IMMUNOLOGY

HYPERSENSITIVITY

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"HEAL US TO HEAL OTHERS"

INTRODUCTION

- 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.**

- Hypersensitivity is a reflection of excessive or aberrant immune responses. Immune responses are themselves capable of causing tissue injury and disease.

DEFINITION

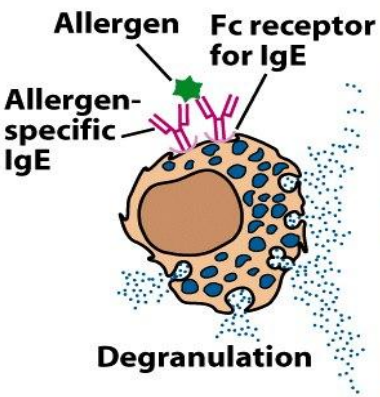
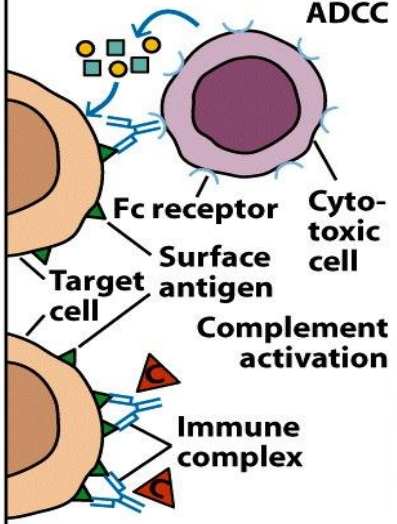
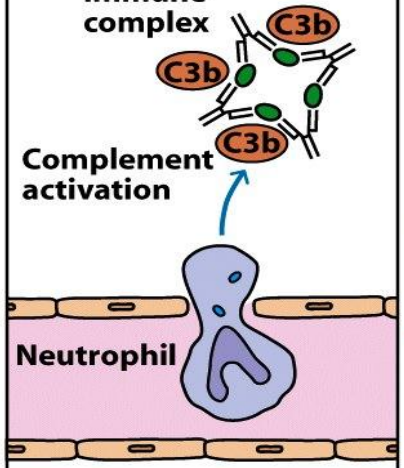
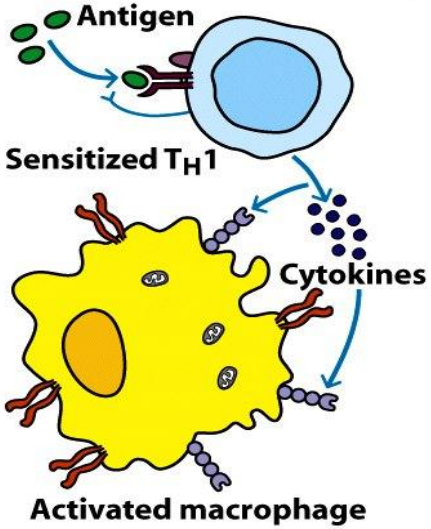
- Hypersensitivity (hypersensitivity reaction) refers to undesirable immune reactions produced by the normal immune system.

- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.

Classification

Hypersensitivity reactions are classified into four basic types, suggested by Philip Gell & Robin Coombs.

- Type I – Immediate or IgE Mediated (atopic, or anaphylactic) Hypersensitivity
- Type II – Antibody-dependent Cytotoxic Hypersensitivity
- Type III – Immune complex Mediated Hypersensitivity
- Type IV - Cell-mediated or delayed Hypersensitivity

 **Type I**	 **Type II**	 **Type III**	 **Type IV**
IgE-Mediated Hypersensitivity	**IgG- or IgM-Mediated Cytotoxic Hypersensitivity**	**Immune Complex–Mediated Hypersensitivity**	**Cell-Mediated Hypersensitivity**
Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	**Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC.**	**Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.**	**Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.**
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	**Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.**	**Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.**	**Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.**

TYPE I HYPERSENSITIVITY

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- Type I hypersensitivity is also known as **immediate** or IgE-Mediated Hypersensitivity or **anaphylactic** hypersensitivity.
- Type I hypersensitivity is an allergic reaction provoked by re-exposure to a specific **antigen.**
- **Occur within minutes of exposure to antigen. ie, t**he reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.
- Exposure may be by **ingestion, inhalation, injection**, or direct contact.
- This reaction is mediated by **IgE antibodies and** causes an **inflammatory** response leading to an immediate (within seconds to minutes) reaction.
- The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from **anaphylactic shock**.

