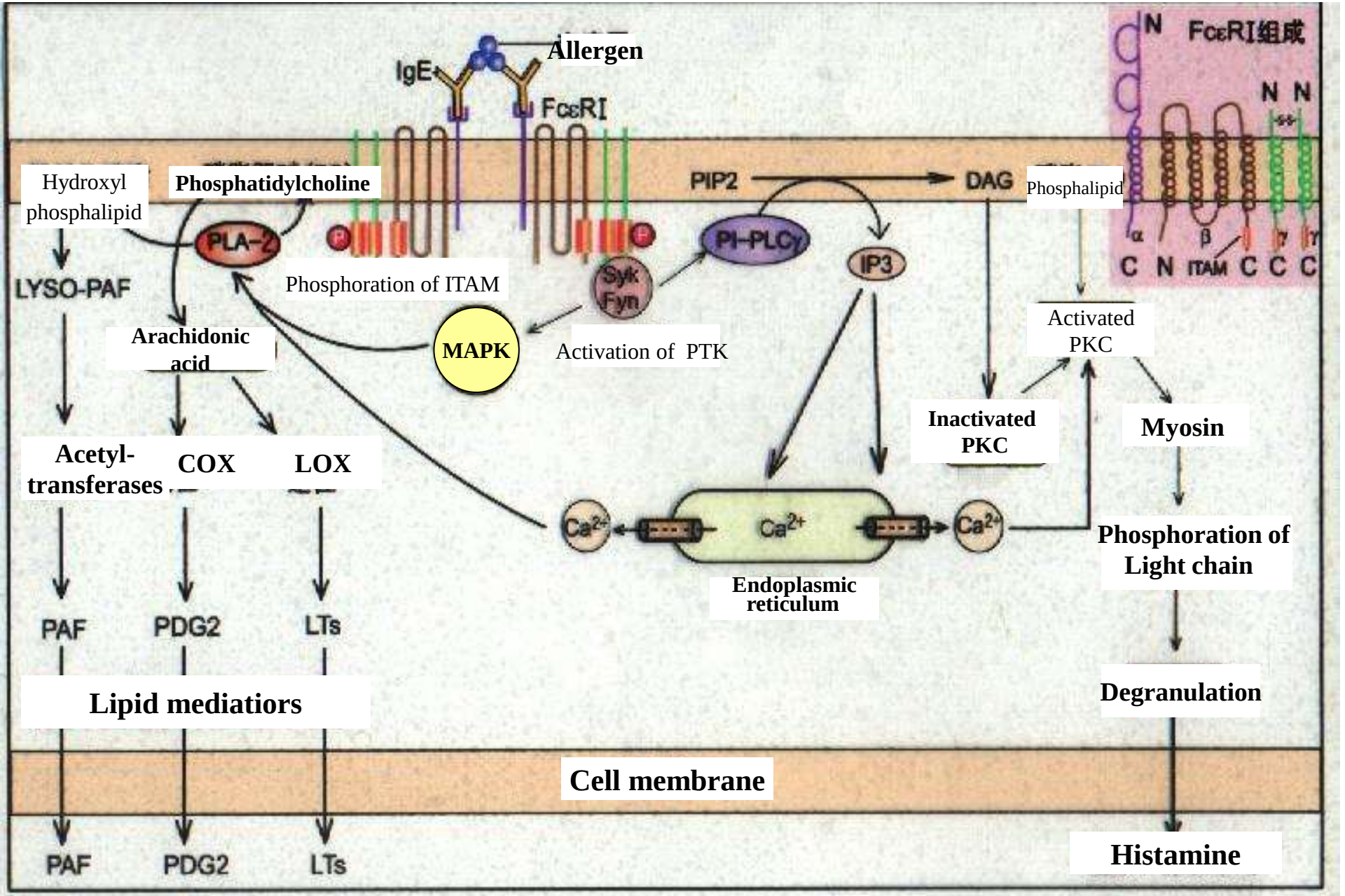
- Mediated by new-synthesized lipid mediators
- Take up 8-12hours to develop
- Last several days

Mechanism of type I hypersensitivity





The process of type I hypersensitivity



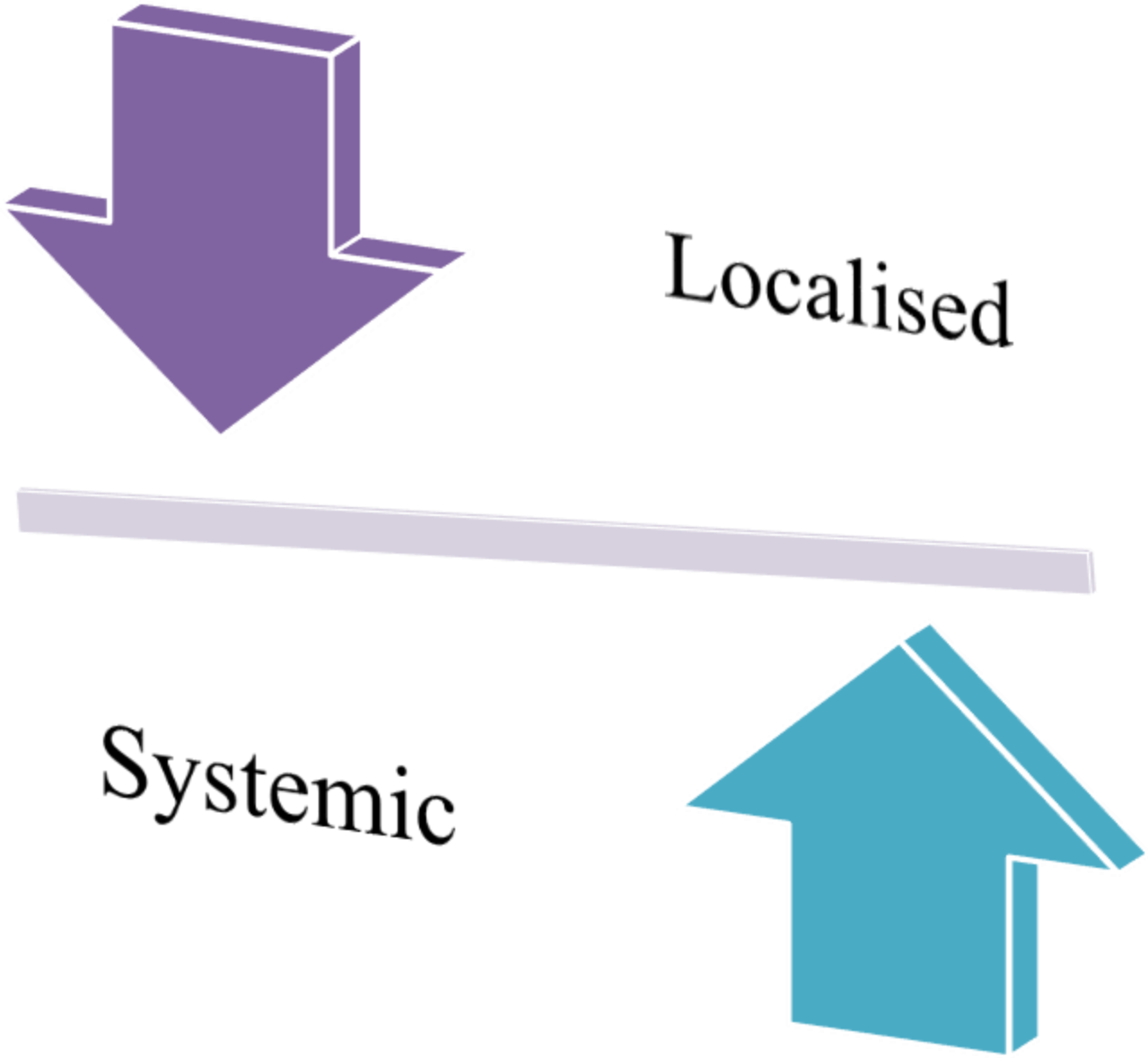
Degranulation ,release and synthesis
of biological mediators of primed target cells

The chemically active effectors within the granules released via degranulation are called **mediators**. This group includes:

Mediator	Effects
Primary	
Histamine	Increased vascular permeability; smooth-muscle contraction
Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; generation of complement split products

Secondary	
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells

ANAPHYLAXIS



Systemic Anaphylaxis

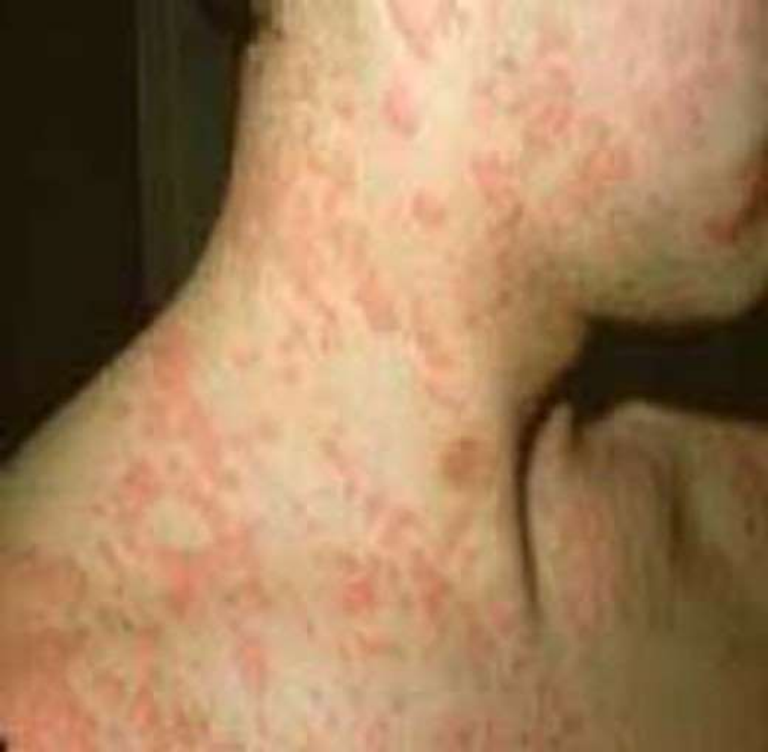
- The clinical features of systemic anaphylaxis include itching, erythema, contraction of respiratory bronchioles, diarrhoea, pulmonary oedema, pulmonary haemorrhage, shock and death.

- Examples of systemic anaphylaxis :-
  i) Administration of antisera e.g. anti-tetanus serum (ATS)
  ii) Administration of drugs e.g. penicillin
  iii) Sting by wasp or bee.

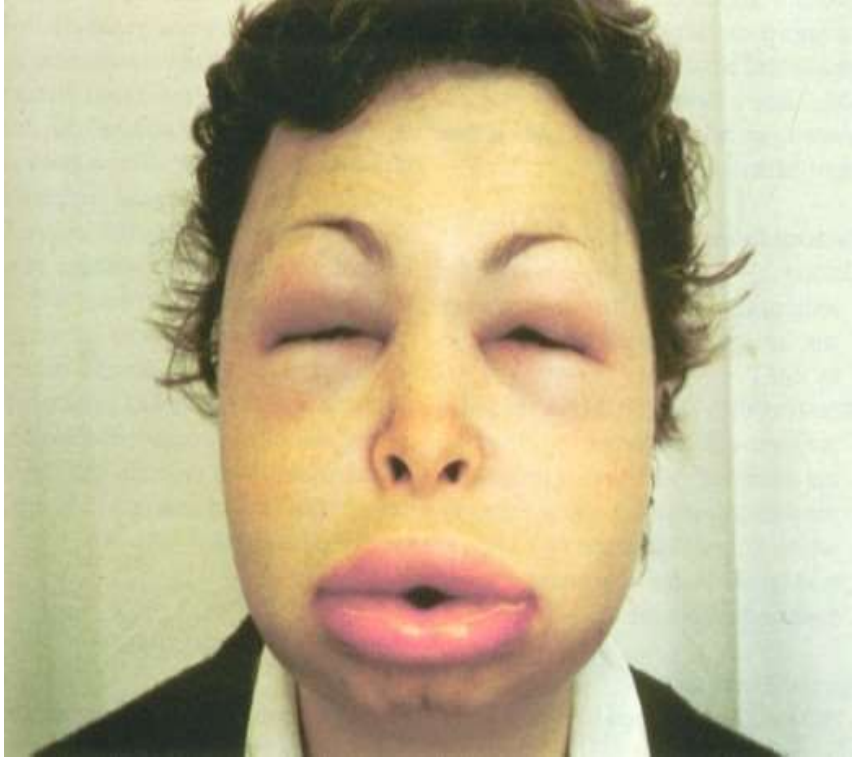
Pathophysiology of Systemic Anaphylaxis

- Systemic vasodilation and smooth muscle contraction leading to severe bronchiole constriction, edema, and shock.

- Similar to systemic inflammation.



wheal\ urticarial rash



Thick lips and periorbital edema (angioedema)

Localised Anaphylaxis

- Local anaphylaxis is common, affecting about 10% of population. About 50% of these conditions are familial with genetic predisposition and therefore also called atopic reactions

HAY FEVER (seasonal allergic rhinitis) due to pollen sensitisation of conjunctiva and nasal passages

BRONCHIAL ASTHMA due to allergy to inhaled allergens like house dust

FOOD ALLERGY to ingested allergens like fish, cow's milk etc

CUTANEOUS ANAPHYLAXIS due to contact of antigen with skin characterised by urticaria, wheal and flare

ANGIOEDEMA, an autosomal dominant inherited disorder characterised by laryngeal oedema, oedema of eyelids, lips, tongue and trunk.

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

Therapy of type I hypersensitivity

The basic **4A's** in the management of anaphylactic reaction :-

- **A**ntihistaminic agent (benedryl 20-50mg)
- **A**drenaline 0.5 ml of 1:1000 i.m
- **A**minophylline 0.5mg i.m
- **A**irway oxygen

- Other---

  Adrenaline inhalents

  Hydrocortisone sodium succinate 100mg i.m

  Cricothyrotomy for airway maintainance if required

Therapy of type I hypersensitivity

1. **Allergen avoidance :** Atopy patch test

2. **Desensitivity therapy / Hyposensitization :**

i) Allogenic serum desensitivity therapy:

Repeated injection small amounts of allergen (allergy shots)

ii) Specific allergen desensitivity therapy

IgG+allergen → Neutralizing antibody, → Blocking antibody

3. Drug therapy :

i) Stabilization of triggering cells

Sodium cromoglycate — stabilize the membrane, inhibit mast cell degranulation

ii) Mediator antagonism

Chlor-Trimeton — Antihistamine

Acetylsalicylic acid — Bradykinin antagonism

iii) Improve the responsibility of target organs

4. Allergen immunotherapy : Rehabilitates the immune system and involves administering increasing doses of allergens to accustom the body to substances that are generally harmless (pollen, house dust mites) and thereby induce specific long-term tolerance.

Allergen immunotherapy can be administered under the tongue (sublingually with drops or tablets) or by injections under the skin (subcutaneous).

I)Type II Hypersensitivity (Cytotoxic Reaction)

- Cytotoxic reactions are defined as those reactions which cause injury to the cell by combining humoral antibodies with cell surface antigens; blood cells being affected more commonly.

Characteristic features

Primed IgG or IgM + Antigen or hapten on membrane

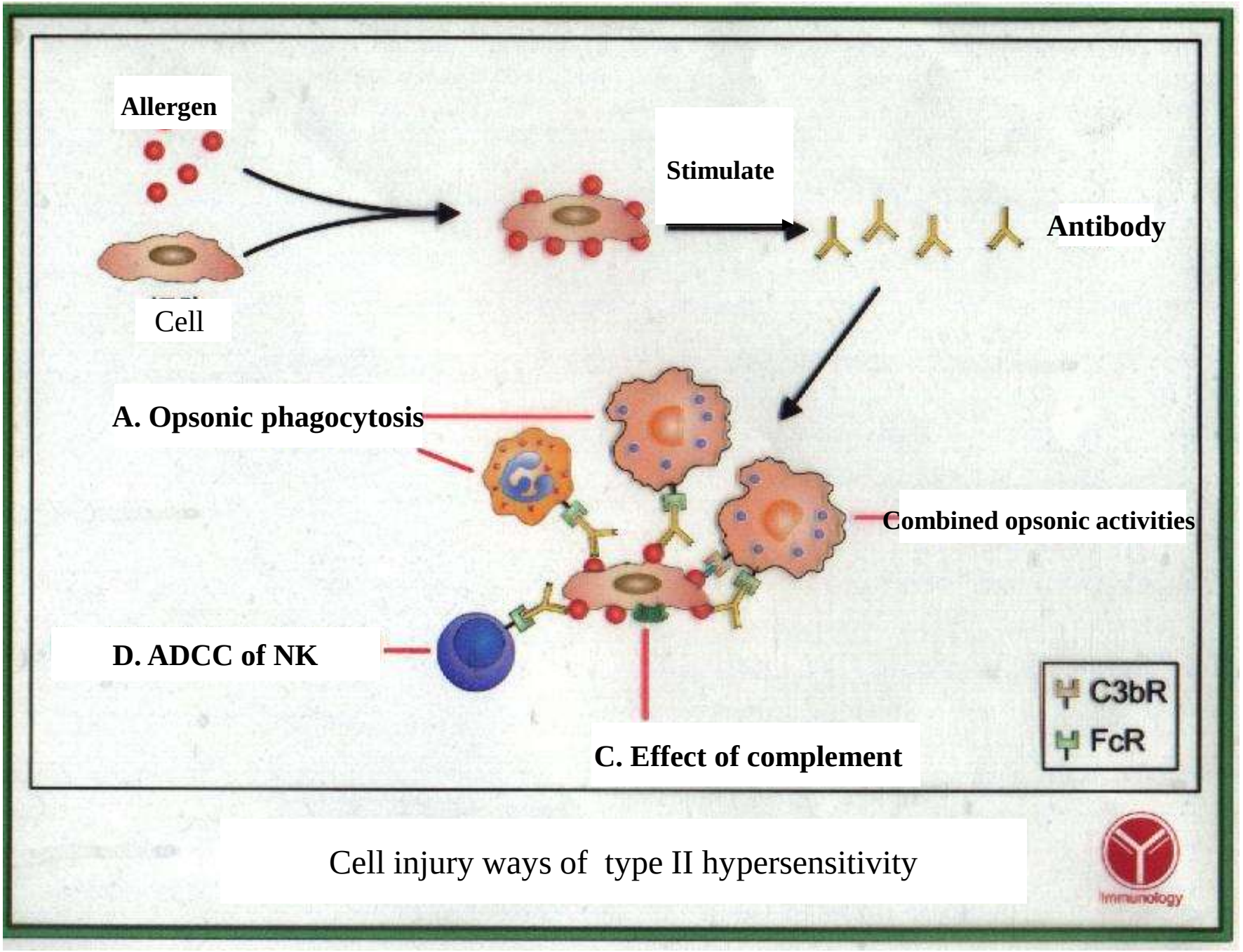
↓

Injury and dysfunction of target cells

- Involves the antibody mediated destruction of cells.

- Can mediate cell destruction by activating the complement system to create pores in the membrane of the foreign cell.

- Can also be mediated by ***Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)*** where the Fc receptors bind to Fc receptor of antibody on the target cell and promote killing.



