
بسم الله الرحمن الرحيم

Allergy & Hypersensitivity

(Ph.D)

OBJECTIVES

By the end of this lecture students of 3rd year should be able to

1. Define and classify the hypersensitivity reactions.
2. Describe the pathophysiology of allergy and hypersensitivity.
3. Compare immediate and delayed hypersensitivity reactions.
4. List the diseases associated with hypersensitivity reactions.

Hypersensitivity

- the exaggerated or inappropriate immune response that is harmful to host, mediated by **pre-existing** immunity to an antigen.
- Hypersensitivity reaction require a pre-sensitized (immune) state of the host.
- **Allergy** is used appropriately to the IgE mediated immune reaction (Type I: Immediate hypersensitivity reaction).

Types of hypersensitivity reactions

Antibody-mediated

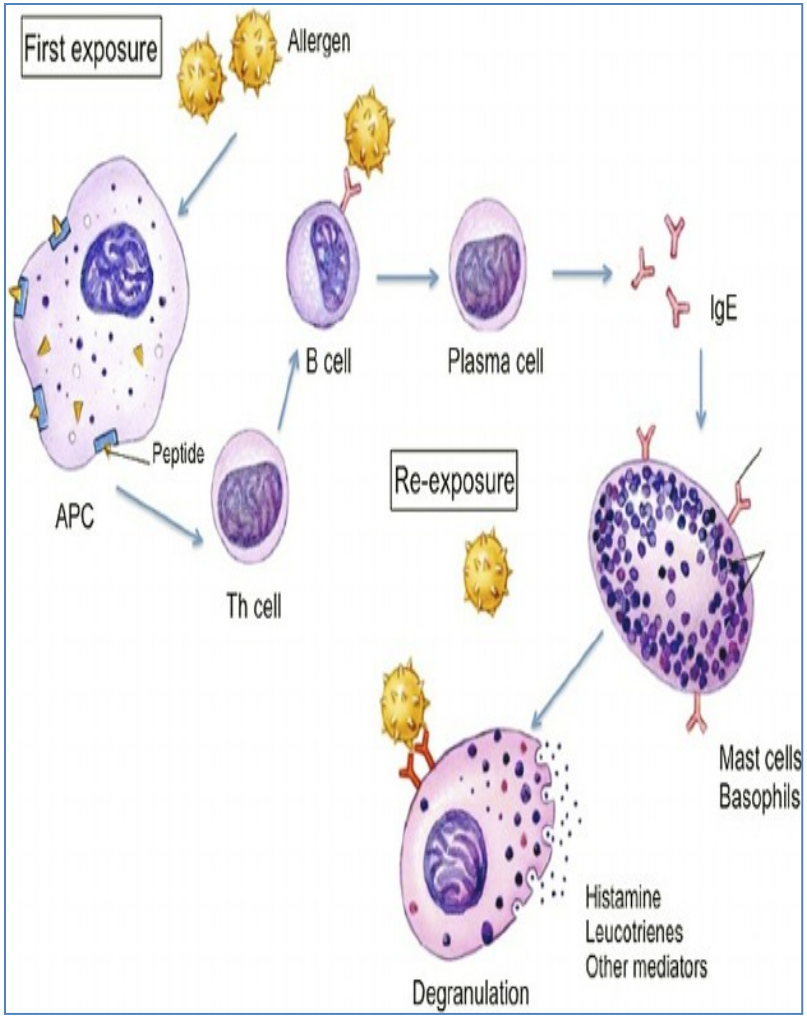
Type I:	Immediate (anaphylactic) hypersensitivity reaction (IgE mediated).
Type II:	Cytotoxic hypersensitivity reaction (IgG mediated).
Type III:	Immune-complex hypersensitivity reaction (IgG mediated).

Cell-mediated

Type IV:	delayed (cell mediated) hypersensitivity reaction

TYPE I: ANAPHYLACTIC OR IMMEDIATE HYPERSENSITIVITY REACTION

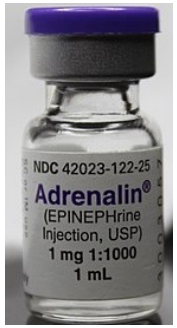
- This anaphylactic reaction is mediated when an allergen crosslinks with specific IgE, on the surface of mast cells,
- It results in degranulation and release of several mediators (histamine) and subsequent swelling and vasodilation.
- It occurs within minutes after **second encounter** with the antigen (allergen).