COMPONENTS OF TYPE I REACTION

- Allergens
- Reagenic Antibody (IgE)
- Mast Cells and Basophils
- IgE-Binding Fc Receptors

Allergen

- Type I Hypersensitive reaction is induced by certain types of antigens, referred to as allergens.
- Allergens are nonparasite antigens that can stimulate a type I hypersensitivity response.
- Allergens bind to IgE and trigger degranulation of chemical mediators.

TABLE 15-1 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

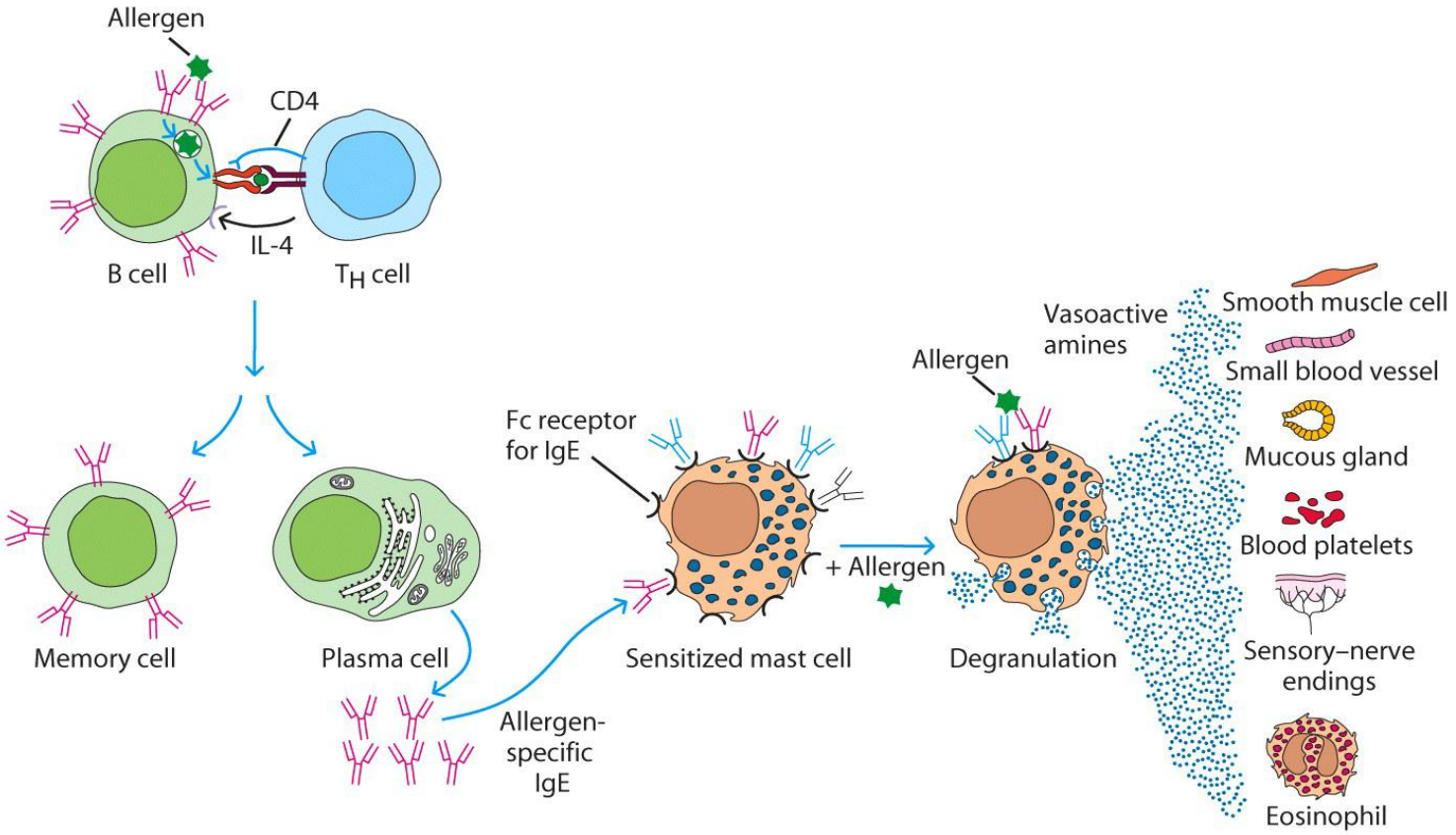
Insect products
- Bee venom
- Wasp venom
- Ant venom
- Cockroach calyx
- Dust mites