Cell injury ways of type II hypersensitivity

Mechanism of type II hypersensitivity

1. Surface antigen on target cells

Target cells: Normal tissue cell, changed or modified self tissue cells

Antigen : Blood group antigen,

Drug antigen,

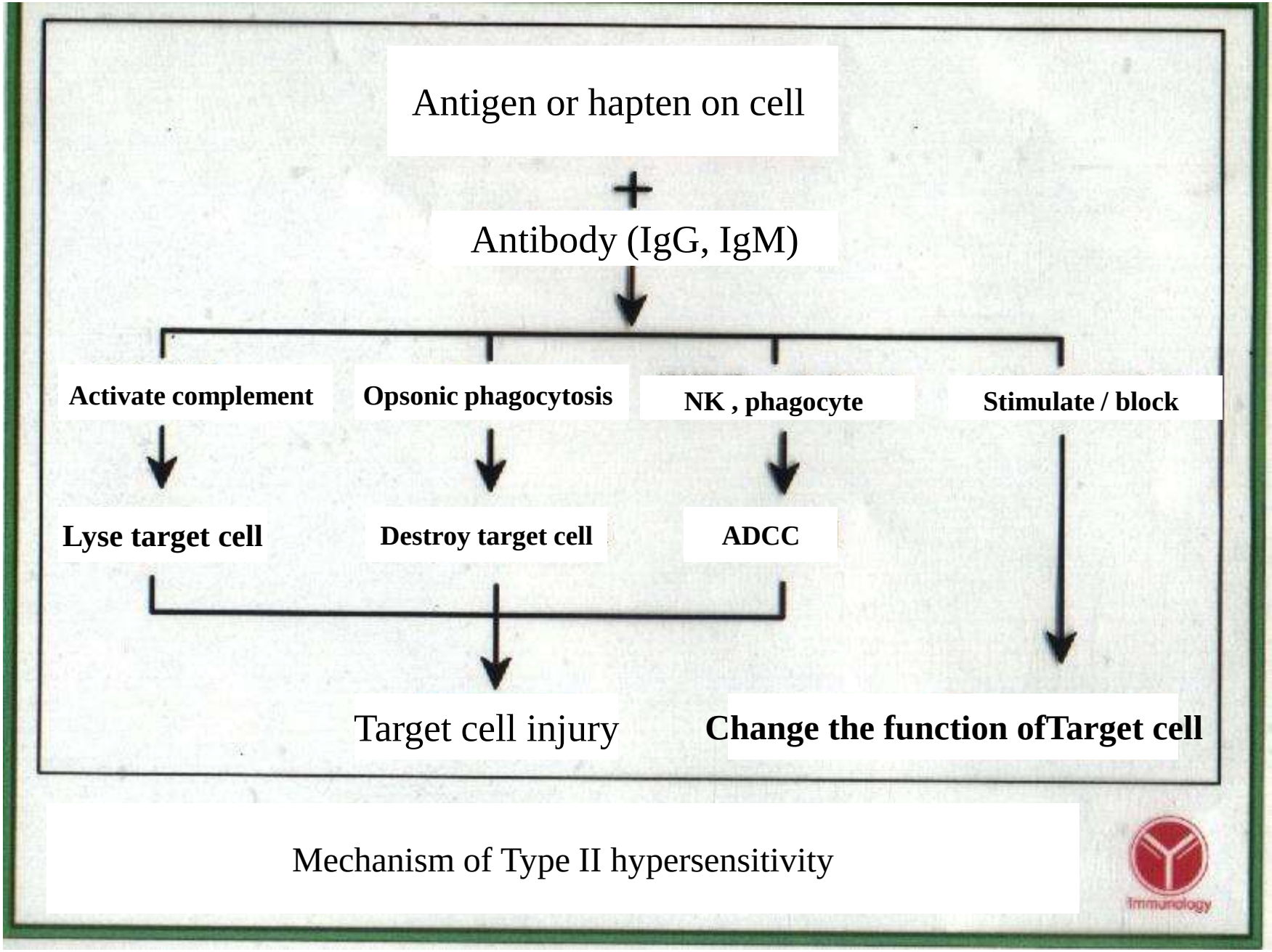
Self-antigen modified by physical factors or infection

Common antigen,

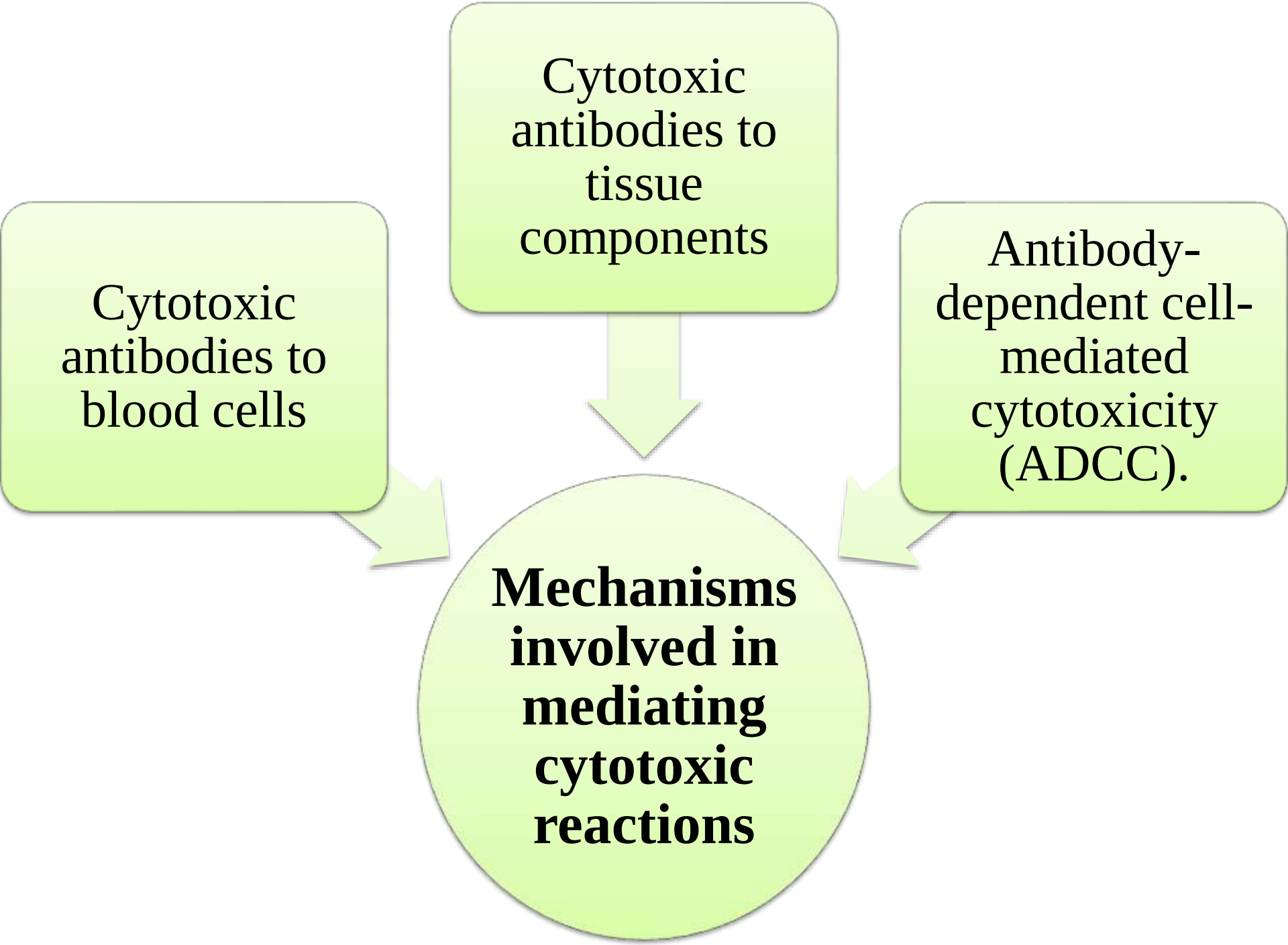
Antigen-antibody complex

2. Antibody, complement and modified self-cell

Activate complement	——	Lyse target cells
Opsonic phogacytosis	——	Destroy target cells
Mϕ、NK、 T	——	ADCC
Stimulating or blocking effect	——	Promote /surpress the target cell funcion



Mechanism of Type II hypersensitivity

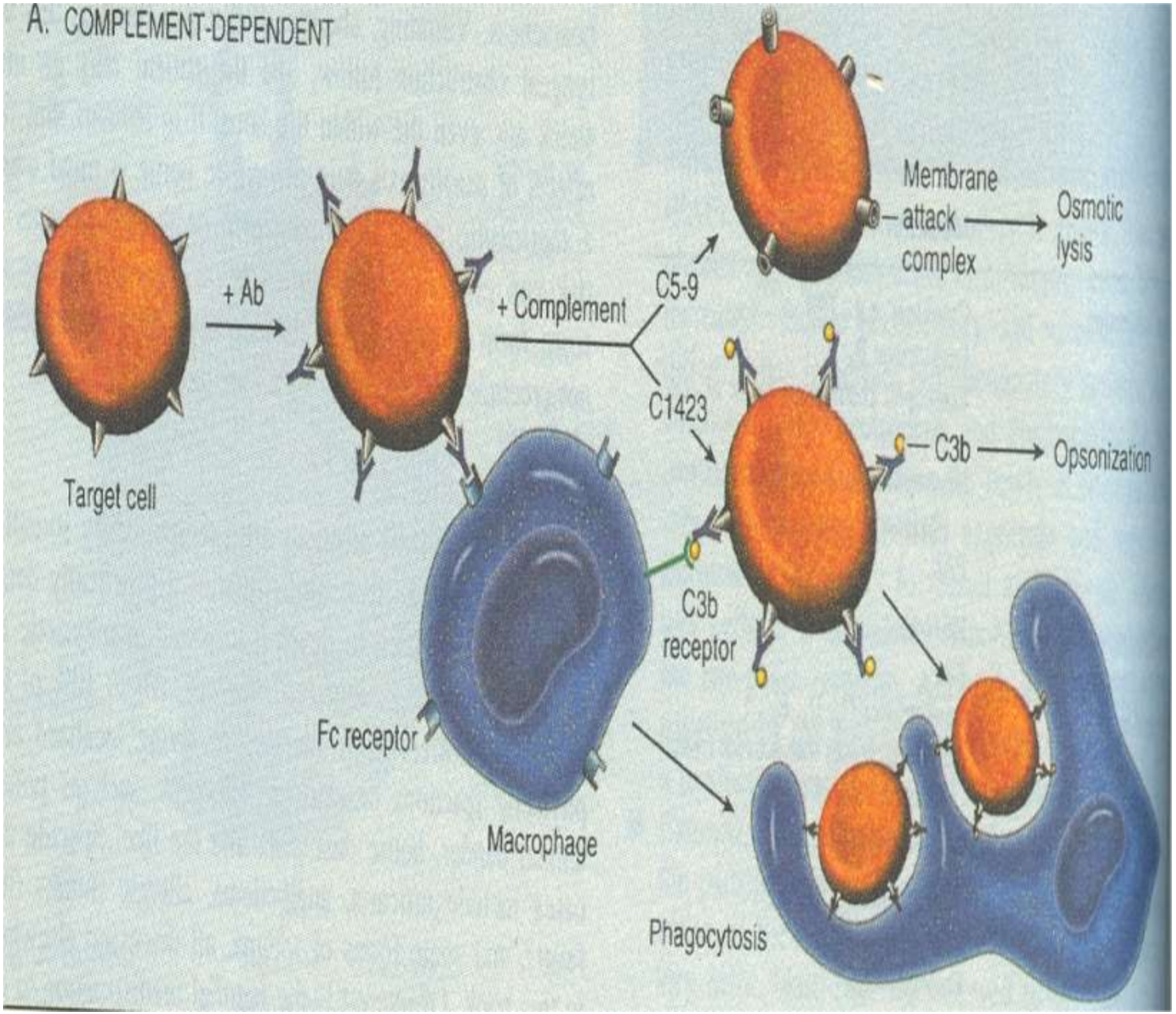

Cytotoxic antibodies to tissue components
Cytotoxic antibodies to blood cells
Antibody-dependent cell-mediated cytotoxicity (ADCC).
Mechanisms involved in mediating cytotoxic reactions

A. CYTOTOXIC ANTIBODIES TO BLOOD CELLS

- Involves direct cytolysis of blood cells (red blood cells, leucocytes and platelets) by combining the cell surface antigen with IgG or IgM class antibodies.

- Complement system is activated resulting in injury to the cell membrane.

- Cell surface is made susceptible to phagocytosis due to coating or opsonisation from serum factors or opsonins.


A. COMPLEMENT-DEPENDENT
Target cell
+ Ab
+ Complement
C5-9
Membrane attack complex
Osmotic lysis
C1423
C3b
Opsonization
C3b receptor
Fc receptor
Macrophage
Phagocytosis

Autoimmune hemolytic anemia and type II drug reaction

FOREIGN ANTIGEN OR HAPTEN

1. Penicillin — RBC — hemolytic anemia

2.Quinine — Platelet — thrombocytopenic purpura

3.Pyramidone — Granulocyte — agranulocytosis

SELF-ANTIGEN

Drug

↓

conversion from a hapten to a full antigen

↓

induce self antibody

↓

autoimmune hemolytic anemia

Drug-Induced Hemolytic Anemia

- Where certain antibiotics can be absorbed nonspecifically to the proteins on RBC membranes.
- Sometimes antibodies form inducing complement-mediated lysis and thus progressive anemia.
- Disappears on withdrawal of the drug.

Autoimmune haemolytic anemia

Red cell injury is brought about by autoantibodies reacting with antigens present on red cell surface.

Transfusion reaction

Hemolysis

- **Mismatch of ABO blood group**
- **Severely destroy RBC**

Nonhemolysis

- **Repeat transfusion of allogenic HLA**
- **Drug anaphylactic shock：penicilline**

Transfusion reactions

- Antibodies of the A,B, and O antigens are usually of the IgM class (these antigens are call *isohemagglutinins*)

- For example an A individual produce isohemagglutinins to B-like epitopes but not to A epitopes because they are self

- Person who are transfused with the wrong blood type will produce anti-hemmagglutinins causing complement mediated lysis

- Antibodies are usually of the IgG class

- Transfusion reactions can be delayed or immediate but have different Ig isohemagglutinins

- Immediate reactions has a complement-mediated lysis triggered by IgM isohemagglutinins

- Delayed reactions induce clonal selection and the productions of IgG which is less effective in activating the complement.
- This leads to incomplete complement-mediated lysis

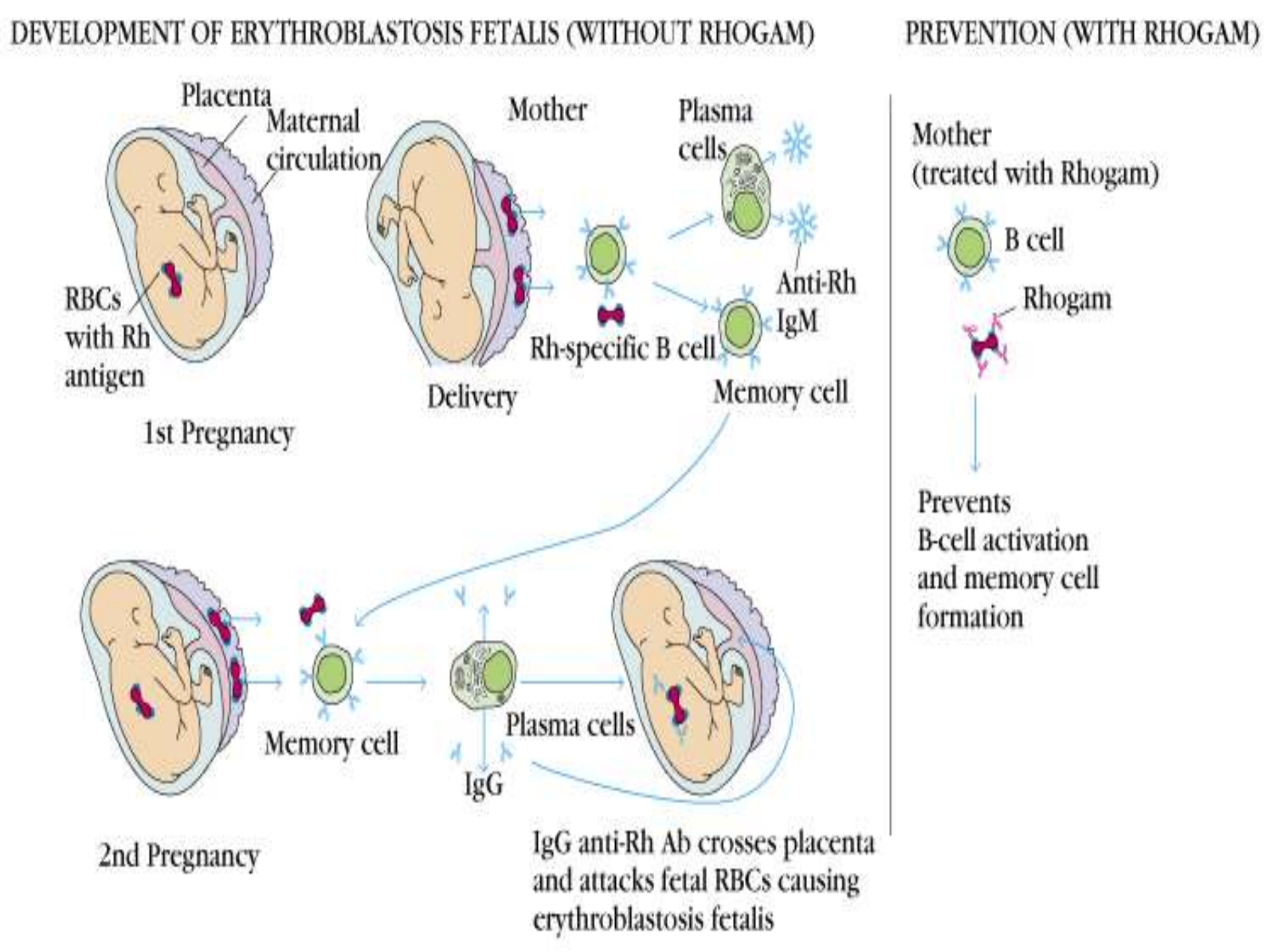
- Cross-matching can detect antibodies in the sera to prevent this

Haemolytic disease of the newborn

- Fetal red cells are destroyed by maternal isoantibodies crossing placenta

- This is where maternal IgG antibodies specific for fetal blood group antigens cross the placenta and destroy fetal RBC's

- Erythroblastosis fetalis - severe hemolytic disease of newborns
  - Most commonly develops when an Rh^+ fetus expresses an Rh antigen on it's blood that and Rh^- mother doesn't recognize


DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)
PREVENTION (WITH RHOGAM)
Placenta
Maternal circulation
RBCs with Rh antigen
1st Pregnancy
Mother
Delivery
Plasma cells
Anti-Rh IgM
Rh-specific B cell
Memory cell
Memory cell
Plasma cells
IgG
2nd Pregnancy
IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis
Mother (treated with Rhogam)
B cell
Rhogam
Prevents B-cell activation and memory cell formation

During the 1st pregnancy small amounts of fetal blood pass through the placenta but not enough to induce a response

During delivery larger amounts of fetal blood cross the placenta causing an activation of B-cells that are Rh specific thus leading to memory B-cells (anti-Rh antibodies)

The IgM antibody clears the Rh^+ cells from the mother

In subsequent pregnancies with an Rh^+ fetus, the Rh^+ RBC cross the placenta activating the memory B-cells

These in turn cross the placenta and damage the fetal RBC because they are seen as “foreign”