Pathophysiology of allergy and hypersensitivity

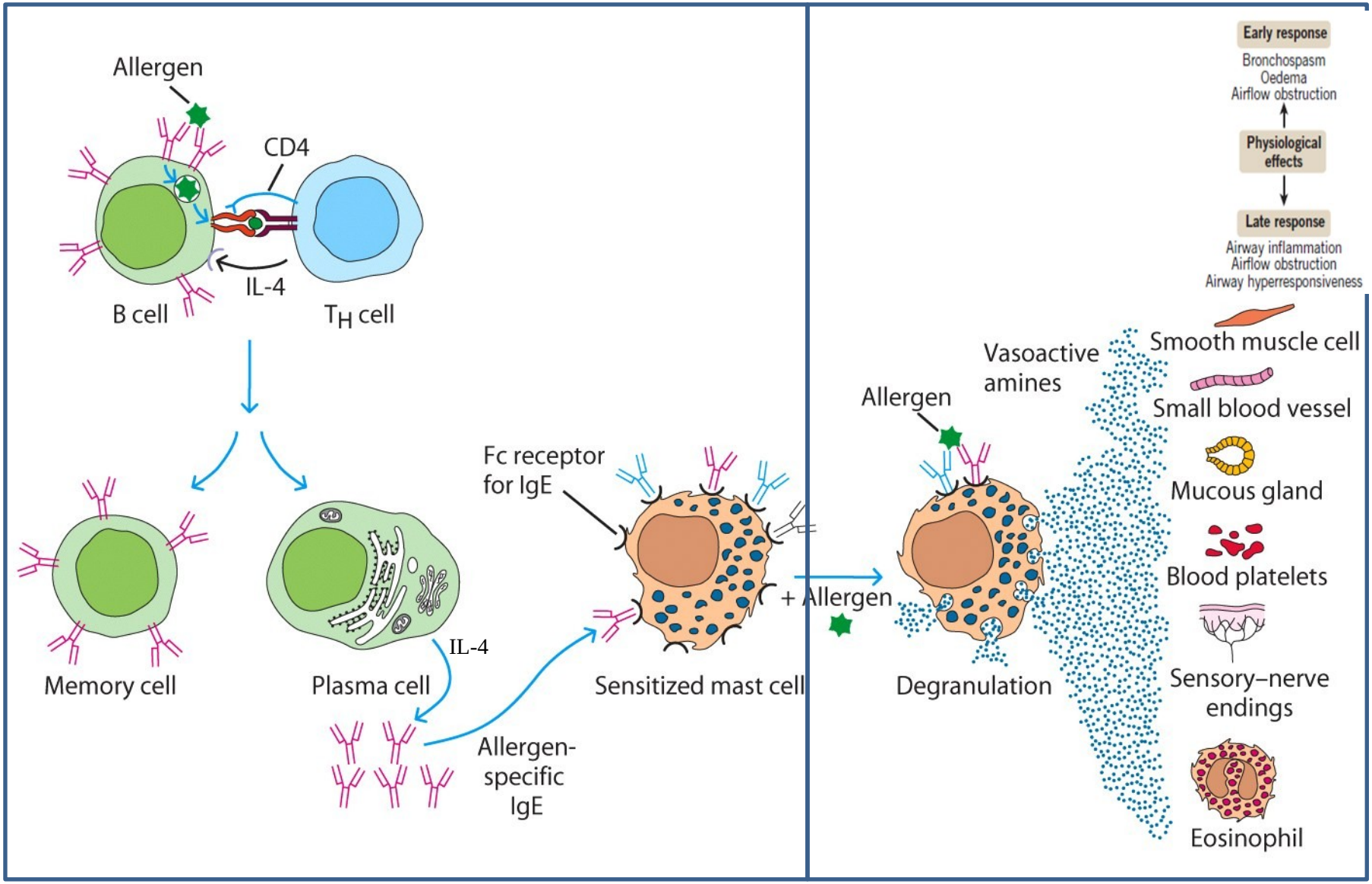
- The production of IgE, in response to certain antigens, **allergens** is necessary .
- IgE has very high affinity for its Fc receptor on mast cells and basophils. (mast cells are connective tissue cells, numerous in respiratory & GI tracts and near the blood vessels, while basophil (<1%) are the circulating leukocytes)
- When IgE pileup on cells, the person is **sensitized**.
- Sensitization requires a minimum of **one week**.

- A subsequent exposure to the same allergen cross links the cell-bound IgE, causing degranulation and release of mediators, that lead to erythema, edema (wheal & flare), itching & burning (due to sensory nerve excitation) **(Immediate phase)**.
- **Late phase:** After approx 6 hours, the secretion of leukotriene (SRS-A) and other mediators like eosinophilic chemotactic factor, serotonin, prostaglandins and thromboxane cause influx of neutrophils and eosinophils that leads to erythema and induration.
- Complement is NOT involved.
- **Epinephrine increases the activity of adenyl cyclase which increases cAMP, which inhibit further degranulation.**



Sensitization

2nd exposure



Antigens

Any substance capable to trigger an immune response

is called **antigen**

- Dust
- Pollens
- Foods (nuts, sea food, shellfish)
- Bee venom
- Drugs
- Microorganisms
- Chemicals & latex rubber gloves
- Blood products used in clinical practice

- Non allergic individuals respond to the same allergen by producing IgG, which does not cause release of mediators from basophil or mast cells (these cells lack IgG receptors)

TABLE 65–2 Important Clinical Aspects of Immediate Hypersensitivities

Main Organ Affected	Disease	Main Symptoms	Typical Allergens	Route of Acquisition
Lung	Asthma	Wheezing, dyspnea, tachypnea	Pollens, house dust (feces of dust mite), animal danders, many occupational airborne allergens	Inhalation
Nose and eyes	Rhinitis, conjunctivitis, "hay fever"	Runny nose, redness and itching of eyes	Pollens	Contact with mucous membranes
Skin	1. Eczema (atopic dermatitis)	Pruritic, vesicular lesions	Uncertain	Uncertain
	2. Urticaria (hives)	Pruritic, bullous lesions	1. Various foods	Ingestion
			2. Drugs	Various
Intestinal tract	Allergic gastroenteropathy	Vomiting, diarrhea	Various foods	Ingestion
Systemic	Anaphylaxis	Shock, hypotension, wheezing	1. Insect venom (e.g., bee venom)	Sting
			2. Drugs (e.g., penicillin)	Various
			3. Foods (e.g., peanuts)	Ingestion

Examples

- **Systemic anaphylaxis**
  - Most severe form of Type I hypersensitivity reaction.
  - There is severe bronchoconstriction and hypotension.
- **Atopy** (hay fever, asthma, & eczema) have familial predisposition.
- **Drug hypersensitivity**.
- **Desensitization**
  - » Acute desensitization
  - » Chronic sensitization