Mold spores

Animal hair and dander

Latex

MECHANISM OF TYPE 1 HYPERSENSITIVITY



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- Most allergic IgE responses occur on mucous membrane surfaces in response to allergens that enter the body by either inhalation or ingestion.
- Exposure to an allergen activates B cells to form IgE secreting plasma cells.
- Secreted IgE molecules bind to IgE specific Fc receptors on mast cells and blood basophils. Such IgE coated mast cells and basophils are said to be sensitized.
- The IgE can attach to Mast cells by Fc receptor, which increases the life span of the IgE. Half-life of IgE in serum is days whereas attached to FcεR it is increased to months.
- Second exposure to the same allergen leads to cross-linking of the bound IgE on sensitized mast cells and basophils causing degranulation of these cells and trigger the release of pharmocologically active mediators, vasoactive amines from mast cells and basophils, act on the surrounding tissues and cause inflammation within few minutes (Immediate hypersensitivity).
- This mediators cause smooth muscle contraction, increased vascular permeability and vasodilation.

Mediators of Type I Hypersensitivity

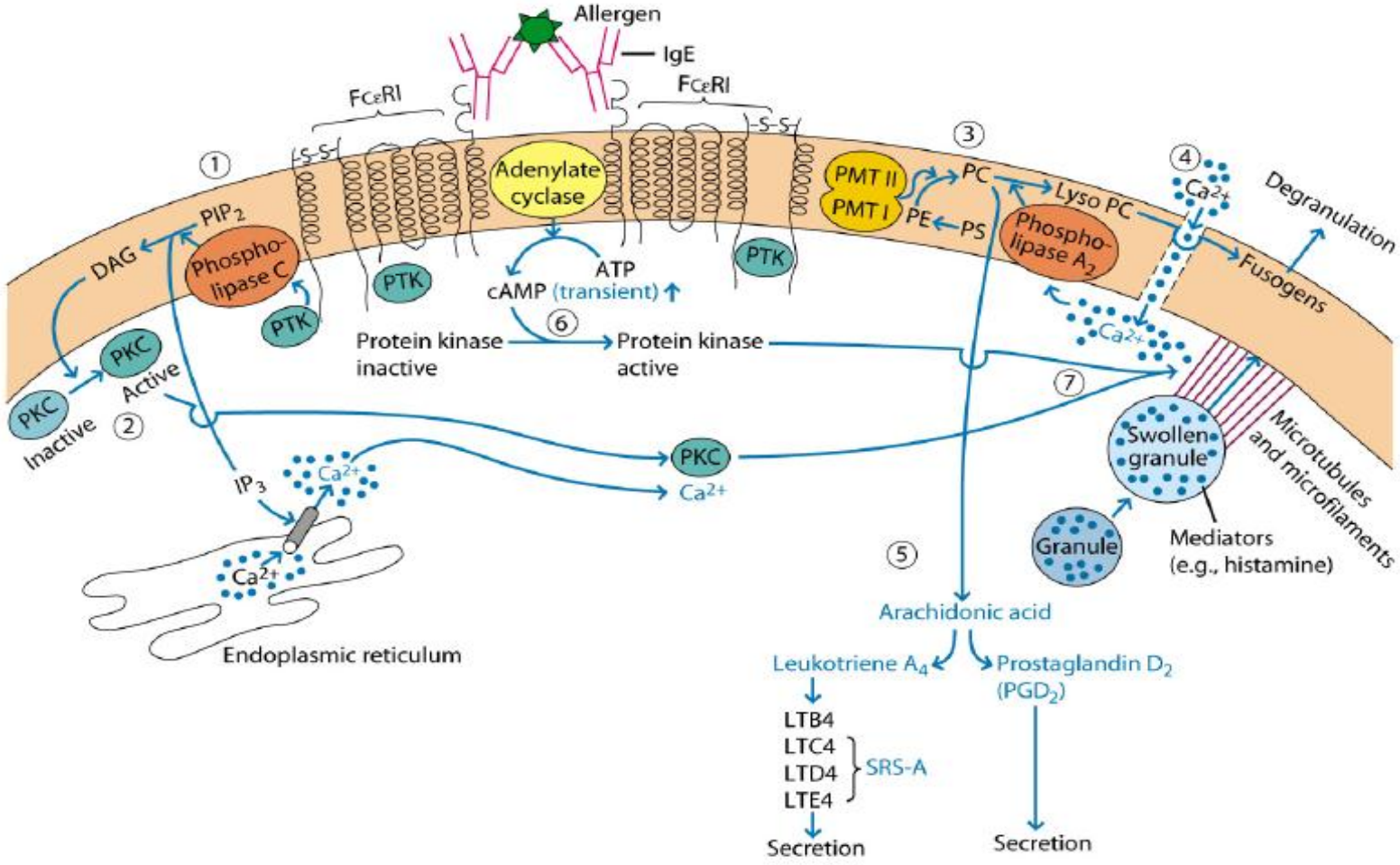
TABLE 15-3 Principal mediators involved in type I hypersensitivity

Mediator	Effects
	PRIMARY
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	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
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF	Various effects (see Table 12-1)

- IgE mediated degranulation begins when an allergen cross-links IgE that is bound (fixed) to the Fc receptor on the surface of a mast cell or basophil.