Treatment of Erythroblastosis fetalis

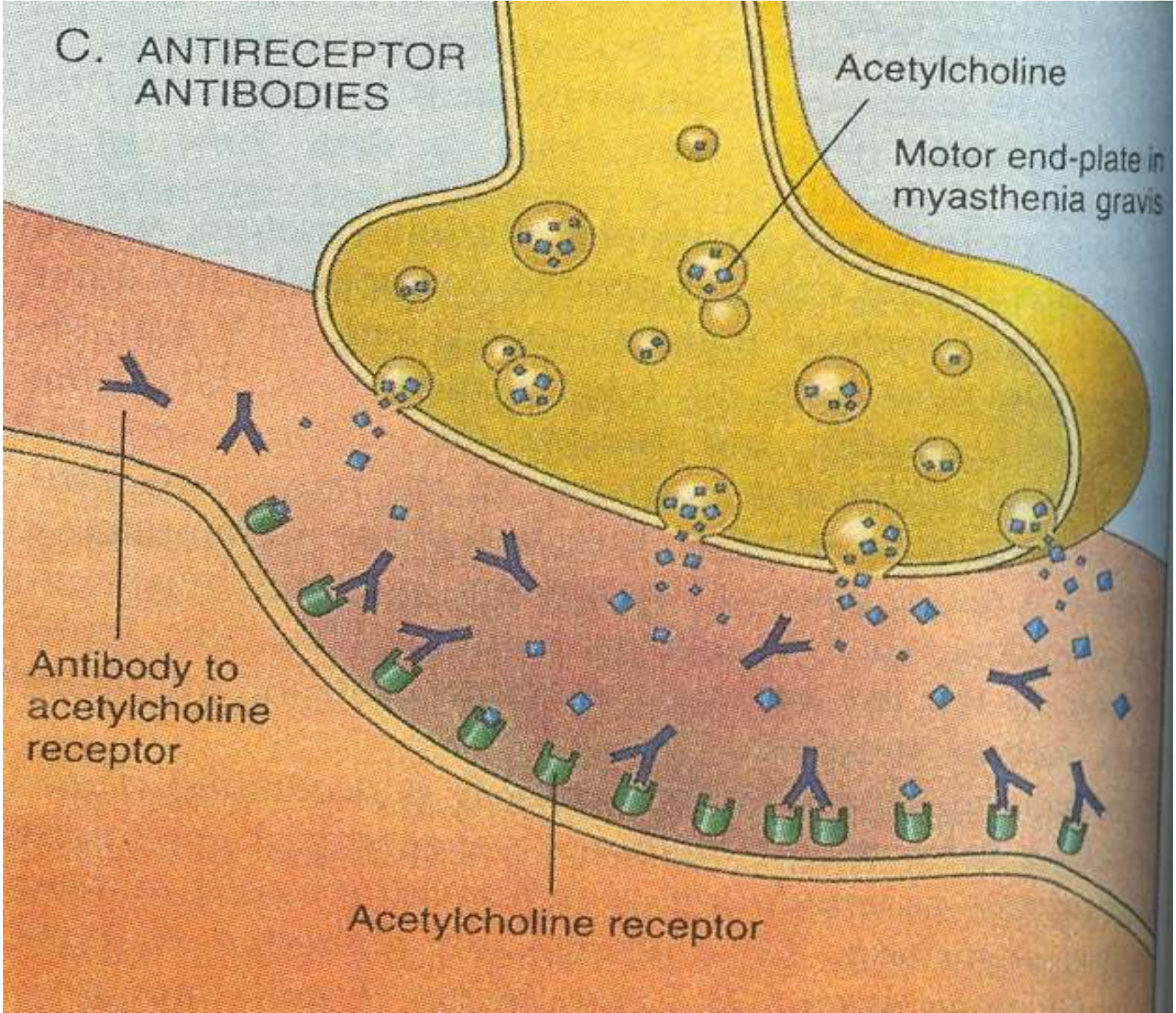
- This type of reaction can be prevented by administering antibodies against the Rh antigen within 25-48 hours after the 1st delivery
- **Rhogam** - is the antibody that is injected
  - it will bind to the fetal RBC that enter the mother's circulation and facilitate the clearance of them before B-cell activation
  - In subsequent pregnancies the mother is unlikely to produce IgG anti-Rh antibodies
  - If the mother doesn't receive this injection there are other ways to treat this, depending on the severity

B. CYTOTOXIC ANTIBODIES TO TISSUE COMPONENTS

- Cell injury may be brought about by autoantibodies reacting, with some components of tissue cells in certain diseases,

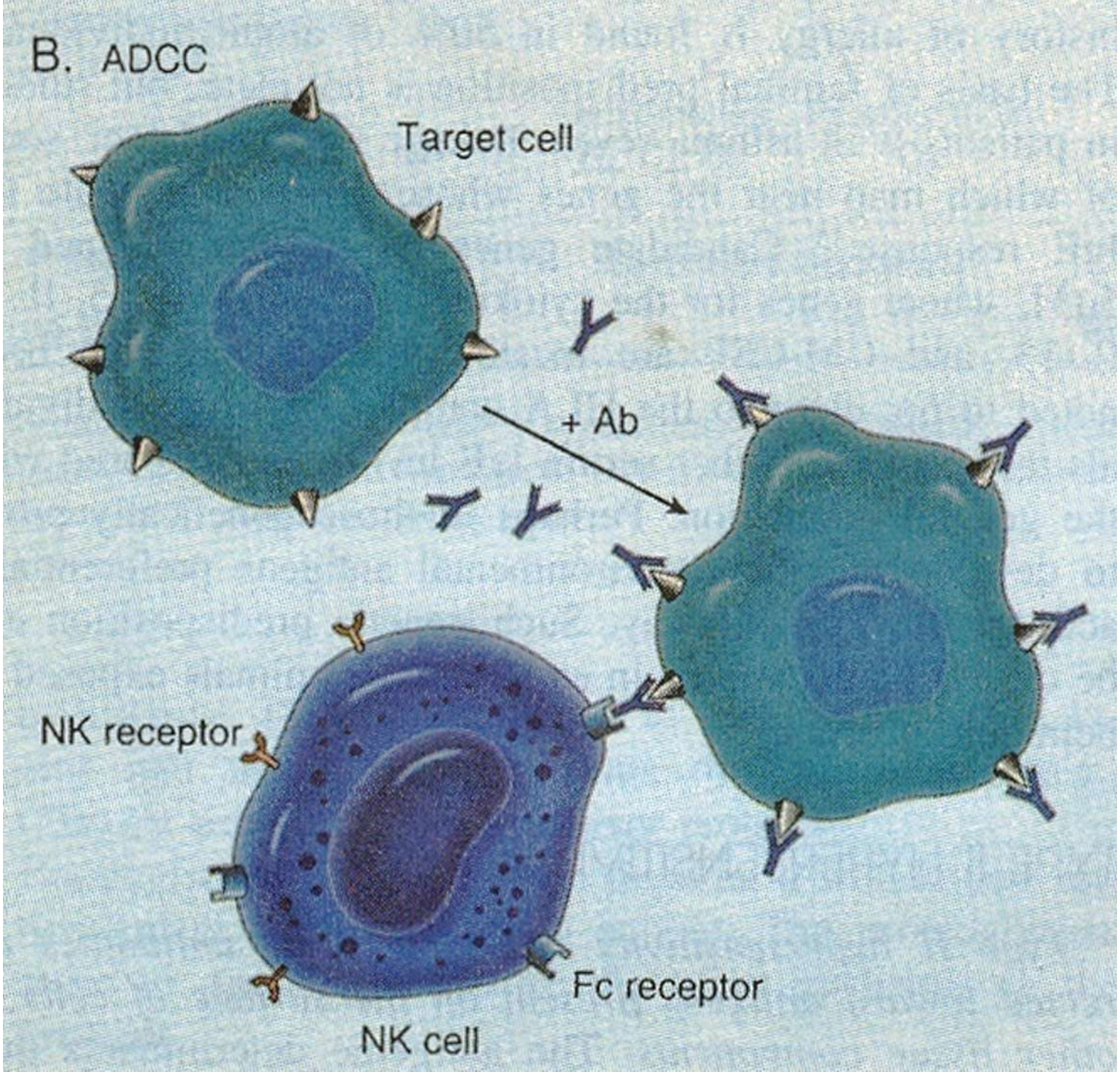
- *Example –*

  In *myasthenia gravis*, antibody to acetylcholine receptors of skeletal muscle is formed which blocks neuromuscular transmission at the motor end-plate resulting in muscle weakness


C. ANTIRECEPTOR ANTIBODIES
Acetylcholine
Motor end-plate in myasthenia gravis
Antibody to acetylcholine receptor
Acetylcholine receptor

C. ANTIBODY-DEPENDENT CELL MEDIATED CYTOTOXICITY (ADCC)

- Mediated by leucocytes like monocytes, neutrophils, eosinophils & NK cells.
- Antibodies involved - mostly IgG
- The cellular injury occurs by lysis of antibody-coated target cells through Fc receptors on leucocytes.
- The *examples* of target cells killed by this mechanism are tumour cells, parasites etc.


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

OTHER DISEASES

1.Anti -glomerular basement membrane nephritis

β-Hemolytic streptococcus and human glomerular basement membrane ---- cross reaction

Common antigen ---nephrotoxic nephritis

2. Super acute rejection in allogenic organ transplantation

3. Goodpasture syndrome

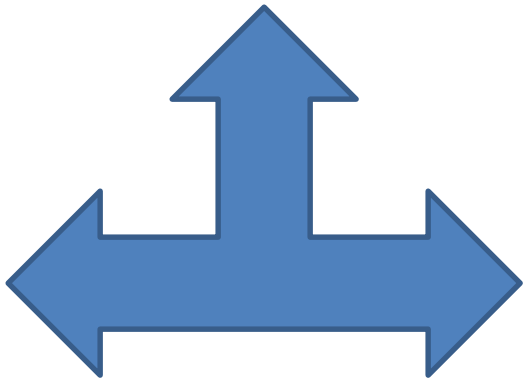
4.Hyperthyroidism or hypothyroidism—receptor diseases

III) Type III Hypersensitivity (Immune Complex Reaction)

Type III reactions results from formation of immune complexes by direct antigen-antibody (Ag-Ab) combination as a result of which the complement system gets activated causing cell injury.

Antigens causes immune complex mediated tissue injury

Exogenous Antigens



Endogenous Antigens

Exogenous Antigens

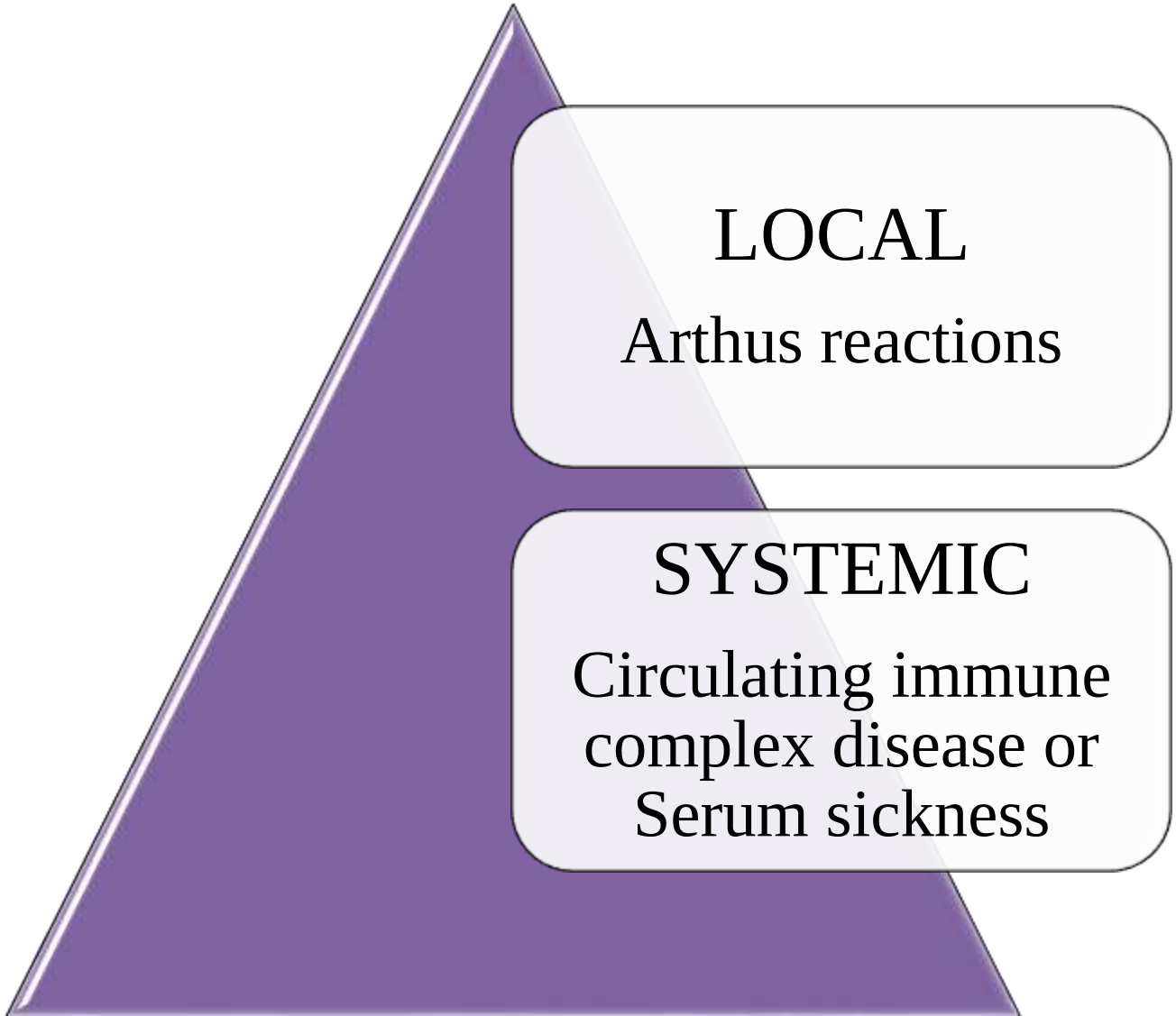
- Infectious agents (bacteria, viruses, fungi, parasites)
- Certain drugs & chemicals

Endogenous Antigens

- Blood components

  (Ig, tumour antigens)
- Antigens in cells & tissues (nuclear antigens in SLE)

Depending upon the distribution & location of antigens, Type III are of 2 types



1. Local : Arthus Reaction

- Localised inflammatory reaction, usually an immune complex vasculitis of skin of an individual with circulating antibody.

- Large immune complexes formed due to excess of antibodies, which precipitate locally in the vessel wall causing fibrinoid necrosis.

Injection of an Antigen:

- Can lead to an acute Arthus reaction within 4-8 hours
- Localized tissue and vascular damage result from accumulation of fluid (edema) and RBC (erythema)
- Severity can vary from mild swelling to redness to tissue necrosis

EXAMPLES :-

1. Injection of Antitetanus serum
2. Farmer`s lung (allergic alveolitis in response to bacterial antigen from mouldy hay)
3. Insect bite:
    - May first have a rapid type I reaction
    - Some 4-8 hours later a typical Arthus reaction develops
4. Ulcer
5. Local Human Reaction :- Insulin Dependent Diabetes Mellitus

2. Systematic : Circulating immune complex disease or serum sickness

- Develops when antigen is intravenously administered resulting in formation of large amountsvantigen-antibody complexes and their deposition in the tissues.

- These circulating complexes can’t be cleared by phagocytosis and can cause tissue damaging Type III reactions

- Ag-Ab complexes are deposited at different tissue sites containing basement membrane exposed to circulating blood.

- Following this deposition, there is acute inflammatory reaction & activation of complement system with elaboration of chemotactic factors, vasoactive amines & anaphylatoxins.

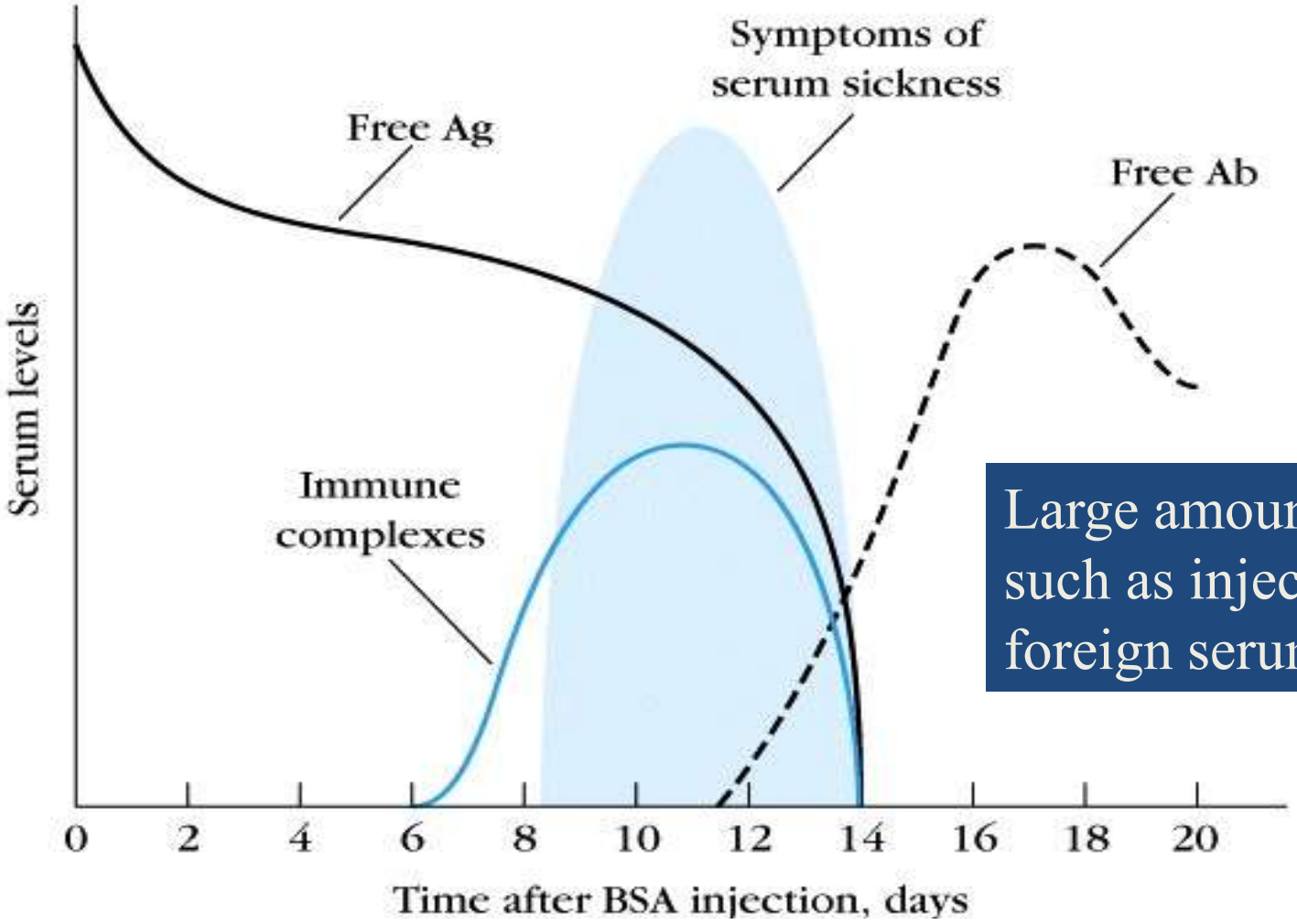
- This all causes type III hypersensitivity reactions