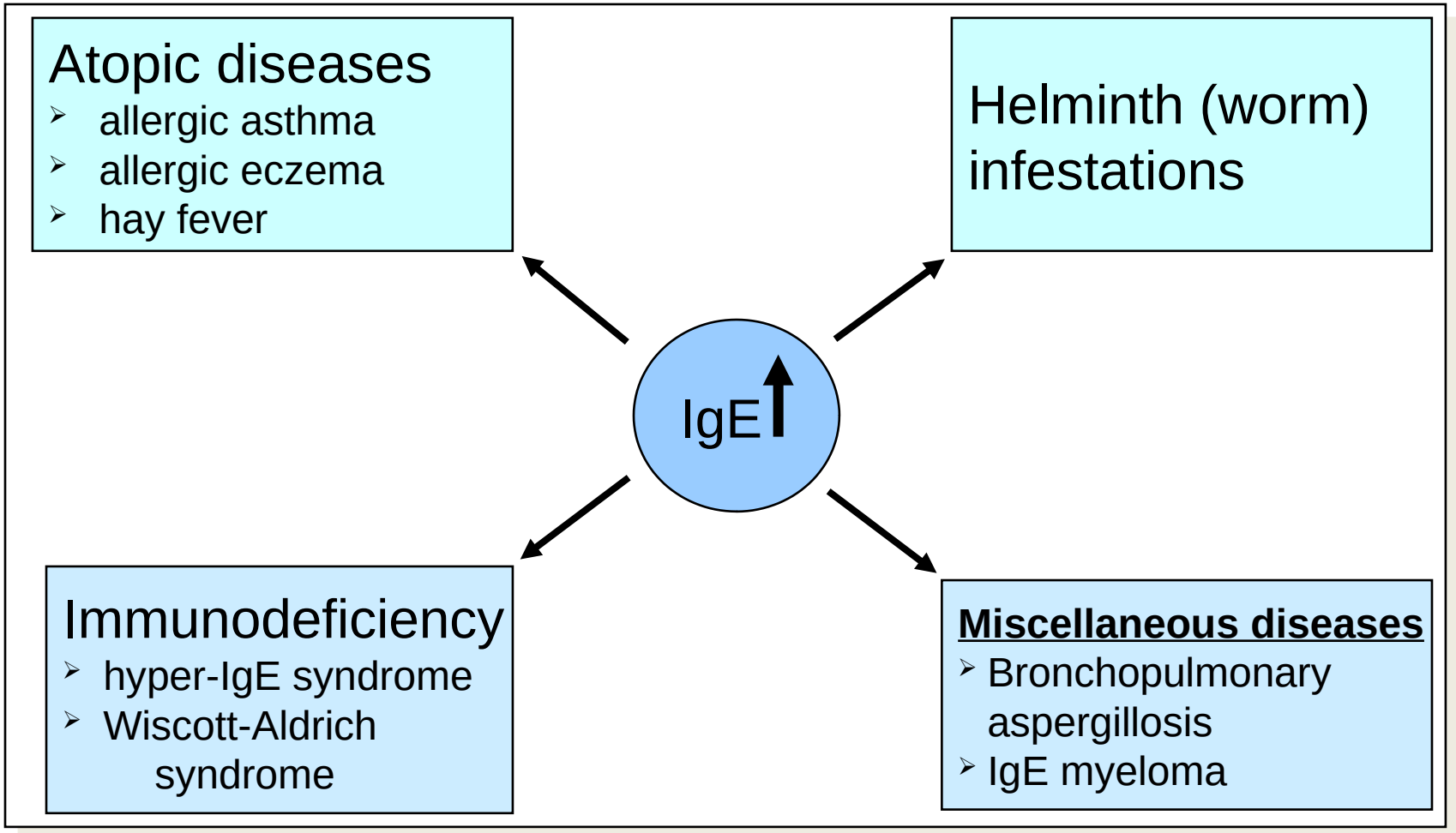
- Allergic asthma.
- Allergic conjunctivitis.
- Allergic rhinitis (“hay fever”)
- **Anaphylaxis**.
- Angioedema.
- Atopic dermatitis (eczema)
- Urticaria (hives)
- Eosinophilia.

Induction of reaction by different allergens

- skin (prick and intradermal) tests resulting in wheal and flare reaction,
- Detection of Total IgE and specific IgE antibodies by a modified enzyme immunoassay (ELISA).
- Increased IgE levels are indicative of atopic condition,