- In itself, the binding of IgE to FcRI apparently has no effect on a target cell. It is only after allergen crosslinks the fixed IgE receptor complex that degranulation proceeds.

INTRACELLULAR EVENTS LEADING TO MAST CELL DEGRANULATION



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CONSEQUENCES OF TYPE 1 REACTION

- Systemic Anaphylaxis
- Localized Anaphylaxis (Atopy)
  - Allergic rhinitis (Hey Fever)
  - Asthma
  - Atopic dermatitis (Eczema)
  - Food Allergies

Systemic Anaphylaxis

- **Anaphylaxis** - The symptoms resulting from allergic responses are known as anaphylaxis.
- Systemic anaphylaxis is a shock-like and often fatal state whose onset occurs within minutes of a type I hypersensitivity reaction.
- A wide range of antigens have been shown to trigger this reaction in susceptible humans including the venome from bee, wasp, hornet and ant stings; drugs such as penicillin, insulin, antitoxins; sea food and nuts.
- If not treated quickly, these reactions can be fatal.

TREATMENT

- Epinephrine – relaxing the smooth muscle & reducing vascular permeability.

  - Improve cardiac output

  - Increases cAMP levels in the mast cells, thereby blocking further degranulation.

Localized Anaphylaxis (Atopy)

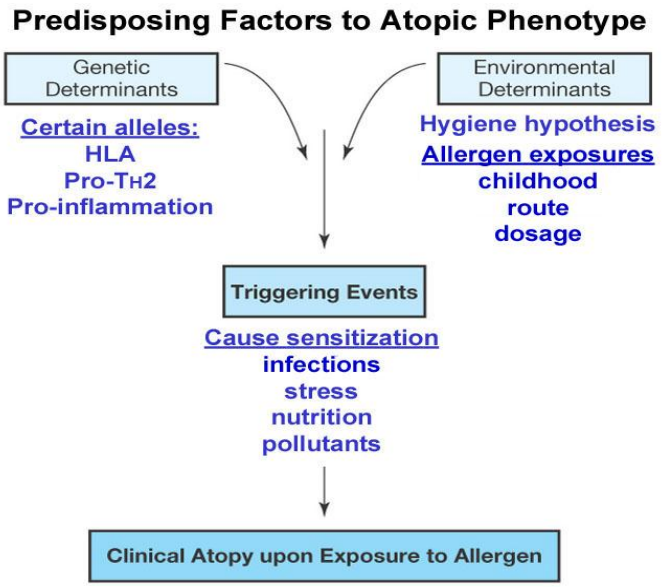
- **Atopy** – Atopy is the term for the genetic trait to have a predisposition for localized anaphylaxis.
  - Atopic individuals have higher levels of IgE and eosinophils.

What factors affect predisposition toward Type I hypersensitivities?

Genetic factors

Environmental factors

Hygiene hypothesis



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

- ❖ **Allergic rhinitis (Hay fever)**
- ❖ **Asthma**
- ❖ **Atopic Dermatitis (Eczema)**
- ❖ **Food allergies**

❖Allergic Rhinitis

– commonly known as hey fever.

– results from the reaction of airborne allergens with sensitized mast cells in the conjuctivae and nasal mucosa to induce the release of pharmocologically active mediators from mast cells.

– These mediators then cause localized vasodilation and increased capillary permeability.

– Symptoms include watery exudation of the conjunctivae, nasal mucosa and upper respiratory tract as well as sneezing and coughing.