- **Eg of circulating immune complex diseases are:-**
  - Skin diseases
  - Various forms of Glomerulonephritis
- **Other conditions caused by Type III-**

1. Infectious Diseases
   - Meningitis
   - Hepatitis
   - Mononucleosis
2. Drug Reactions
   - Allergies to penicillin and sulfonamides
3. Autoimmune Collagen Diseases
   - Systematic lupus erythematosus
   - Rheumatoid arthritis

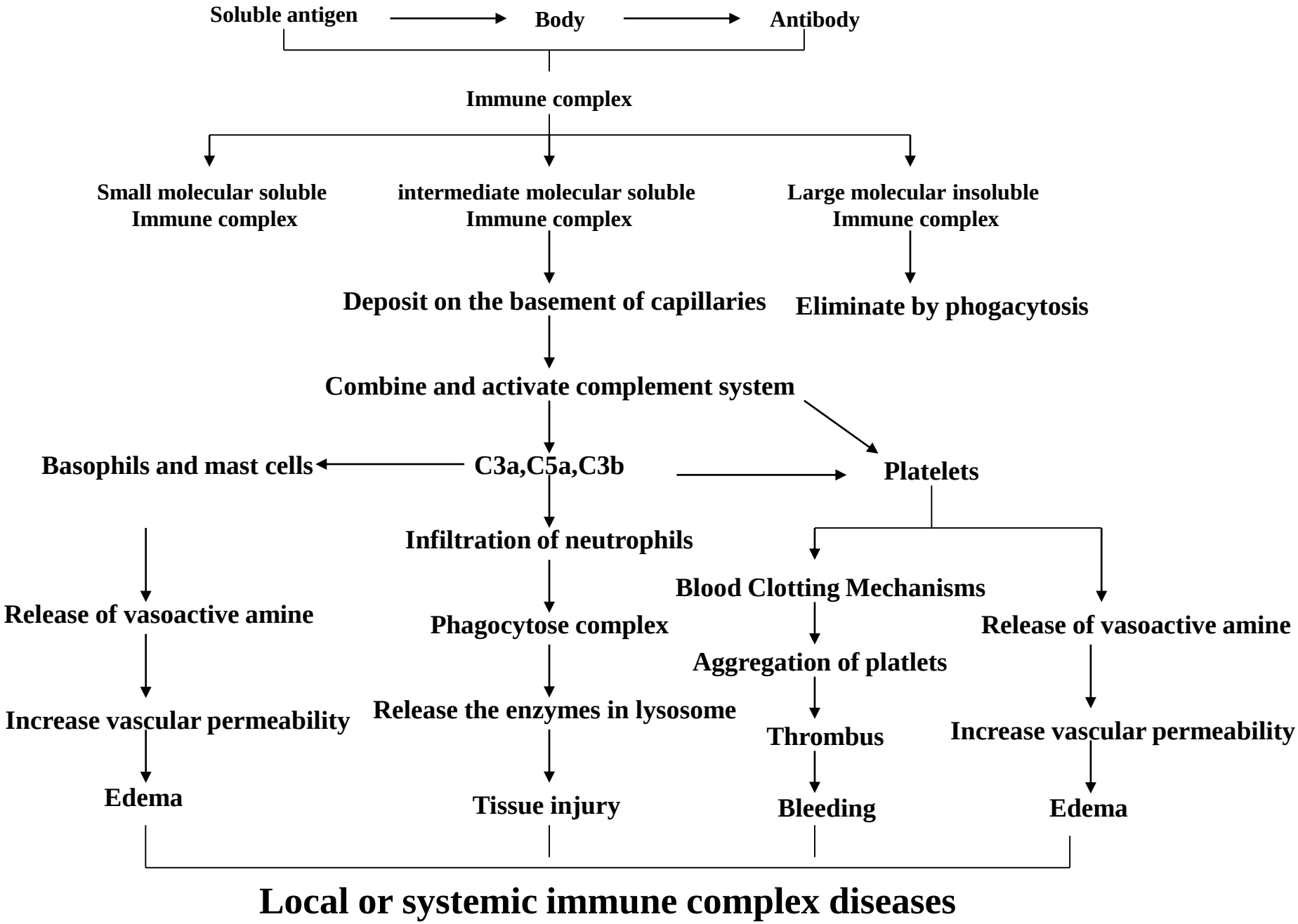
Serum Sickness

Systemic immune complex disease



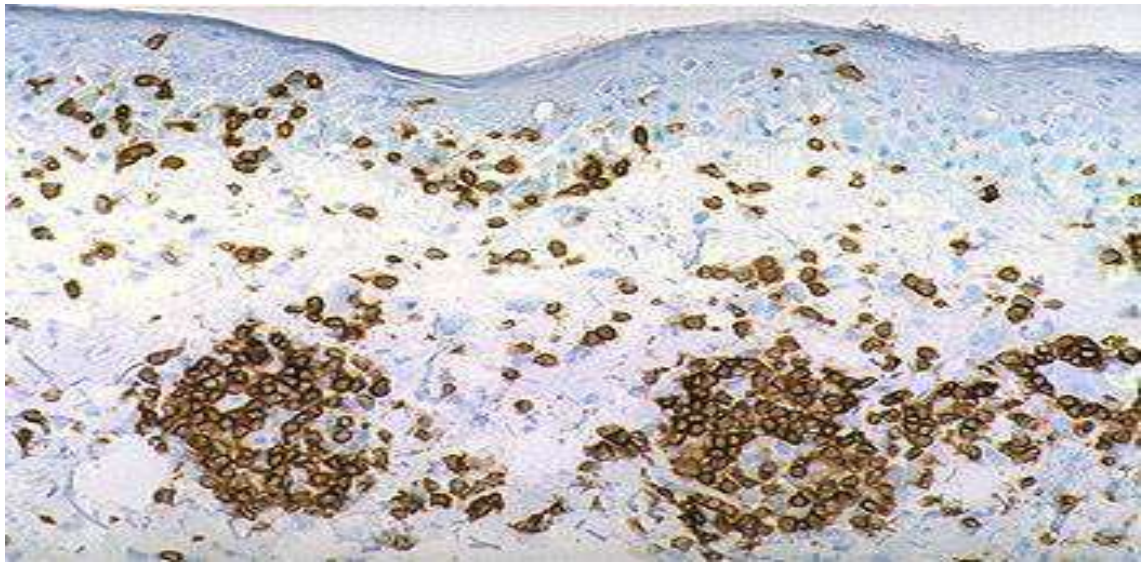
Large amounts of antigen such as injection of foreign serum.

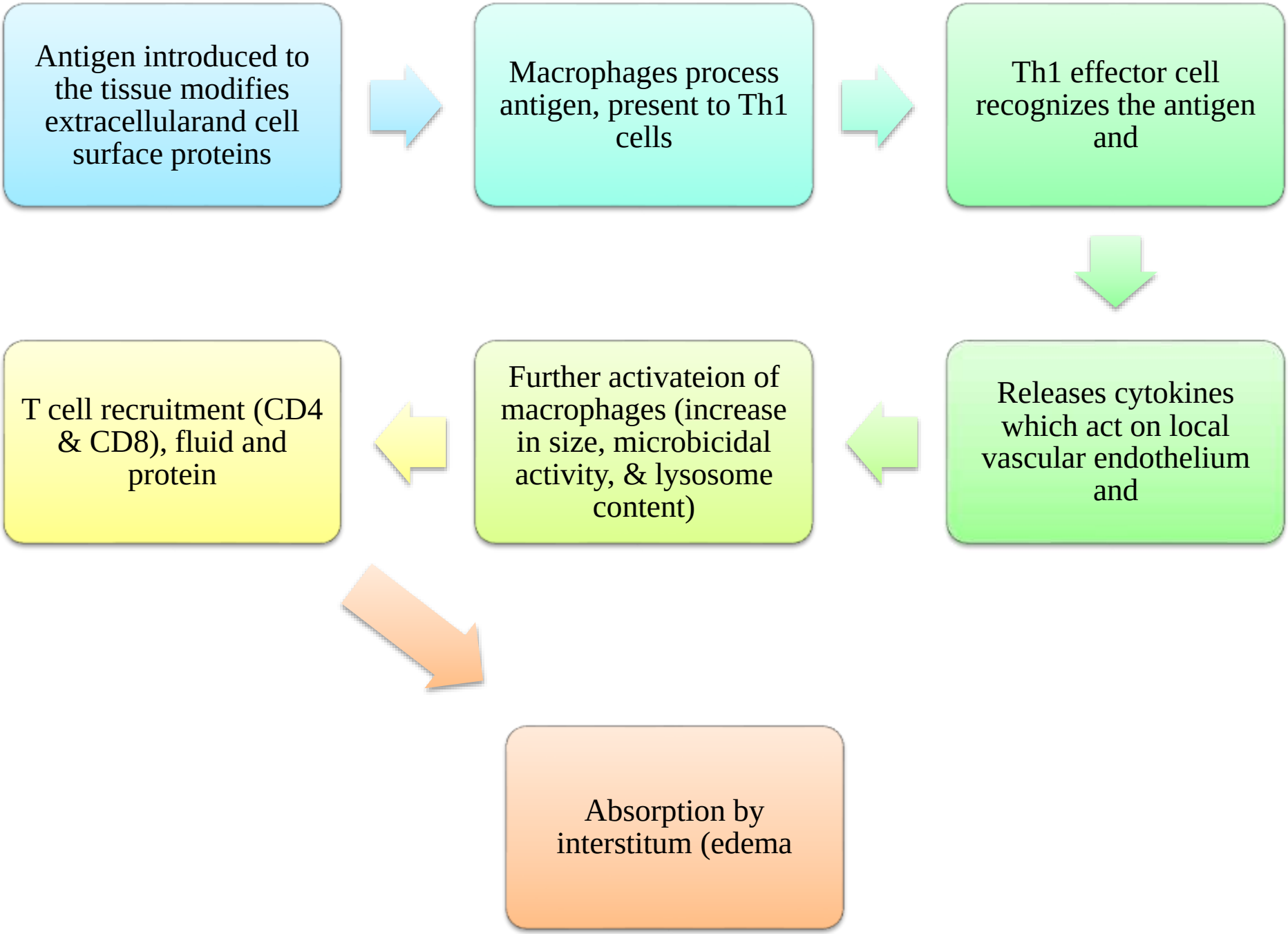
Days after Antigen Injection


Soluble antigen
Body
Antibody
Immune complex
Small molecular soluble Immune complex
intermediate molecular soluble Immune complex
Large molecular insoluble Immune complex
Deposit on the basement of capillaries
Eliminate by phogacytosis
Combine and activate complement system
Basophils and mast cells
C3a,C5a,C3b
Platelets
Infiltration of neutrophils
Blood Clotting Mechanisms
Release of vasoactive amine
Phagocytose complex
Release of vasoactive amine
Aggregation of platlets
Increase vascular permeability
Release the enzymes in lysosome
Thrombus
Increase vascular permeability
Edema
Tissue injury
Bleeding
Edema
Local or systemic immune complex diseases

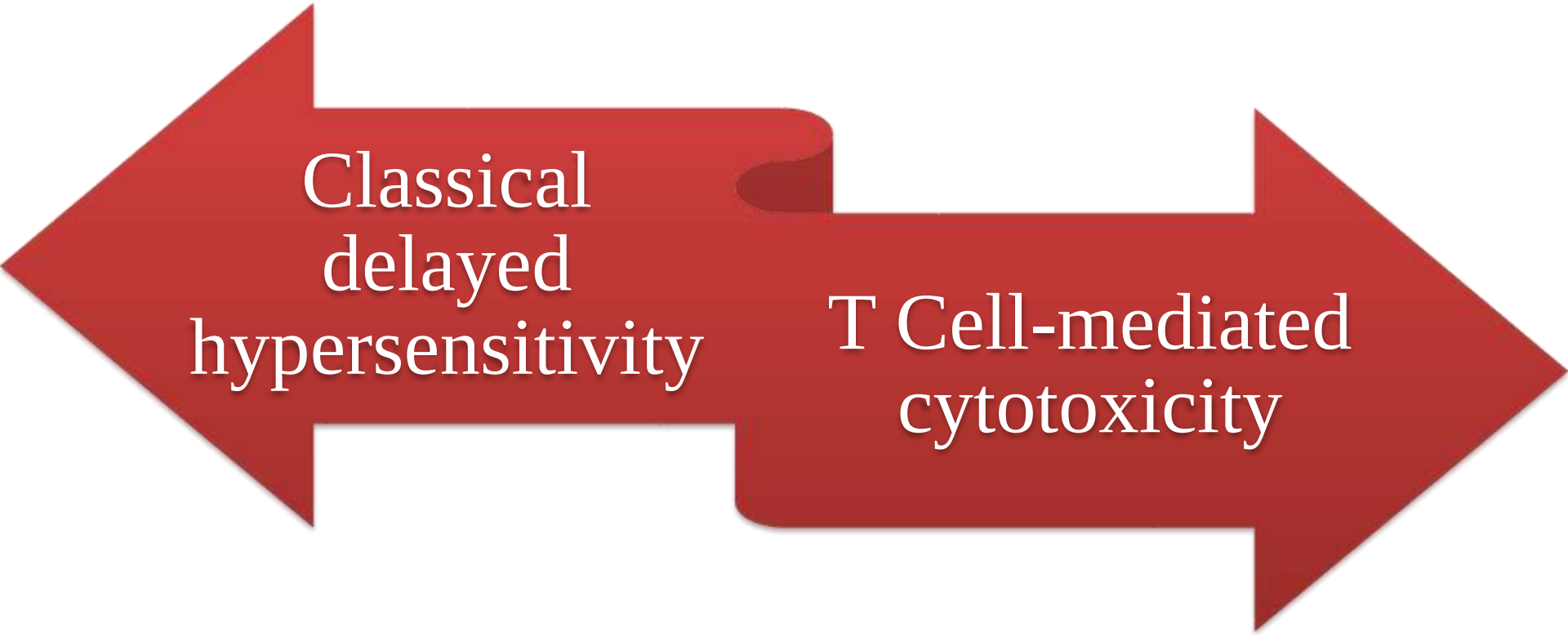
IV) Type IV Hypersensitivity (Delayed or Cell Mediated Reaction)

1. Mediated by specificallysensitised T lymphocytes produced in the cell-mediated immune response.
2. The delay in the appearance of a type IV hypersensitivity reaction (2-3 days) is due to the time it takes to recruit antigen-specific T cells and other cells to the site of antigen localization and to develop the inflammatory response.




Antigen introduced to the tissue modifies extracellularand cell surface proteins
Macrophages process antigen, present to Th1 cells
Th1 effector cell recognizes the antigen and
Releases cytokines which act on local vascular endothelium and
Further activateion of macrophages (increase in size, microbicidal activity, & lysosome content)
T cell recruitment (CD4 & CD8), fluid and protein
Absorption by interstitum (edema

Types of Cell mediated Reactions



Classical delayed hypersensitivity

- Mediated by specifically sensitised CD4+ T cell subpopulation on contact with antigen.
- These cells possess surface receptors which bind to the antigen, resulting in cell injury characterised by slowly developing inflammatory response

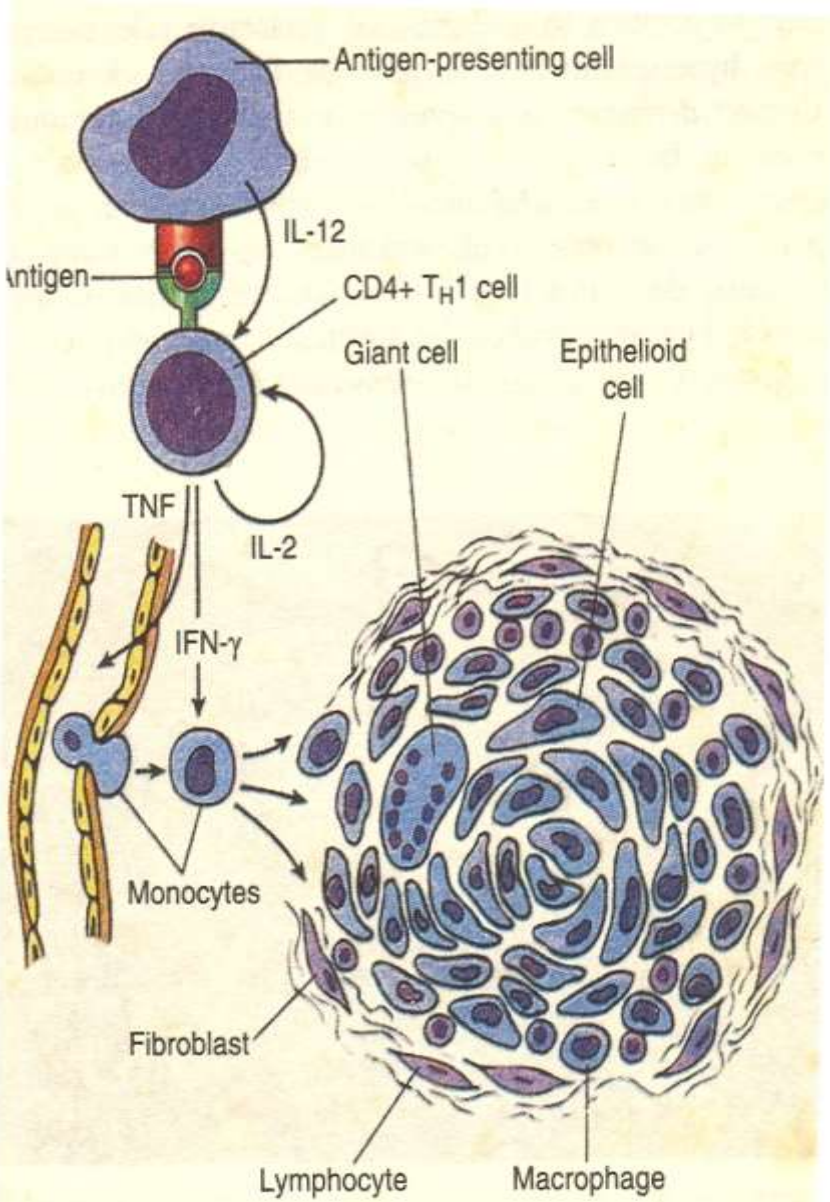


Figure 7-17

Schematic illustration of the events that give rise to the formation granuloma in type IV hypersensitivity reactions. Note the role played T cell–derived cytokines.

T Cell-mediated cytotoxicity

CD8+ subpopulation of T lymphocytes are the cytotoxic T cells are generated in response to antigens like virus-infected cells, tumour cells and incompatible transplanted tissue or cells.