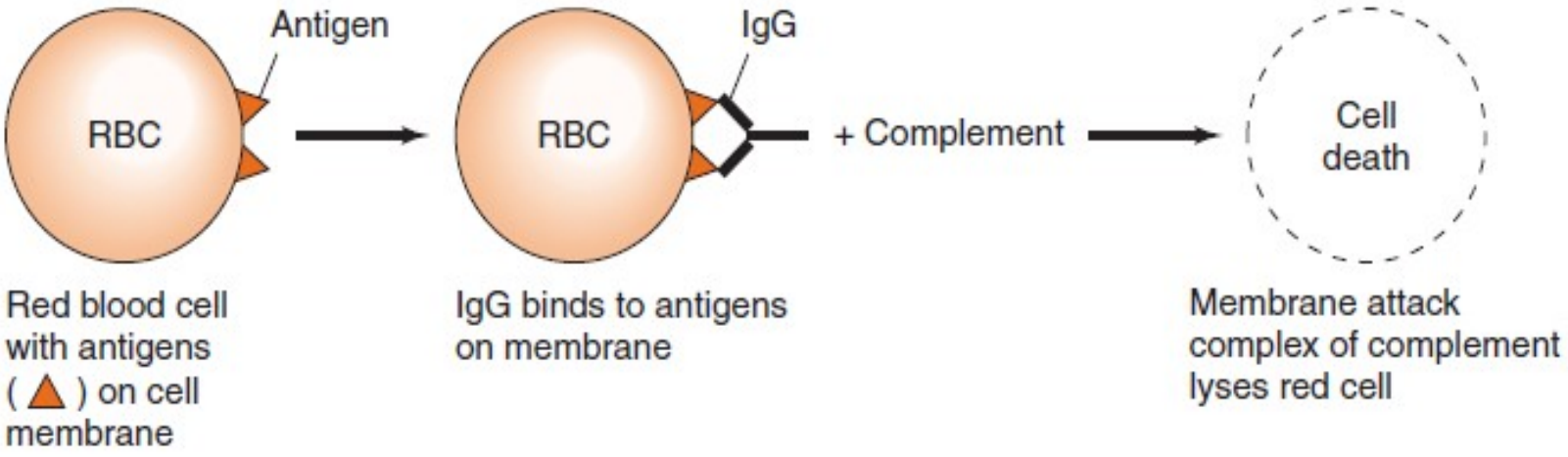
weal and flare response

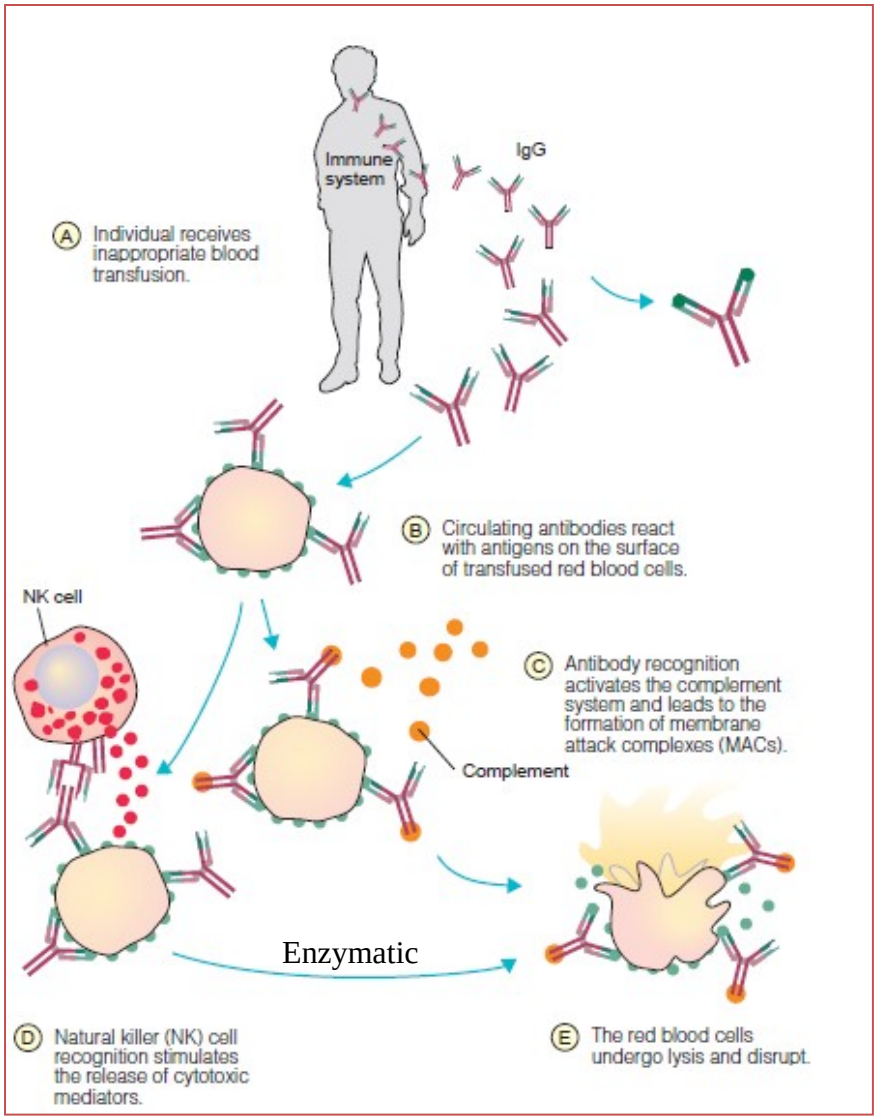
Increased IgE levels



- A **cytotoxic hypersensitivity** is a cell-damaging immune response occurs when antibody reacts with antigens **of the cell membrane (RBC)**,
- **Complement** is activated that generates membrane attack complex and complement mediated lysis of cell.
- **phagocytes** are attracted, that cause enzymatic damage of cell membrane.
- The reaction time is from minutes to hours

cytotoxic hypersensitivity





The diagram depicts antibody- complement-mediated lysis of a nucleated cell as a consequence of formation of the membrane attack complex

& antibody dependent cell-mediated cytotoxicity through the action of NK.

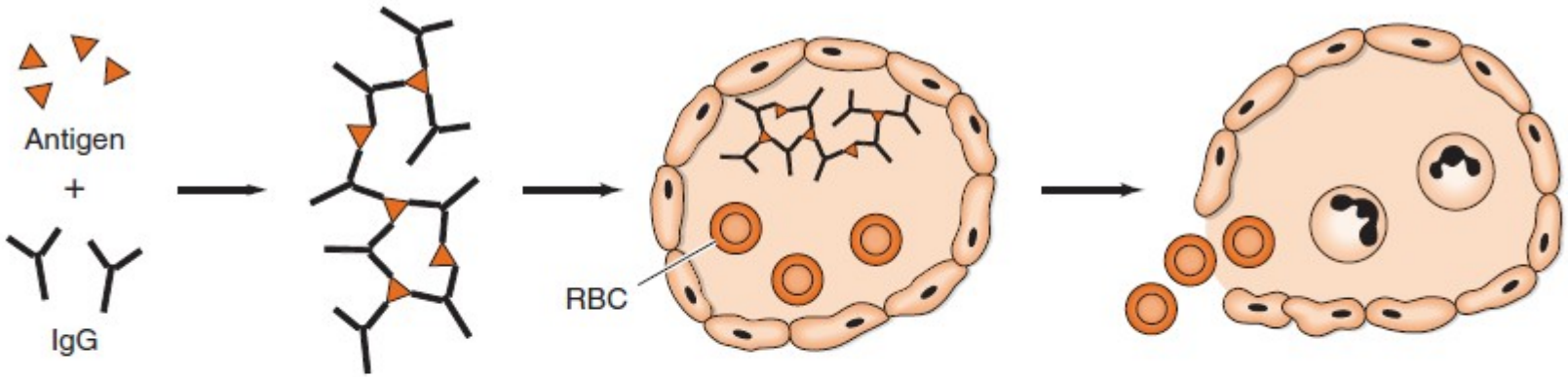
Clinical examples of Type II hypersensitivity

- Drug-induced haemolytic anaemia
- ABO blood transfusion reactions,
- Rh hemolytic disease of newborn,
- Drug induced - granulocytopenia and thrombocytopenia.
- In Goodpasteur's syndrome, antibodies to antigens on basement membrane of kidneys and lungs, activates complement and causes severe damage to the renal & pulmonary basement membranes; Goodpasture's nephritis (renal and lung basement membrane) and pemphigus (skin intercellular protein, desmosome).

TYPE III: IMMUNE COMPLEX HYPERSENSITIVITY

- Normally, immune complexes are promptly removed by the reticuloendothelial system.
- In immune complex hypersensitivity the antigen–antibody complexes, deposit in tissues & induce an inflammatory response.
- Immune complexes activate the complement system. Polymorphs are attracted to the site, with inflammation and tissue injury.