Mechanism of type IV hypersensitivity

Formation of effector and memory T cells

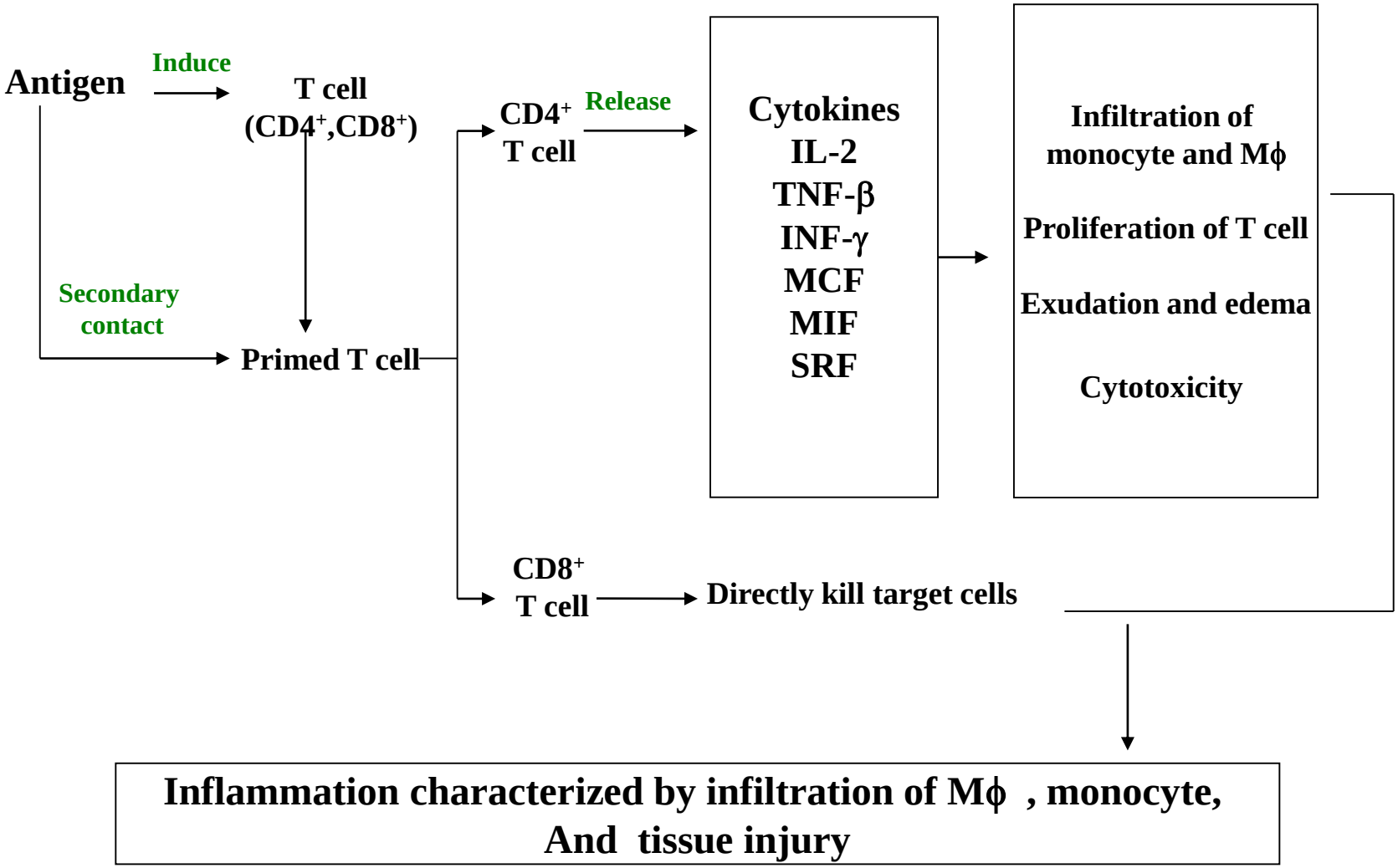
Inflammation and cytotoxicity caused by effector T cells

1) Inflammation and tissue injury mediated by CD4+Th1

   Release chemokines and cytokines

   Immune injury mainly caused by infiltration of mononuclear cells and lymphocytes

2) Cytotoxicity of CD8+CTL



Mechanism of type IV hypersensitivity

Stages of a Type IV Hypersensitivity Reaction

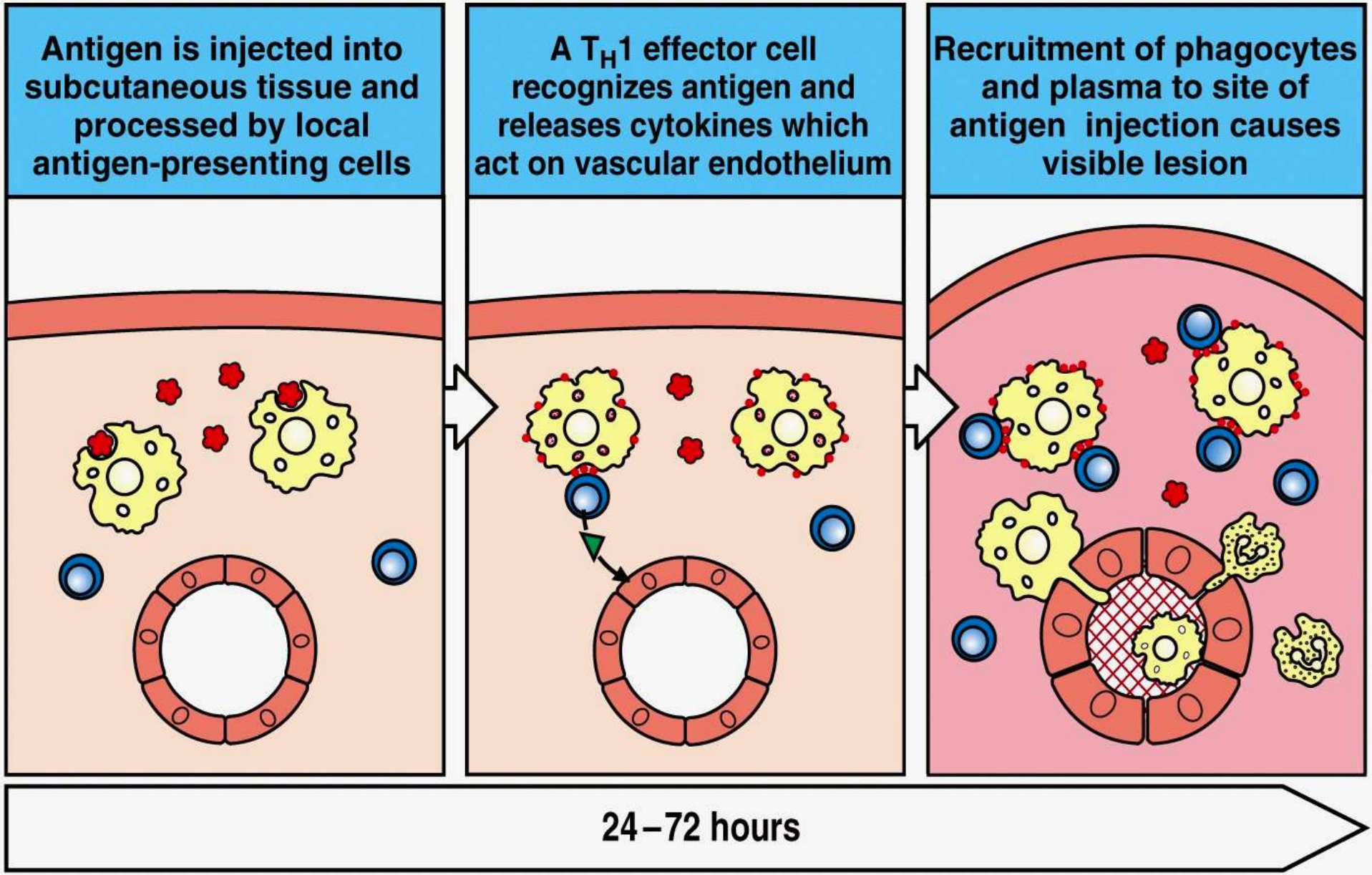


Figure 12-25 Immunobiology, 6/e. (© Garland Science 2005)

Th1 derived cytokines and chemokines direct Type IV reactions

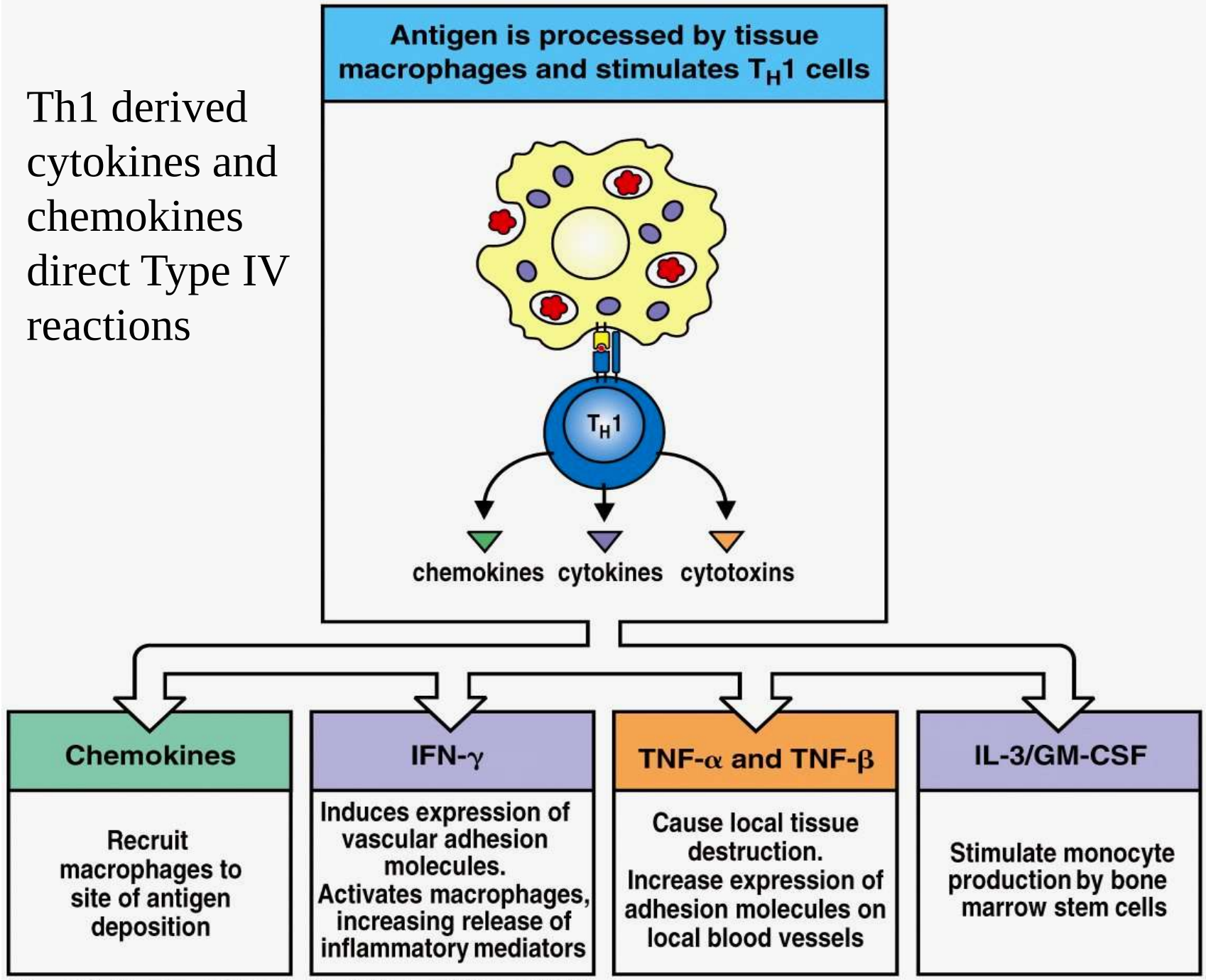


Figure 12-26 Immunobiology, 6/e. (© Garland Science 2005)

Delayed Type Hypersensitivity (DTH)

TABLE 14-3 INTRACELLULAR PATHOGENS AND CONTACT ANTIGENS THAT INDUCE DELAYED-TYPE HYPERSENSITIVITY

Intracellular bacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Listeria monocytogenes*
- *Brucella abortus*

Intracellular fungi
- *Pneumocystis carinii*
- *Candida albicans*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*

Intracellular parasites
- *Leishmania* sp.

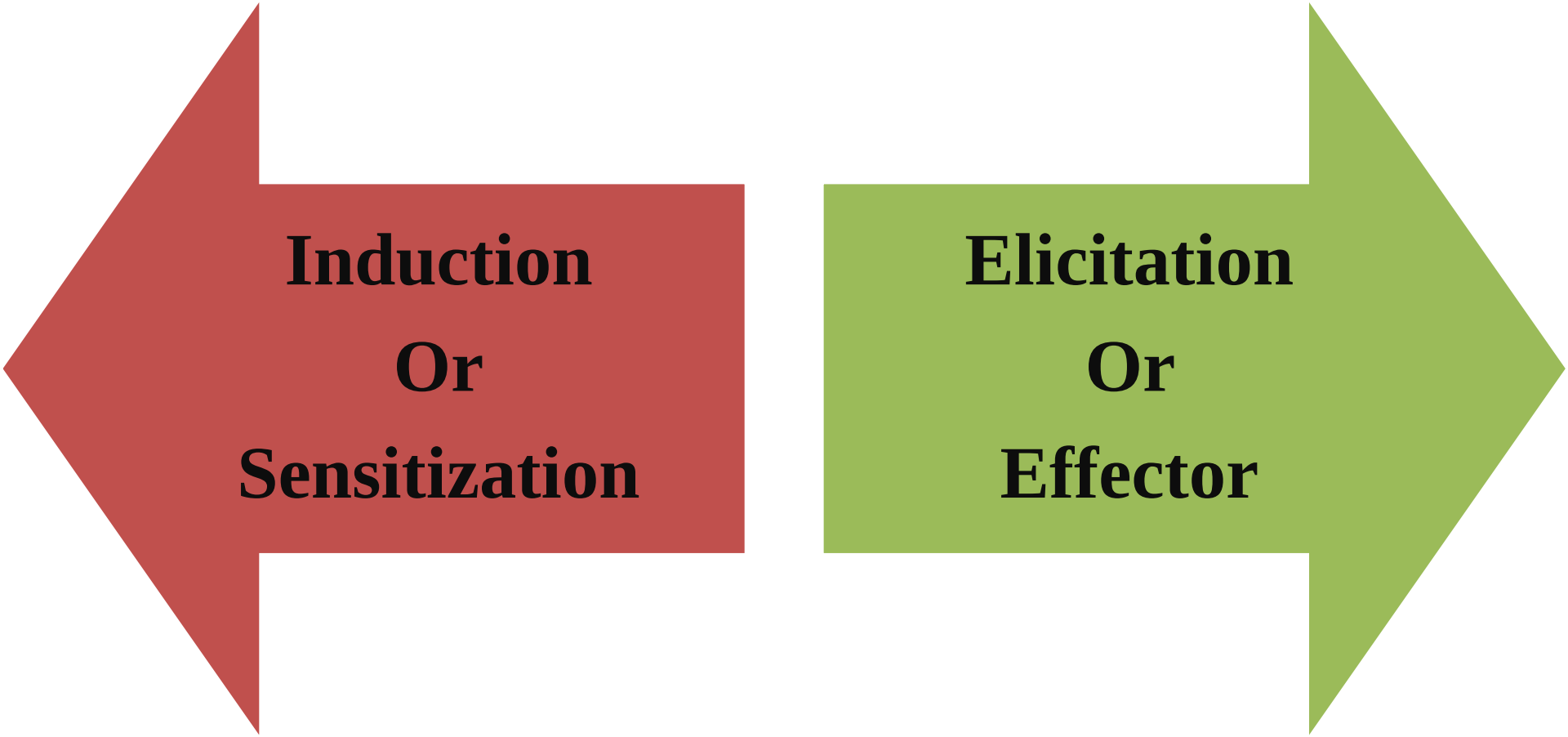
Intracellular viruses
- Herpes simplex virus
- Variola (smallpox)
- Measles virus

Contact antigens
- Picrylchloride
- Hair dyes
- Nickel salts
- Poison ivy
- Poison oak

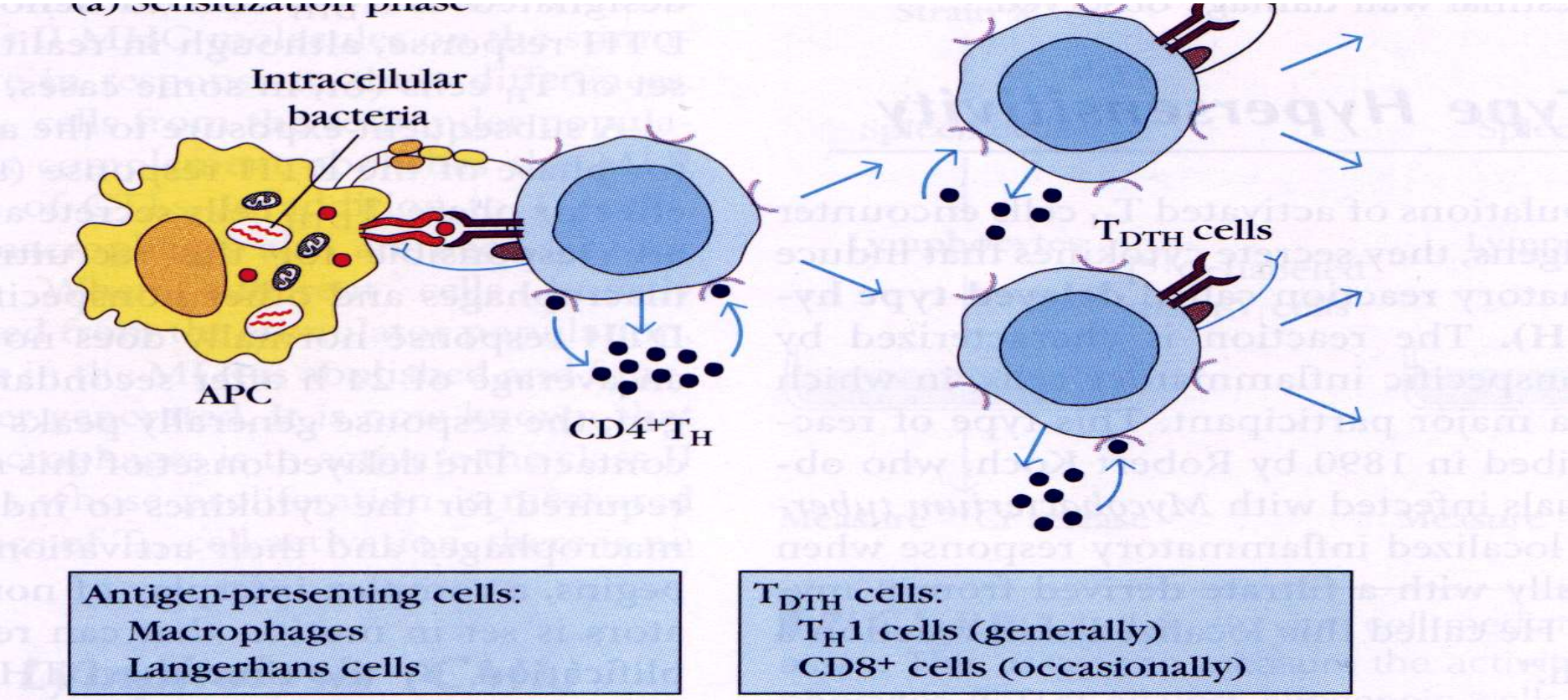
DTH is a type of immune response classified by **Th1 and macrophage** activation that results in tissue damage.

DTH can be the result of Chronic infection or Exposure to some antigens.

PHASES OF DTH RESPONSE



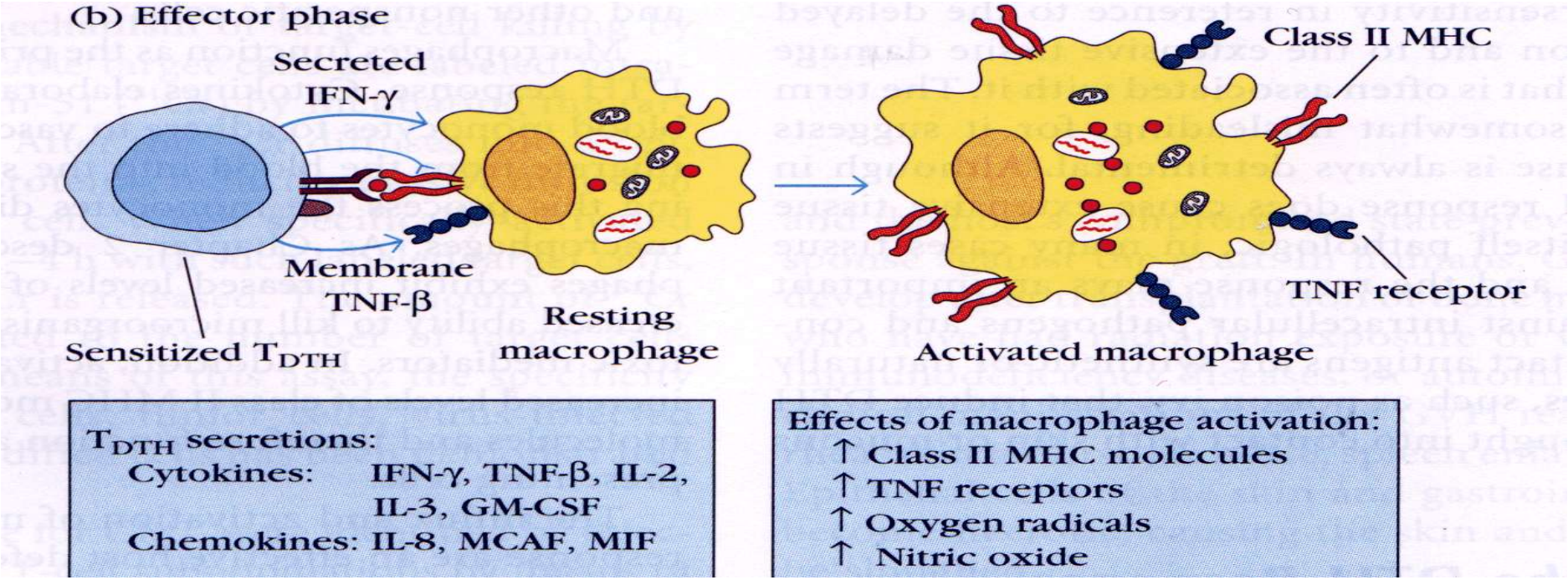
Sensitization Phase



Occurs 1-2 weeks after primary contact with Ag

- T_H cells are activated and clonally expanded by Ag presented together with class II MHC on an appropriate APC, such as macrophages or Langerhan cell (dendritic epidermal cell)
- Generally CD4+ cells of the T_H1 subtype are activated during sensitization and designated as T_{DTH} cells

Effector Phase



Occurs upon subsequent exposure to the Ag

- T_{DTH} cells secrete a variety of cytokines and chemokines, which recruit and activate macrophages
- Macrophage activation promotes phagocytic activity and increased concentration of lytic enzymes for more effective killing
- Activated macrophages are also more effective in presenting Ag and function as the primary effector cell

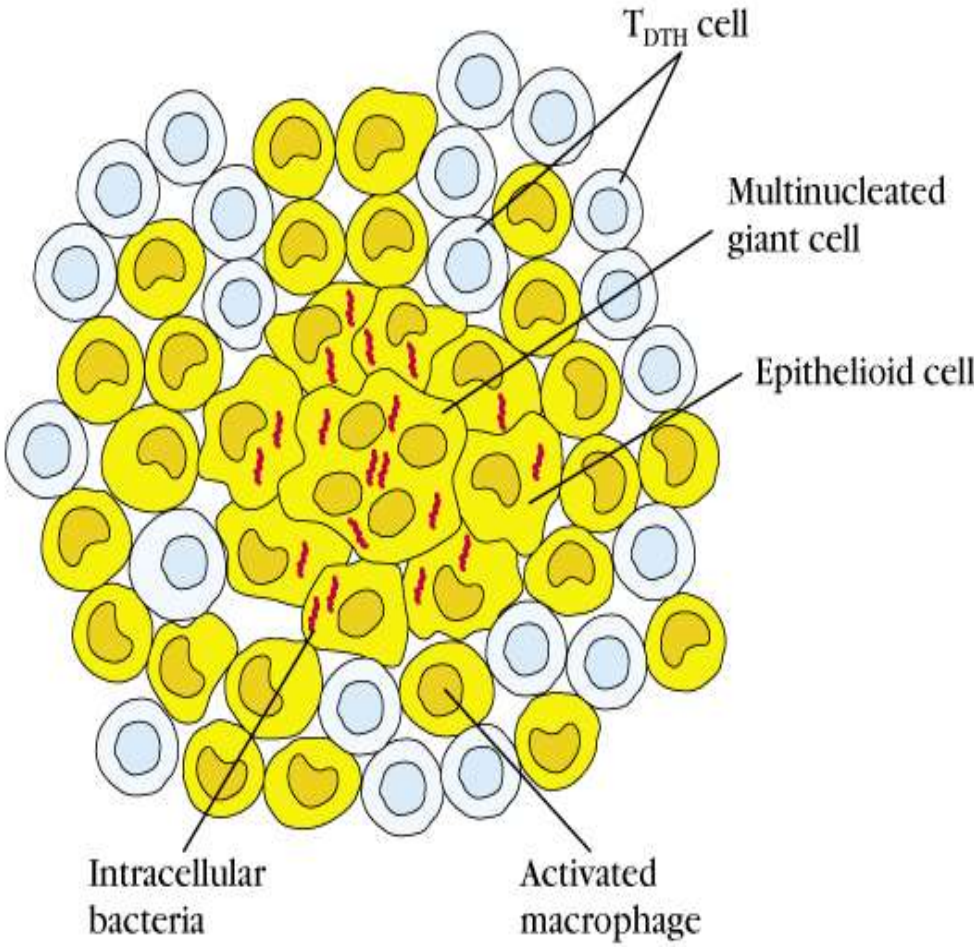
Chemical Factors Involved

- **IL-12:** (macrophages). Drives differentiation of T cells, induces IFN-gamma secretion
- **IFN-gamma** (T cells). Further activates macrophages
- **IL-2:** (T cells). Increases T cell proliferation within tissue
- **IL-3:** (T cells). Stimulates monocyte production
- **TNF** (T cells). Increase secretion of Nitric Oxide & Prostacyclins by endothelial cells, local tissue destruction, and increase expression of adhesion molecules on vessels
- **E- selectins:** vascular adhesion molecule, increases mononuclear cell attachment

Prolongation of DTH Response

A granuloma develops…

- Continuous activation of macrophages induces the macrophages to adhere closely to one another, assuming an epithelioid shape and sometimes fusing together to form giant, multinucleated cells.



Detrimental Effects of DTH Response

- The initial response of the DTH is nonspecific and often results in significant damage to healthy tissue.

- In some cases, a DTH response can cause such extensive tissue damage that the response itself is pathogenic.

- Example: *Mycobacterium tuberculosis* – an accumulation of activated macrophages whose lysosomal enzymes destroy healthy lung tissue. In this case, tissue damage far outweighs any beneficial effects.

How Important is the DTH Response?

- The AIDS virus illustrates the **vitally** important role of the DTH response in protecting against various intracellular pathogens.

- The disease cause severe depletion of CD4+ T cells, which results in a loss of the DTH response.

- AIDS patients develop life-threatening infections from intracellular pathogens that normally would not occur in individuals with intact DTH responses.

Common disease of type IV hypersensitivity

1) Infectious delayed type hypersensitivity

OT(Old Tuberculin) test

2) Contact dermatitis :

Paint, drug red rash, papula, water blister, dermatitis

3) Acute rejection of allogenic transplantation and

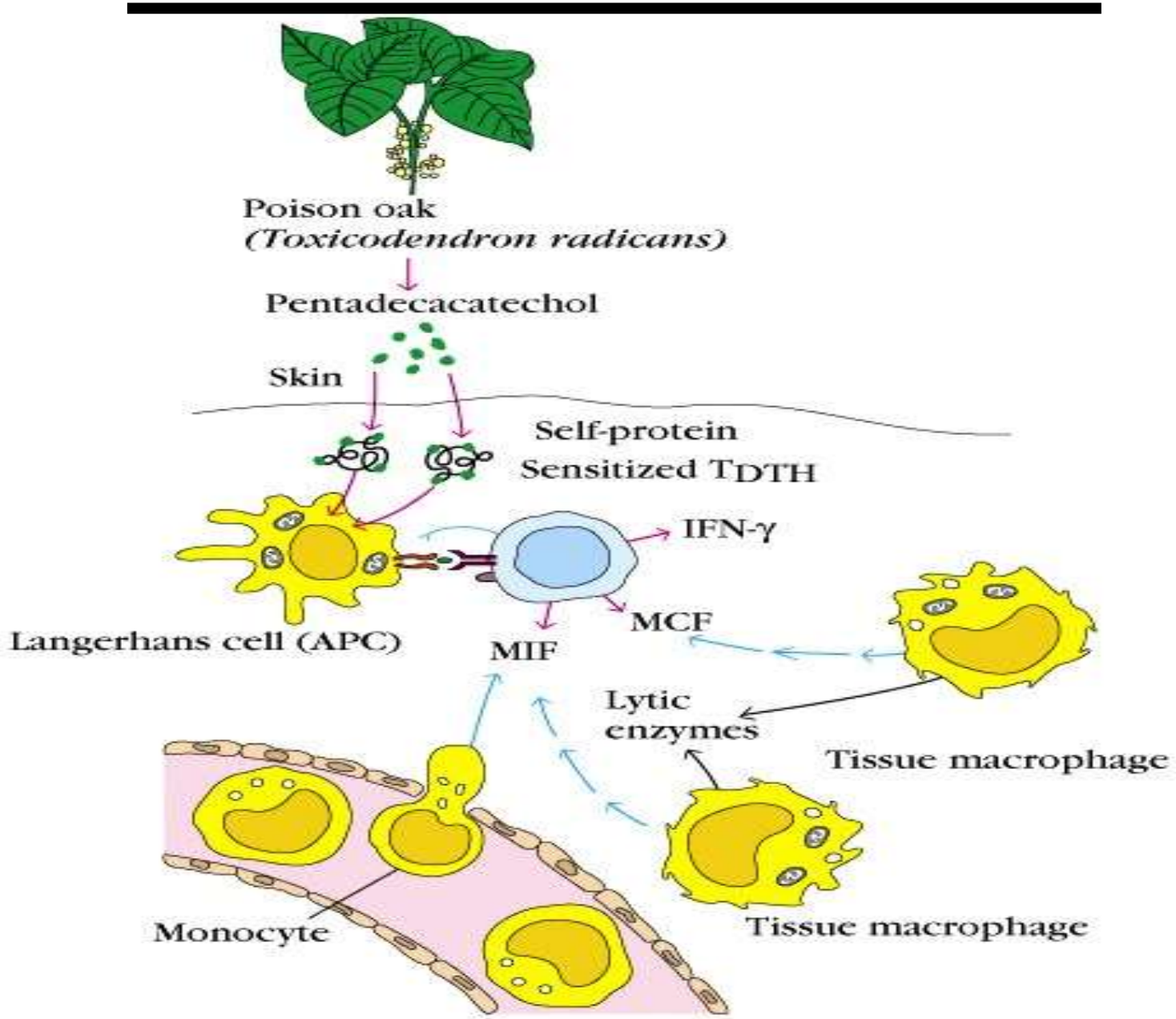
immune response in local tumor mass

TUBERCULIN REACTION

- On intradermal injection of tuberculoprotein (PPD), an unsensitised individual develops no response **(tuberculin negative).**

- A person who has developed cell-mediated immunity to tuberculoprotein as a result of BCG immunisation (exposed to tuberculous infection) develops typical delayed inflammatory reaction, reaching its peak in 48 hours **(tuberculin positive)**, after which it subsides slowly.

Contact Dermatitis



Allergic Contact Dermatitis: A type IV reaction

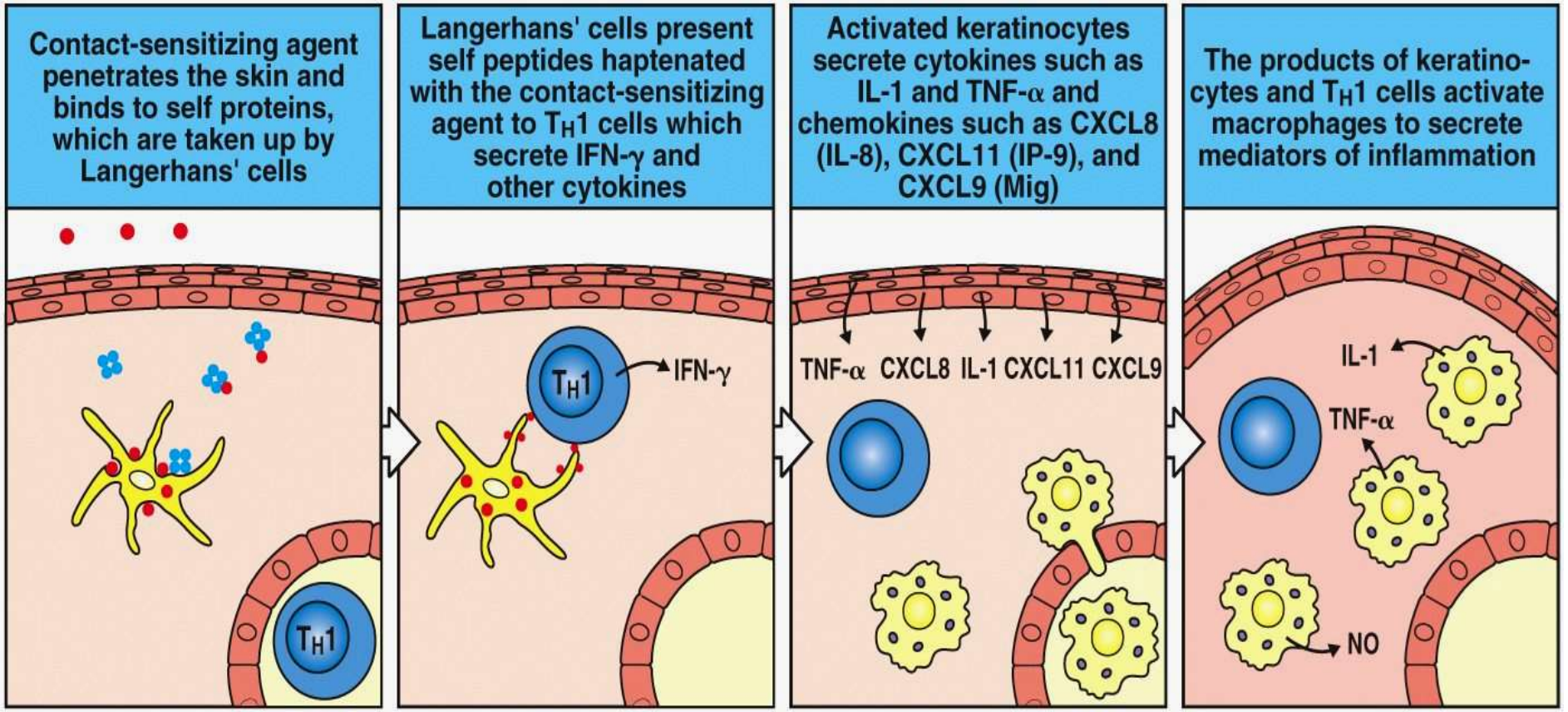


Figure 12-27 Immunobiology, 6/e. (© Garland Science 2005)

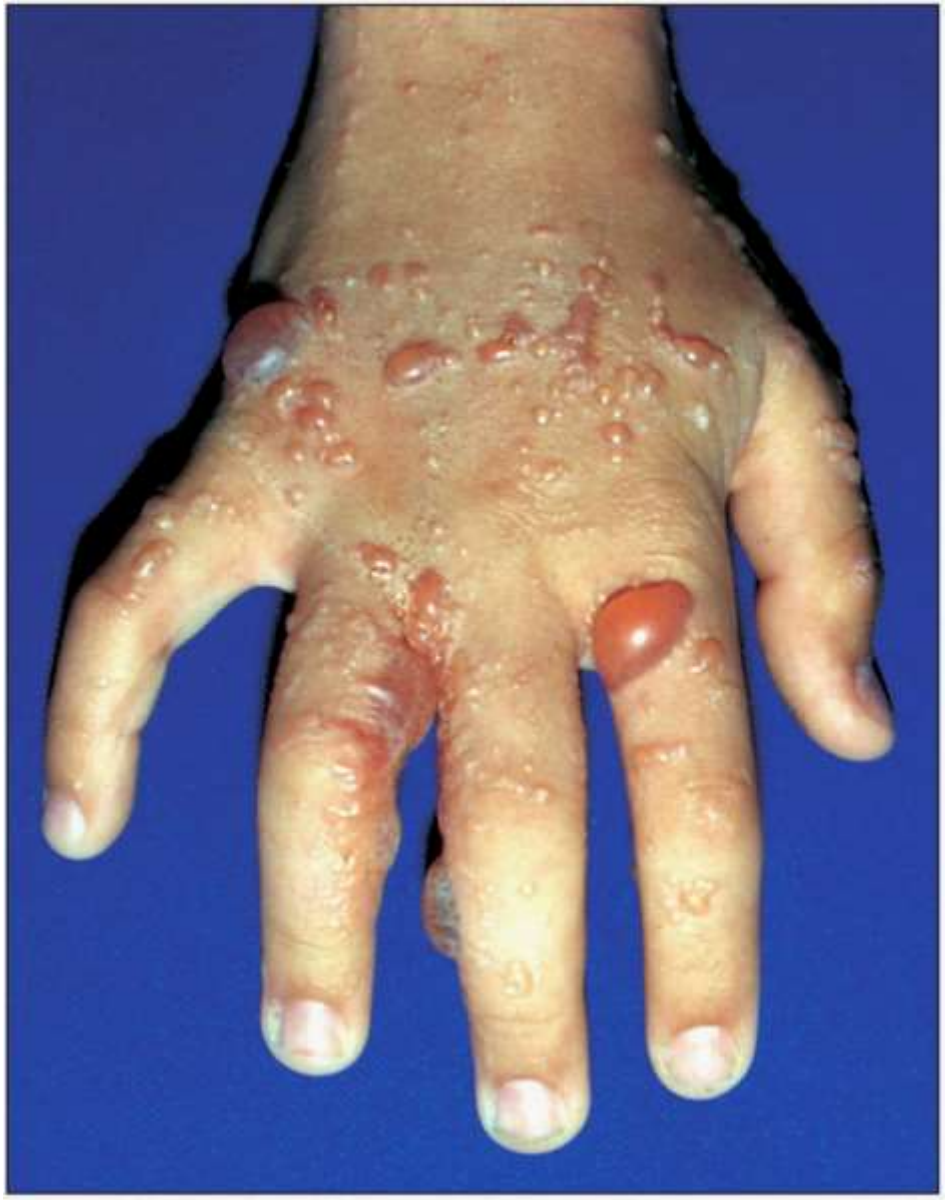


Figure 12-28 Immunobiology, 6/e. (© Garland Science 2005)

Blistering skin lesions on hand of patient with poison ivy

contact dermatitis (a type IV reaction)