Type III: hypersensitivity



Antigen–antibody complexes form in blood

Immune complexes are deposited on blood vessel wall, complement is activated, and C3a and C5a are released

Neutrophils are attracted by C5a; they release enzymes that destroy the endothelium and red cells escape from within the blood vessels

- In persistent microbial or viral infections, immune complexes may be deposited in organs (e.g., the kidneys), resulting in kidney damage.
- In autoimmune disorders, “self” antigens may elicit antibodies that bind to organ antigens or deposit in organs as complexes, especially in joints (arthritis), kidneys (nephritis), or blood vessels (vasculitis).

Type III: hypersensitivity

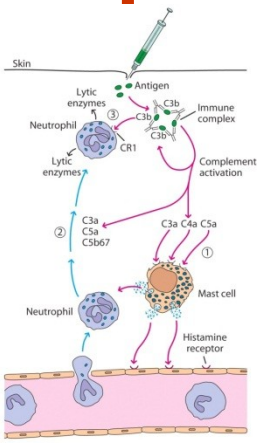
Immune-complex mediated

Mostly IgG (although IgM may also be involved)

Ag-Ab complexes in soluble state

Normally cleared by RES

Occasionally deposit in tissue / OR if in large amount



activate complement system

C3a & C5a are produced

inflammation

Vasodilatation

Polys are attracted to the site

Lysosomal enzymes of neutrophils are released

induce tissue injury

Vasculitis and arthus reaction

Damage to endothelium causes escape of RBC from within the blood vessels

- The reaction may take 3 - 10 hours after exposure to the antigen.
- Immune complexes can become deposited in walls of small blood vessels in alveoli anaphylaxis

Arthus reaction is a localized inflammation

while

Serum sickness

Hands affected by RA

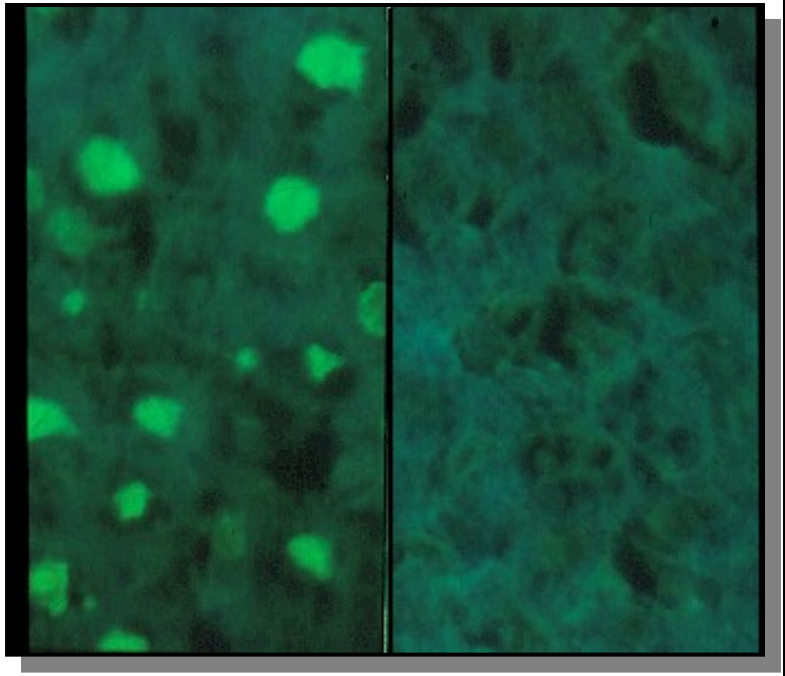
Glomerulonephritis

- **Acute post-streptococcal glomerulonephritis** is the immune complex disease
- immunoglobulin & C3 are deposited along glomerular basement membrane
- These deposits fix complement attracts neutrophils enzymes are released inflammation & damage to the glomerular basement membrane occur.

IgA nephropathy Berger's disease

- A common familial form of glomerulonephritis.
- Deposition of galactose deficient IgA on glomerular basement membrane; react with other antibodies and form clumps.
- Deposits fix complement attracts neutrophils enzymes are released inflammation & damage to the glomerular basement membrane.
- Cause not known
- Course of disease varies (some asymptomatic, some have mild symptom & in other, it rapidly progresses to renal failure).
- It is diagnosed by renal biopsy.

Systemic lupus erythematosus

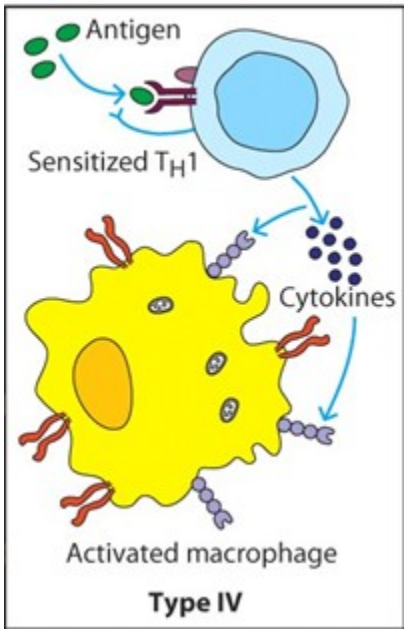


SLE (Systemic lupus erythematosus)

- Chronic Inflammatory autoimmune disease
- Effects mainly skin of the face, joints & kidneys
- Antibodies are formed against DNA & other components of nucleus
- Immune complexes activates complement
- Activation of complement produces C5a, that attracts neutrophils enzymes are released tissue damage occur.