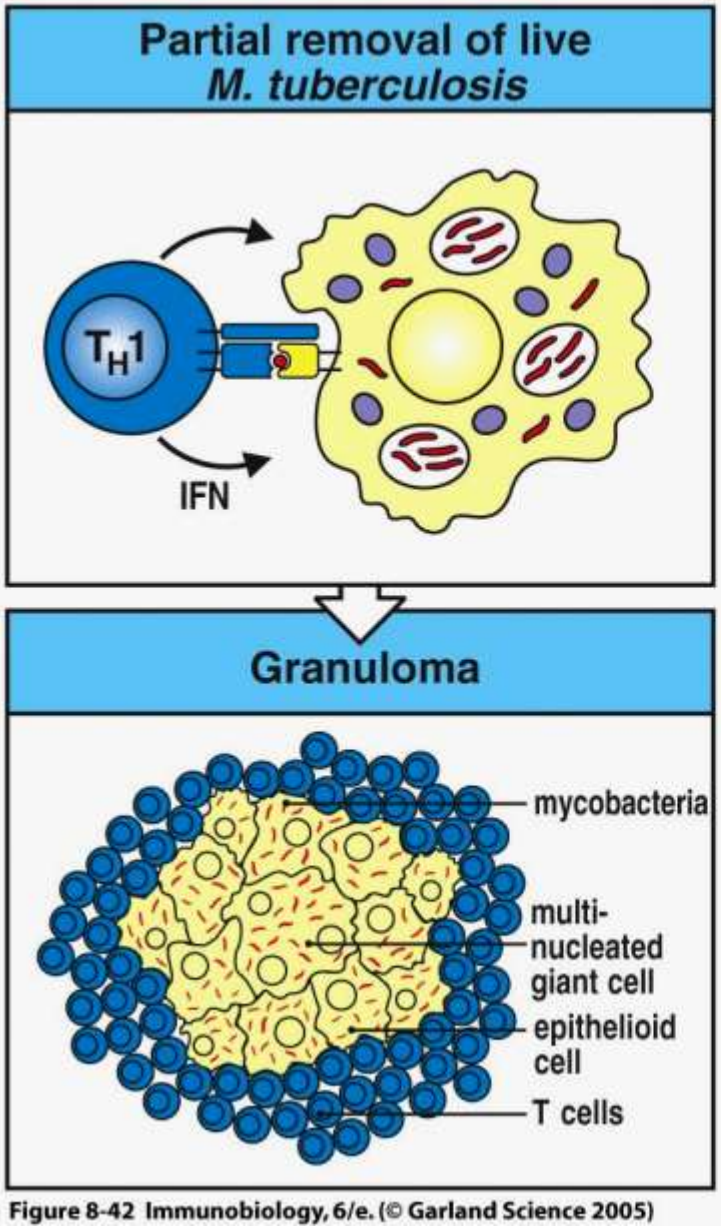
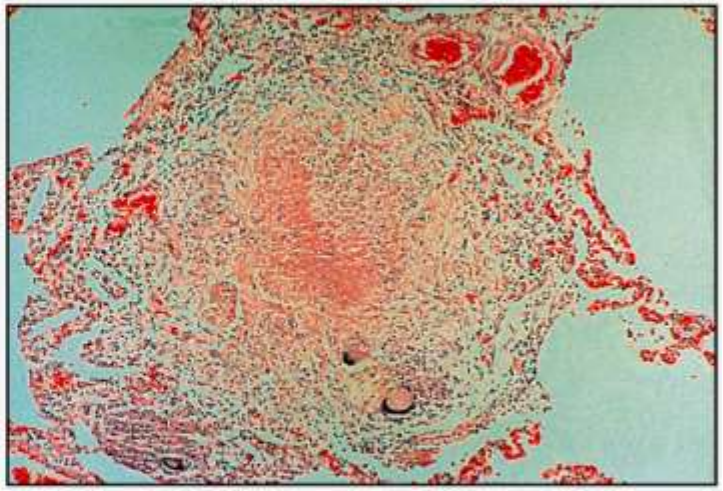


Figure 8-42 Immunobiology, 6/e. (© Garland Science 2005)

Granulomatous inflammation is a consequence of chronic Type IV reactions



Type IV Hypersensitivity Reactions

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells		
Syndrome	**Antigen**	**Consequence**
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitiveenteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

Figure 12-24 Immunobiology, 6/e. (© Garland Science 2005)

V) Type V Hypersensitivity

- occurs when IgG class antibodies directed towards cell surface antigens have a stimulating effect on their target

- E.g.s Graves disease(also considered as type II hypersensitivity reaction)

- Instead of dysfunction, there is antibody mediated stimulation of cell function. So, some have isolated this special type and have named it type V hypersensitivity reaction.

HYPERSENSITIVITY DUE TO VARIOUS DENTAL MATERIALS

LOCAL ANAESTHESIA

Allergy in case of anaesthetics may be :-

1) Methyparaben allergy (preservative)

2) Epinephrine allergy (vasoconstrictor)

3) Latex allergy (plunger and diaphragm at the ends of the cartridge)

4) Topical anaesthetic allergy (benzocaine, tetracaine)

CLINICAL MANIFESTATIONS

- Immediate reactions develop within seconds to hours includes type I,II,III
- Delayed reactins shows manifestations in hours to days.

SIGNS AND SYMPTOMS

1 Dermatological Reactions

Urticaria associated with wheals

Angioedema of face, hand, feet, genitalia

2 Respiratory Reactions

Bronchospasm(distres, dyspnoea, cyanosis, flushing, tachycardia, perspiration)

Laryngeal edema

Reaction progression in generalised anaphylaxis

1. *Early phase skin reactions* including itching, flushing, nausea, conjunctivitis, rhinitis.

2. *Associated GIT disturbance* including vomiting, diarrhoea, abdominal cramps, faecal and urinary incontenance

3. *Respiratorty symptoms* including cough, wheezing, pain in chest, cyanosis, laryngeal edema

4. *CVS symptoms* including tachycardia, hypotention, palpitation, unconscoiusness, cardiac arrest

MANAGEMENT

1. Delayed skin reactions : oral histamine blocker (50g diphenhydramine or 10g chlorpheniramine)
2 Immediate skin reactions : Epinehrine 0.3mg i.m
oral histamine blocker
3. Respiratory reactions : oxygen administration
Epinehrine or bronchodilator
Histamine blocker i.m
4. Laryngeal edema : epinehrine
airway mainantance, emergency call
Histamine blocker i.m , i.v
Hydrocortisone 100mg
Cricothyrotomy

TITANIUM

Ti can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this reactive metal. At the same time, no standard patch test for Ti has so far been developed.

Hypersensitivity reaction to a metal comes from the presence of ions following ingestion, skin or mucosal contact, or from implant corrosion processes. In their ionic form, metals can be bonded with native proteins to form haptenic Antigens ,or can trigger the degranulation of mastocytes and basophiles, being capable of developing **type I or type IV hypersensitive reaction**s according to Schramm and Pitto

Sensitivity to titanium is characterized by the local presence of abundant macrophages and T lymphocytes and the absence of B lymphocytes, indicating type IV hypersensitivity

J Indian Prosthodont Soc (Oct-Dec 2012) 12(4):201–207

METHY METHACRYLATE

Allergy to methyl methacrylate monomer in acrylic resin are less common and usually are of the delayed or contact allergy. Residual monomer left by incomplete polymerization is the allergen in contact stomatitis caused by acrylic resin.

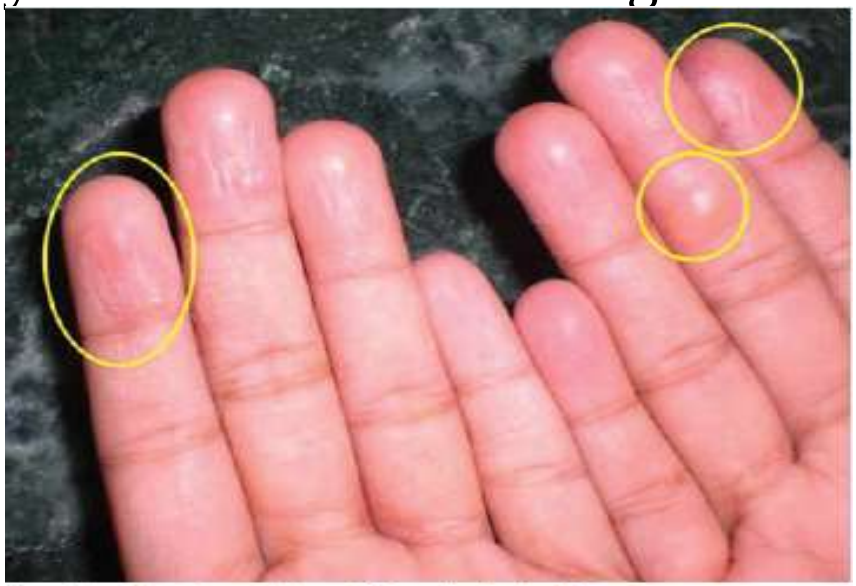


Fig. (1): Allergic reaction of Hands due to Monomer

The patient may complain of a burning sensation, soreness, dryness, or excessive salivation. Examination of the oral mucosa may show punctuate or diffuse redness with or without erosions.

Contact type dermatitis - due to acrylic resin materials acting as haptens via delayed hypersensitivity mechanism, which is observed in several dentists and dental laboratory technicians.

Allergic Stomatitis - The term “sore mouth due to dentures” is applied to any pathologic change of the oral mucosa due to dentures, whether the cause is allergic, traumatic, or toxic.

Patch testing is a reliable method to check for Allergy

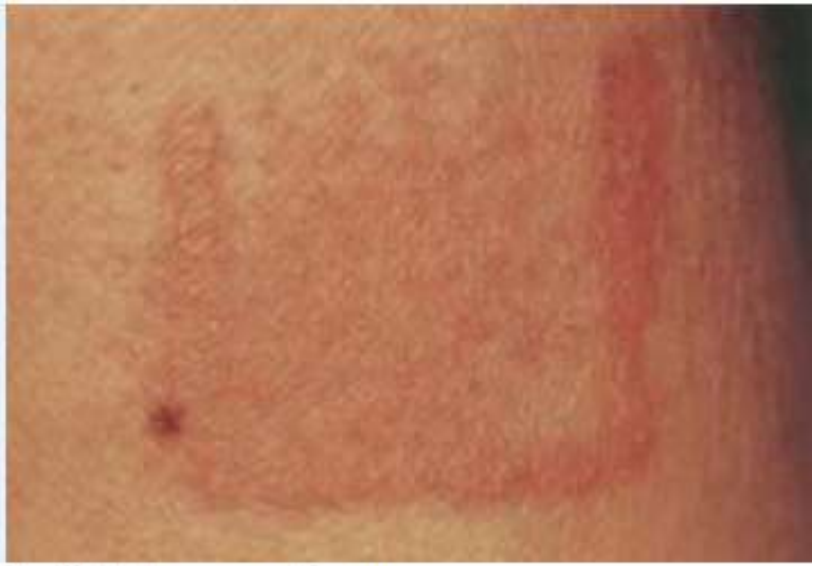


Fig. (2): A large zone of erythema

Clinical Dentistry, Mumbai • September 2012

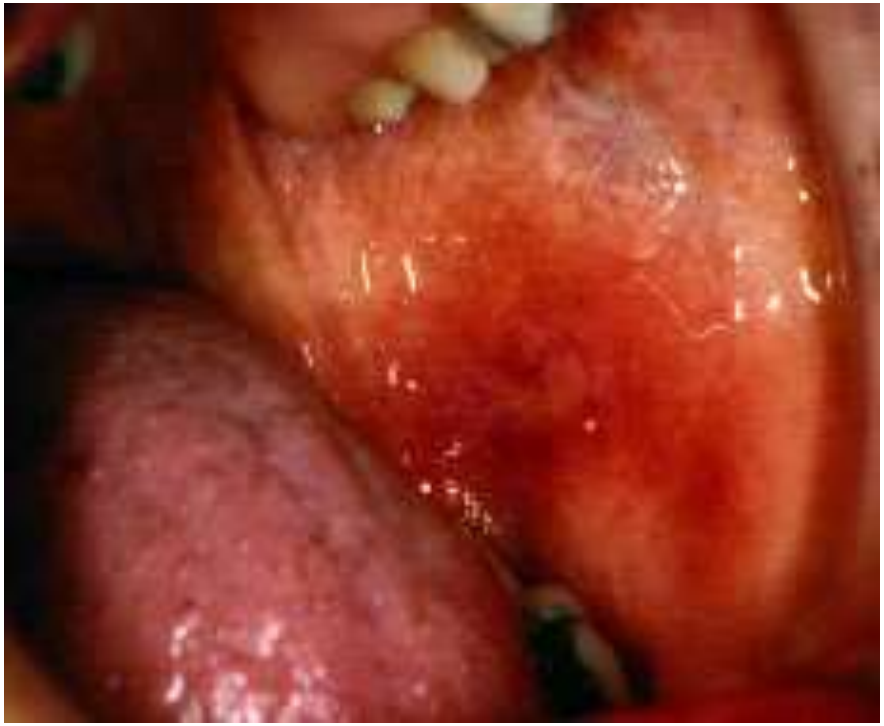
Dr. Suraj R Suvarna

EUGENOL

Eugenol is a material commonly used in dentistry but is not a bio-friendly material when in contact with oral soft tissues

Intra-orally it causes destruction of the interdental col and surrounding gingivae..

Erythema and ulceration in left buccal mucosa, adjacent to UL7 (27) on closure of the mouth

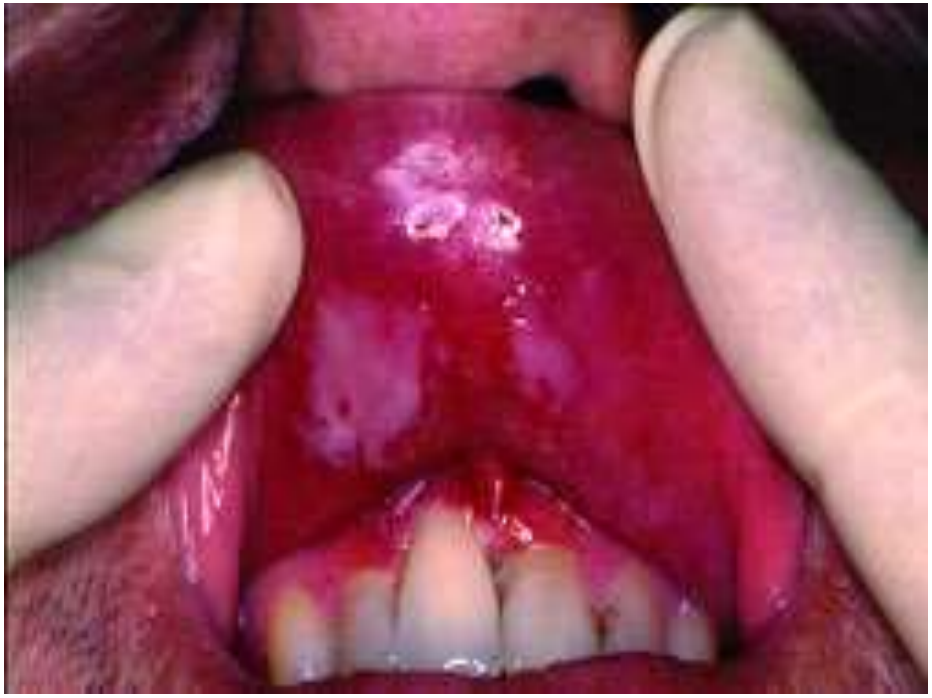


1. Eugenol is generally cytotoxic at **high concentrations** and has an adverse effect on fibroblasts and osteoblast-like cells. Thus at high concentrations it produces necrosis and reduced healing.
   This effect is dose related and will potentially affect all patients.

2. In **lower concentrations**, eugenol can act as a contact allergen evoking a localised delayed hypersensitivity reaction.

3. Rarely, eugenol when placed in the mouth, can cause a more significant generalised allergic response.

Erythema and ulceration on the inner surface of the upper lip and around the gingival margin ofUR1 (11)



The patient was prescribed benzydamine hydrochloride mouthwash and triamcinolone in orobase for relief of his acute symptoms

BRITISH DENTAL JOURNAL VOLUME 193 NO. 5 SEPTEMBER 14 2002
N. Sarrami1 M. N. Pemberton2 M. H. Thornhill3 E. D. Theaker4

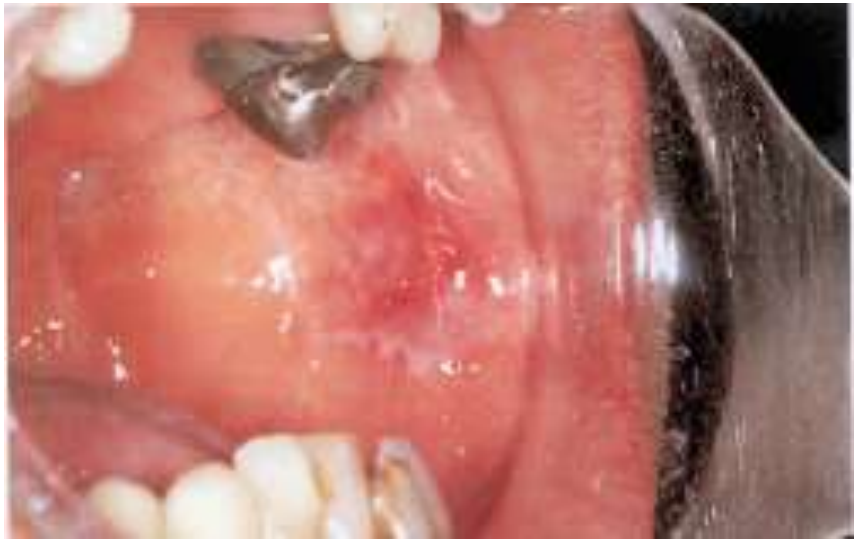
AMALGAM

Hypersensitivity to the constituents of dental amalgam is uncommon.

1. When hypersensitivity reactions occur, they most commonly take the form of delayed type IV lichenoid reactions affecting oral mucosa in direct contact with amalgam fillings.
2. Much more rarely a more acute generalised mucocutaneous response can occur.

BRITISH DENTAL JOURNAL, VOLUME 188, NO. 2, JANUARY 22 2000
B.McGivern, M.Pemberton, E.D. Theaker, J.A.G.Buchanan, and M.H.Thornhill

Buccal lichenoid reaction to a large amalgam restoration of 7



Resolution of the lichenoid reaction following crowning of 7

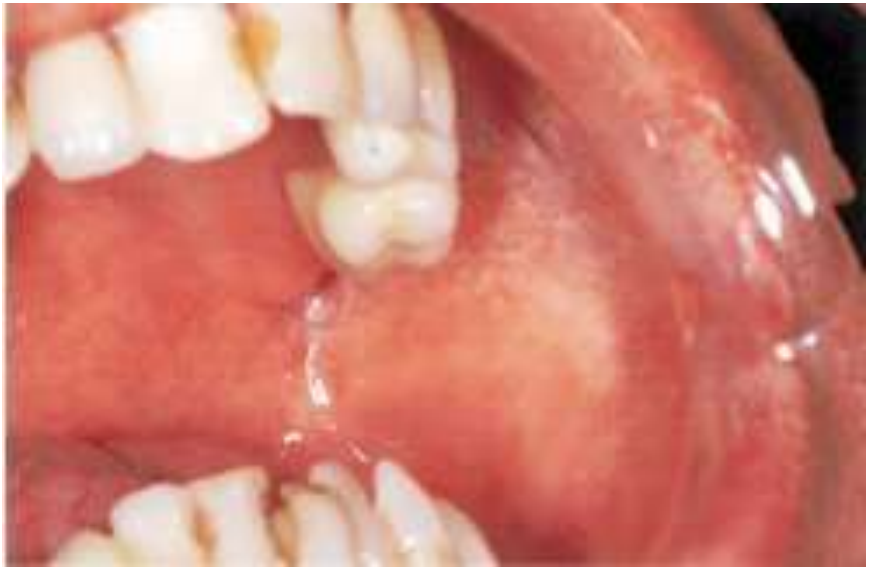
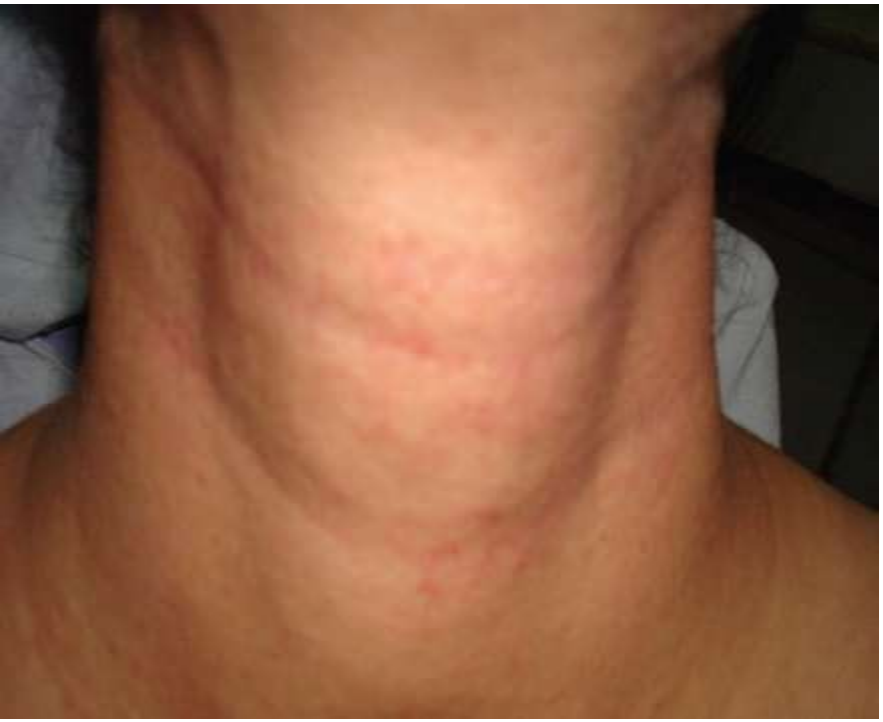
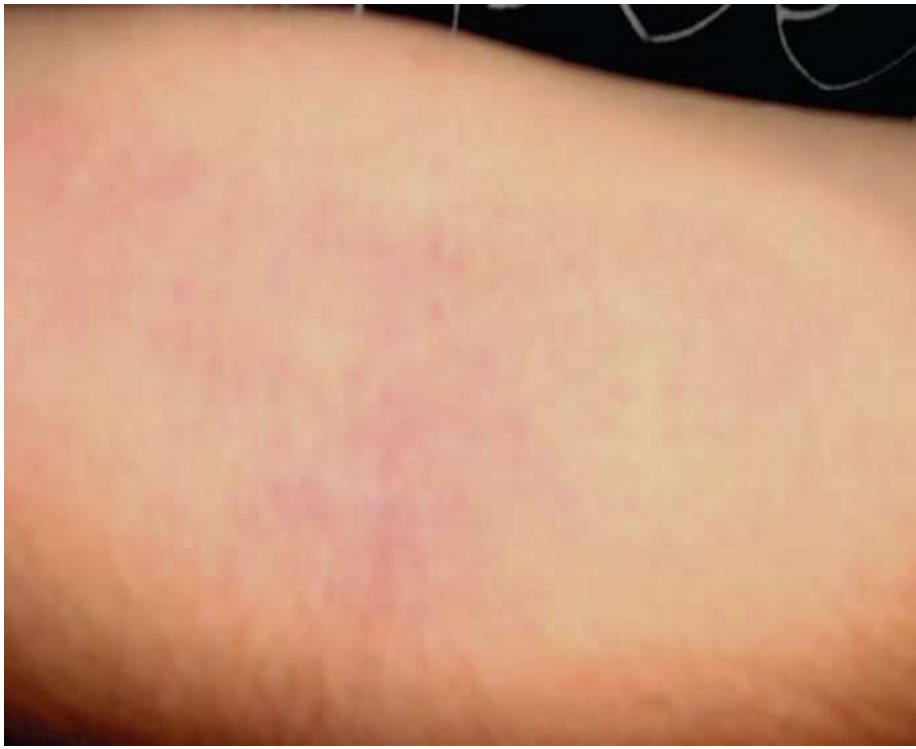


Table 1 **Characteristics of hypersensitivity reactions associated with amalgam restorations**

	Chronic lichenoid reactions	Acute reaction to mercury
Onset	Gradual—may be several years after amalgam was inserted.	Within hours of insertion or removal of a filling.
Location	Buccal or lingual mucosa in intimate contact with the amalgam filling.	Typically skin of face and neck. May be even more generalised. Only 1 in 7 have intra oral features.
Clinical appearance	Resembles lichen planus but not usually bilateral and symmetrical.	Erythematous, pruritic, urticarial skin rash. Intraorally, erythematous, vesiculobullous eruption. Rarely, facial oedema or difficulty breathing.
Duration	Prolonged—lasts as long as the mucosa remains in contact with the filling.	Resolves spontaneously within a few days
Patch test response to mercury	Usually positive by 72 hours.	Positive within 24 hours and often within 2-4 hours. Reaction may spread to surrounding tissues or become generalised.
Response to amalgam removal	Resolution within 12 months	May provoke a reaction. Should be performed with rubber dam and high volume suction to reduce exposure to released mercury.





Red, itchy rash on the neck and arm following contact with mercury while performing amalgam restorations

PREVENTION AND TREATMENT

1. A detailed history of occupation, lifestyle, environment and prevention of exposure to mercury is important.

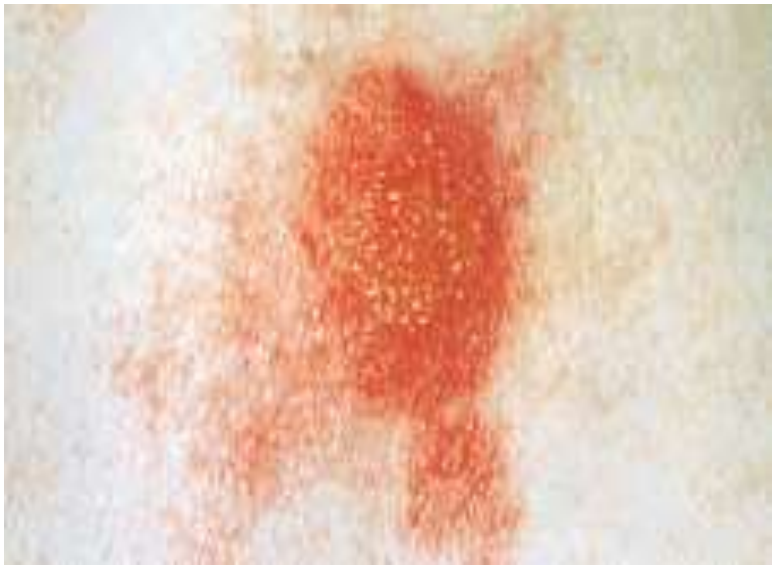
2. Various barrier techniques like using a mask, gloves, hair caps and eye-shields are advised while working.

3. Careful handling of silver amalgam waste

4. Air conditioners and proper ventilation of the operating room, intermittent use of the rotary along with coolant to avoid excess heat, high vacuum suction, proper cleaning and proper handling Of amalgam scraps in a covered container or under sulphide solution is advocated to avoid vapour production.

Dermashield (dimethisone) is a silicone polymer. Pharmologically inert, it has water repellant and surface tension. It adheres to skin and protects it and avoid contact with mercury vapour on the skin. This helps in reducing the lesion's development.

Clonate lotion contains 0.05% clobetasol propionate which is a glucocorticoid used topically for a large variety of dermatological conditions due to their anti-inflammatory, immunosuppressive, vasoconstrictor and antiproliferativev(for scaling lesions) property.



Strong positive skin patch test response, with vesiculation, spreading erythema and oedema, following 24 hours exposure to ammoniated mercury

BRITISH DENTAL JOURNAL VOLUME 205 NO. 7 OCT 11 2008
V. K. Bains,1 K. Loomba,2 A. Loomba3 and R. Bains4

LATEX

Natural rubber latex, which is an extract from the sap of ***Hevea brasiliensis trees***, *contains* 256 proteins,2 including 11 potential allergens.

Exposure to latex poses the risk of sensitizing both clinicians and their patients.

Adverse reactions to latex range from mild irritant contact dermatitis to potentially life threatening hypersensitivity and its risk increases with prolonged and repeated exposure.

Exposure to latex allergens occurs via mucous membranes, the vascular system, inhalation and direct skin contact.

Adverse reactions to latex include nonallergic contact dermatitis, delayed type IV

Immunoglobulin E (IgE) mediated type I responses to latex proteins result in adverse reactions within minutes to hours of exposure ranging from mild irritation to loss of life.

Symptoms include pruritis, erythema, edema, rhinoconjunctivitis, urticaria, dyspnea, palpitations, dizziness, bronchospasm, vasodilation, gastrointestinal cramping, vomiting, hypotension and even death

Box 2 Potentially latex-containing products in the dental clinic

- Gloves[1–14]
- Rubber dams[1,3,5–7,9]
- Amalgam carriers[7]
- Anesthetic carpules (diaphragm and plunger)[1,3,5–7,14]
- Intravenous tubing and bags[1,3]
- Syringes (rubber stoppers covered with silicone)[1,3,6,7,14]
- Bulbs on medicine droppers[1,3,7]
- Bite blocks[1,3,5–9]
- Oxygen masks[1,3]
- Volatile anesthetic masks[1,3,9]
- Operative masks with rubber ties[1,5–7]
- Suction tips and suction tubing[3,5,7]
- Air or water syringe tips and irrigation tubing[7,9]
- Impression materials[7]
- Mixing bowls[3,5,7]
- Orthodontic rubber bands and elastics[1,5–7]
- Polishing discs[3,7]
- Prophy cups[3,5–8]
- Bandages and tape[1,3,7]
- Stethoscopes[1,3,6]
- Blood pressure cuffs[3,6]

“LATEX–FRUIT SYNDROME”

well-documented phenomenon involving IgE antibodies in fruit-allergic patients that cross-react with latex proteins, culminating in allergic responses to latex.

JCDA • www.cda-adc.ca/jcda • May 2009, Vol. 75, No. 4 •
Tara Kean, BSc, DDS; Mary McNally, BSc, DDS, MA

CDC recommendations to help minimize potential adverse reactions to dental items.

1 **Educate** DHCP regarding the signs, symptoms and diagnosis of skin reactions associated with frequent hand hygiene and glove use

2 **Screen** all patients for latex allergy (e.g., take a health history and refer for medical consultation when latex allergy is suspected)

3 **Ensure** a latex-free environment for patients and DHCP with latex allergy

4 **Have** emergency treatment kits with latex-free products available at all times

5 **Develop** a written health program for DHCP that includes policies, procedures and guidelines for contact dermatitiS and latex hypersensitivity

PREVENTION AND TREATMENT

1. Administering prophylactic antihistamines, such as diphenhydramine, or corticosteroids,such as prednisone, before dental treatment to those at known risk

2. Reduce the amount of latex allergens present in their products, which are labeled as "low protein" products (Powder-free gloves)

3. Contact dermatitis and type IV allergy - topical corticosteroids.

4. Mild type I reactions without respiratory distress - topical steroids and antihistamines (50 mg diphenhydramine 4 times a day until swelling resolves).

Cynthia A. Chillock, CDA, RDH, EF, and Charles John Palenik, MS, PhD, MBA; January 2006 RDH

5 Severe type I hypersensitivity with respiratory distress, swelling of the tongue, larynx or pharynx and anaphylaxis - assessment of ABCs (airway, breathing and circulation) and activation of emergency medical services

6 For anaphylaxis - latex-free resuscitation carts are used to administer high-flow oxygen and deliver 0.3–0.5 mL intramuscular or subcutaneous doses of 1:1000 epinephrine15 (0.1 mL/kg every 5 minutes for children).

6 Vitals and ABCs should be continually monitored and cardiopulmonary resuscitation provided if necessary

7 Following stabilization, antihistamines, such as diphenhydramine and corticosteroids, should be prescribed

ORTHODONTICS RELATED

The **causes** comprised the metal parts of fixed appliances, polymer-based activators, retention appliances and brackets, and latex-based elastics or gloves

Most of the reactions associated with the metallic parts of orthodontic appliances were either presumed to be a **nickel allergy** or were unexplained.

The **adverse effects** comprised intra-oral reactions such as marked redness, swelling and soreness of the oral mucosa and palate and similar symptoms of the gingiva and lips.

Occasionally reactions of a systemic nature, compatible with general allergic symptoms are seen.

Ezema of the peri-oral area, the cheeks, chin, neck, scalp, earlobes and skin elsewhere. Occasionally rashes and swelling were seen in the peri-ocular region.

SODIUM HYPOCHLORITE

A 12-year-old girl, with a previous history of bronchial reaction and contact dermatitis to sodium hypochlorite, was referred for root canal treatment.

Complete immunologic evaluation revealed a mild hypersensitivity condition, as it was assessed by the RAST(Radioallergosorbant test) investigation to different allergens and the DTH reactivity expressed though migration inhibition test.

Dandakis C, Lambrianidis T, Boura P. Immunologic evaluation ofdental patient with history of hypersensitivity reaction to sodium hypochlorite. Endod Dent Traumatol 2000; 16: 184–187.

ALGINATE

This study describes a case of fatal anaphylaxis that appeared immediately after the oral mucosa came into contact with an alginate paste used for dental impressions.

The cadaveric examination and the postmortem toxicology report confirmed that the cause of death was anaphylactic shock. The patient was affected by both cardiovascular and lung diseases that worsened the condition and forbade the use of epinephrine.

Int J Prosthodont 2009;22:33–34
Sebastiano Gangemi, PhDa/Elvira Ventura Spagnolo, PhDb/Giulio Cardia, PhDc/Paola L. Minciullo, PhDad.

Severe occlusion of the laryngeal ostium at the cadaveric

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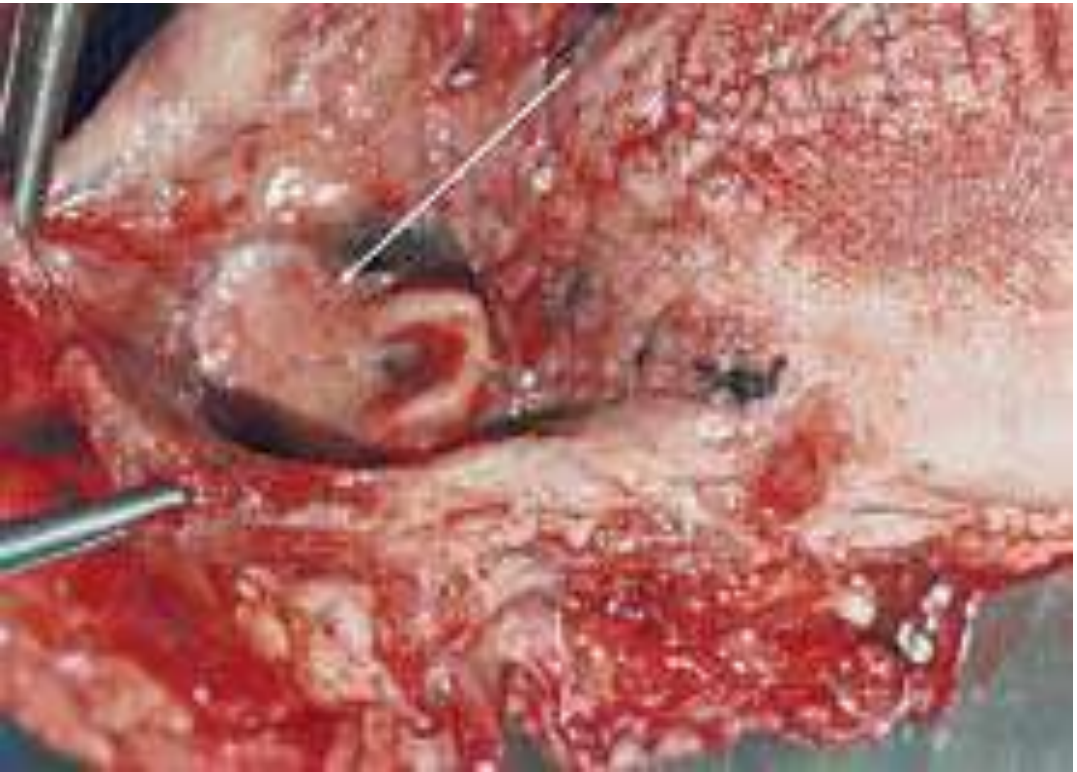
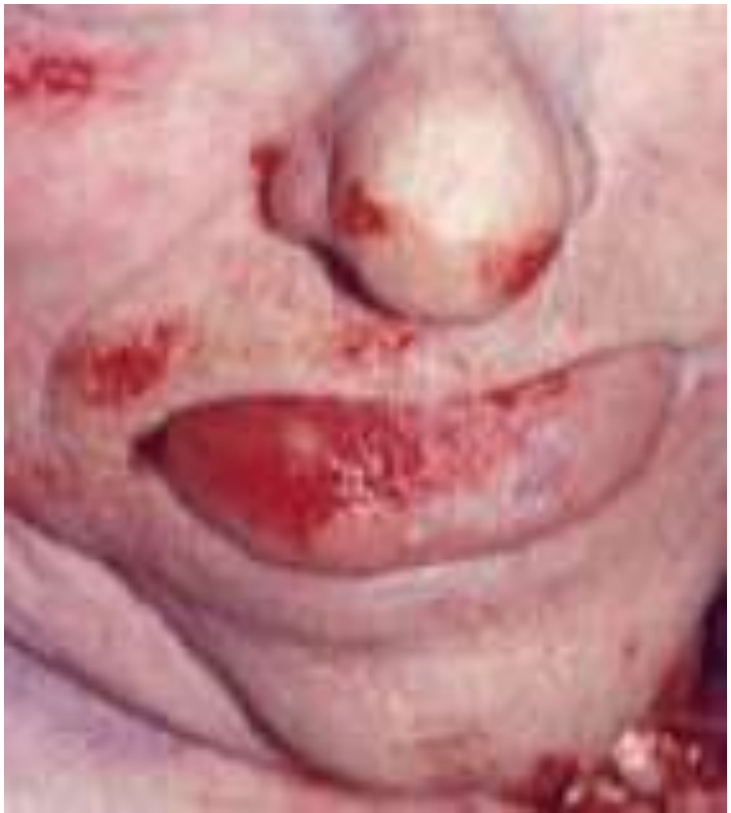


Edema of the tongue.



Hypothesized trigger factor, Kromopan, is not a known allergenic or anaphylactoid. Kromopan is an alginate used to make high-precisionimpressions with chromatic phase indicators.

Among the various Kromopan components, only **phenolphthalein** has been reported as causing toxic epidermal necrolysis and fixed drug eruption

THANK YOU!!!!