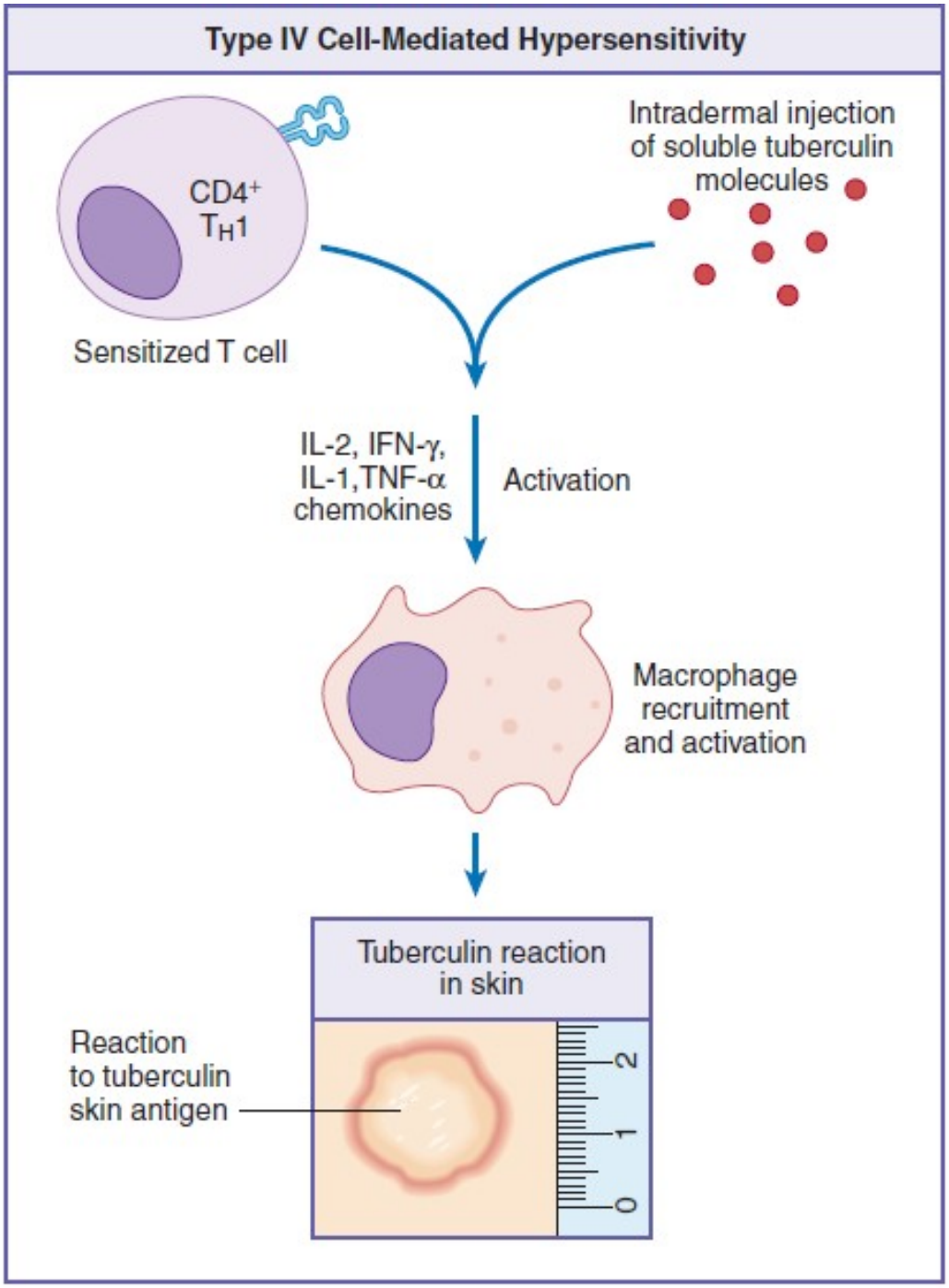
Type IV hypersensitivity (delayed-type hypersensitivity)

- DTH involves **T_H1 cell**– **antigen interactions** that cause activation, cytokine secretion, and potential granuloma formation (induration and surrounding erythema).
- Type IV hypersensitivity requires sensitized lymphocytes that respond 24 to 48 hours after exposure to soluble antigen.
- The reaction is characterized by large influxes of macrophages.
- DTH reactions may involve TH cells (CD4+) or CTLs (CD8+ CTLs).



Type IV hypersensitivity (delayed-type hypersensitivity)

- Clinical examples include
  - tuberculosis, leprosy, and sarcoidosis
  - as well as contact dermatitis
- The tissue injury is primarily due to the vigorous immune response to released antigens rather than to the inciting pathogen itself.


Type IV Cell-Mediated Hypersensitivity
CD4+
TH1
Sensitized T cell
Intradermal injection
of soluble tuberculin
molecules
IL-2, IFN-γ,
IL-1,TNF-α
chemokines
Activation
Macrophage
recruitment
and activation
Tuberculin reaction
in skin
Reaction
to tuberculin
skin antigen
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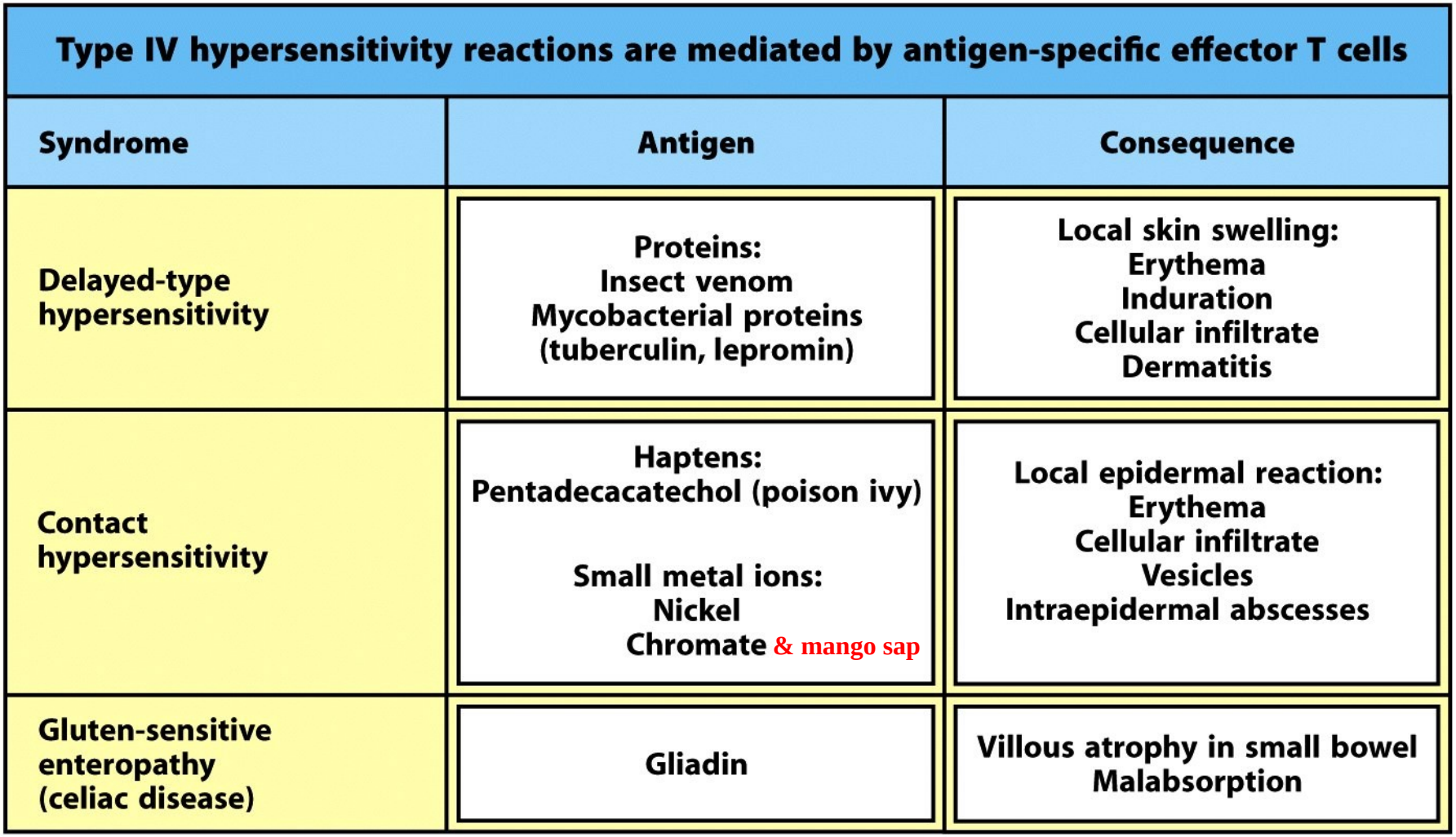


Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

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) Small metal ions: Nickel Chromate & mango sap	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitive enteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

Figure 13-28 Immunobiology, 7ed. (© Garland Science 2008)

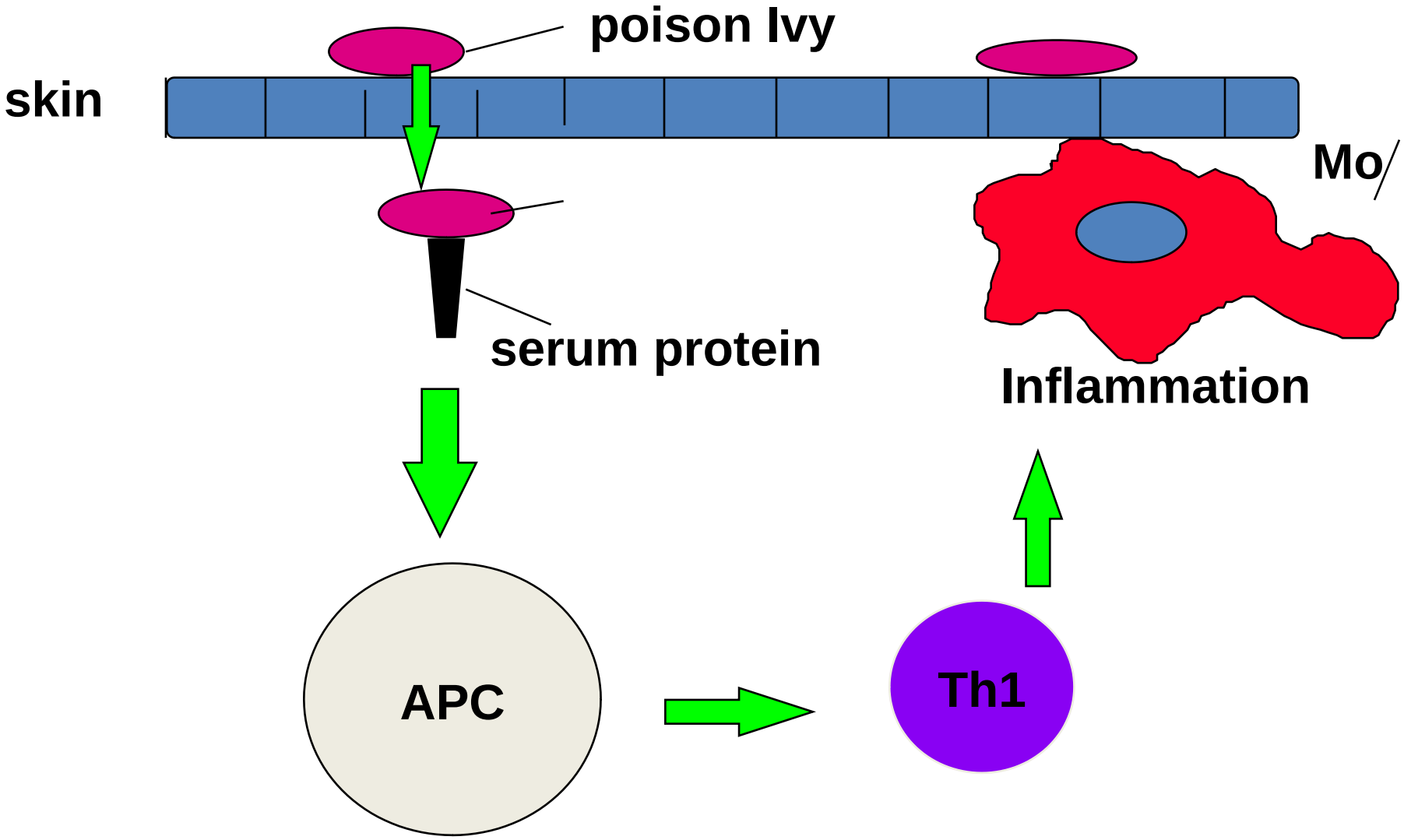
Delayed, takes 24-48hrs (Type IV hypersensitivity)

It is involved in the pathogenesis of many infectious diseases

- tuberculosis, leprosy, brucellosis,
- blastomycosis, histoplasmosis, Candidiasis,
- toxoplasmosis, leishmaniasis, and
- granulomas due to infections and foreign antigens.

- Another form of delayed hypersensitivity is **contact dermatitis** (poison ivy, chemicals, heavy metals, food, cosmetics) in which the lesions are more papular.
    - (Erythema, itching, vesicular rash, eczema & even necrosis)

Mechanism of Type IV Hypersens



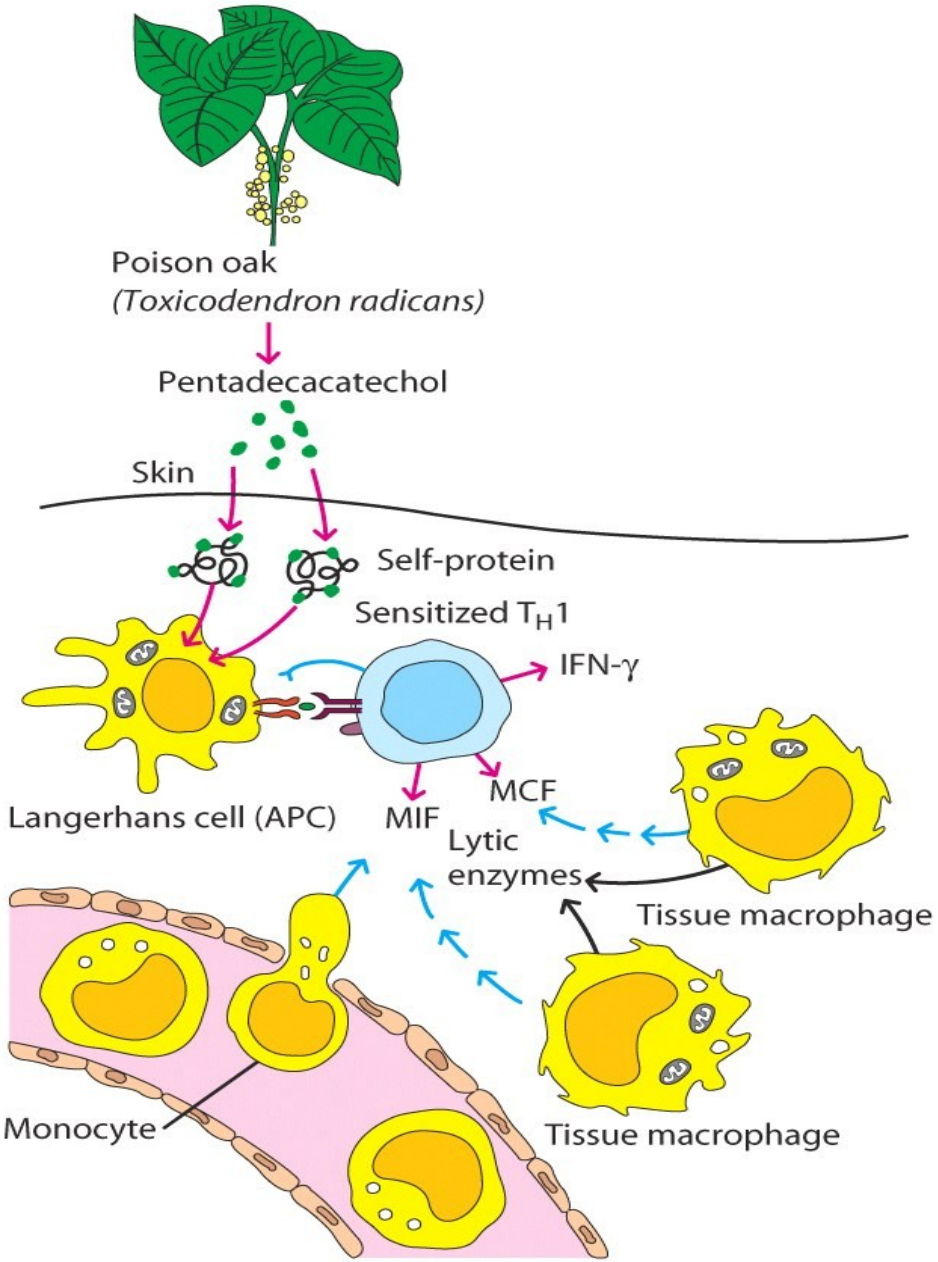


Figure 12-28 Immunobiology, 6/e. (© Garland Science 2005)

GM-CSF= Granulocyte- macrophage colony stmulating factor
MCAF= Monocyte chemotactic and activating factor
MIC= Monocyte migration inhibitory factor

Contact dermatitis reaction to mango

Contact dermatitis reaction to leather

Granuloma in a leprosy patient

Leprosy

Comparison between Immediate & Delayed hypersensitivity

	Type I Immediate Hypersensitivity	Type IV Delayed Hypersensitivity
Onset:	Immediate	Delayed
Duration:	Short: hours	Prolonged: days or longer
Allergens:	Pollen Molds House dust Danders Drugs Antibiotics Soluble proteins and carbohydrates Foods	Drugs Antibiotics Microorganisms: bacteria, viruses, fungi, animal parasites Poison ivy/oak and plant oils Plastics and other chemicals Fabrics, furs Cosmetics
Passive transfer of sensitivity:	With serum	With cells or cell fractions of lymphoid series
Clinical state:	Hay fever Asthma Urticaria Allergic skin conditions Anaphylactic shock	Drug allergies Infectious allergies Tuberculosis Rheumatic fever Histoplasmosis Trichinosis Contact dermatitis

characteristic	Type-I	Type-II	Type-III	Type-IV
antibody	IgE	IgG, IgM	IgG, IgM	none
antigen	exogenous	cell surface	soluble	intracellular
response time	15-30 min.	Min.-hrs	3-8 hours	48-72 hours or longer
appearance	Wheal & flare	Lysis & necrosis	Erythema & edema	Erythema & induration
histology	baso- and eosinophils	Ab and complement	PMN and complement	Monocytes & lymphocytes
transfer with	antibody	antibody	antibody	T-cells
examples	hay fever, asthma	pemphigus, Goodpasture	farmers' lung, SLE	tuberculin test, poison ivy, granuloma

Mantoux test

Thank you