- **Asthma**

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

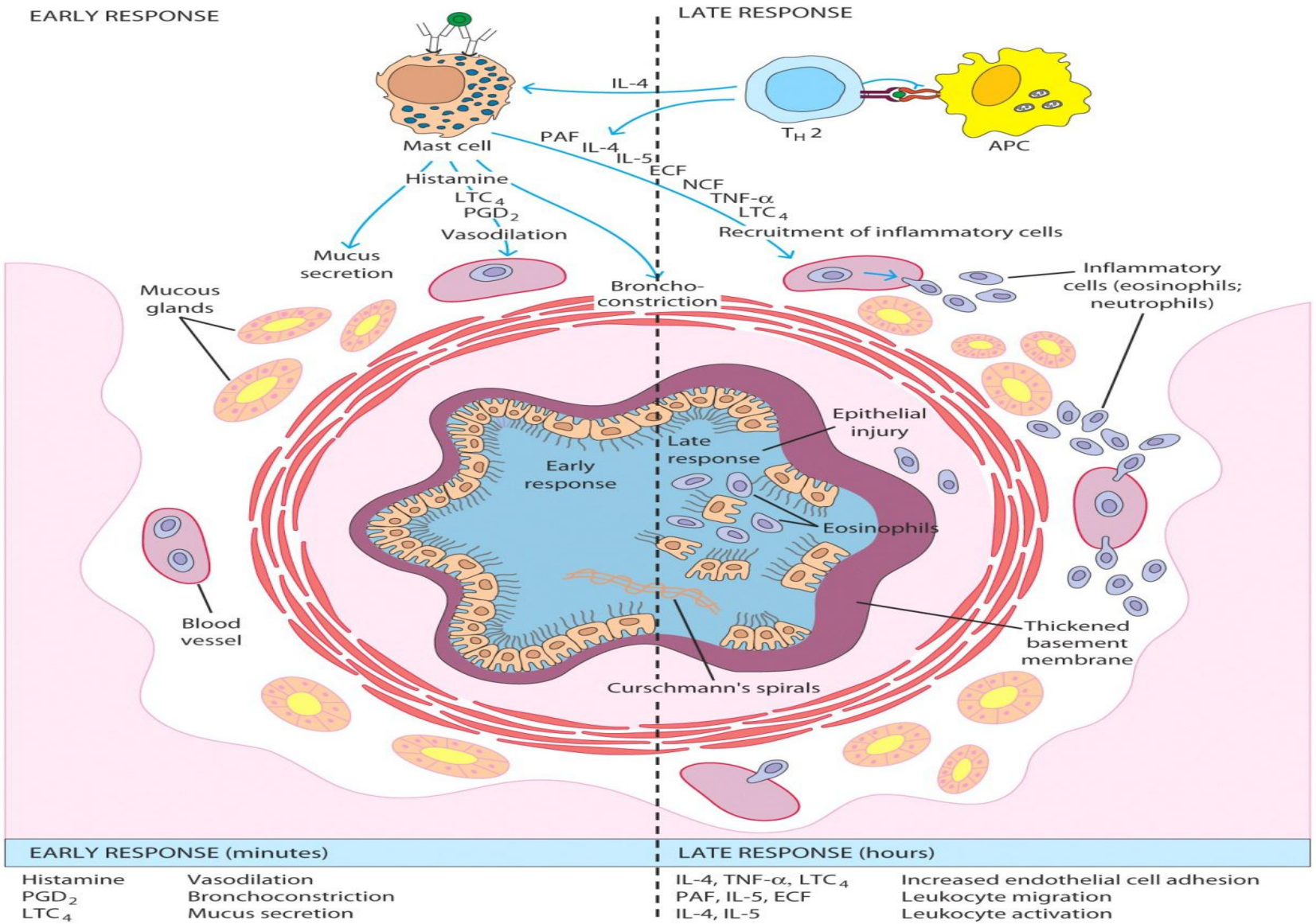
- asthmatic attack can be induced by exercise or cold stimulate intrinsic asthma.

- Asthma is triggered by degranulation of mast cells with release of mediators occur in lower respiratory tract.

- The resulting contraction of the bronchial smooth muscles leads to bronchoconstriction.

- The asthmatic response can be divided into,

- **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

- Early response

  - occurs within minutes of allergen exposure and involves histamine, leukorienes, prostaglandins.

  - cause bronchoconstriction, vasodilation and buildup of mucus.

- Late response

  - occur hours later and involves additional mediators including IL-4, IL-5,IL-16,TNF-alpha, eosinophil chemotactic factor (ECF), and platelet-activating factors (PAF).

Overall effect of asthmatic response

- Mediators increases endothelial cell adhesion as well as inflammatory cells including eosinophils and neutrophils into the bronchial tissue.

Capable of causing

Tissue injury by realising toxic enzymes, oxygen radicals and cytokines

This events lead to

Occulsion of bronchial lumen with mucus, proteins and cellular debris, thickening of the basement membrane, fluid buildup (edema).

- **Atopic Dermatitis**

  - also called as allergic eczema, is an inflammatory disease of skin.

  - observed in young children.

  - serum IgE levels are elevated.

  - allergic individuals developes skin eruptions that are erythematous and filled with pus.

- **Food allergies**

  - allergies to foods are also a major class of type I.

  - allergen crosslinking of IgE on mast cells along the upper or lower GI tract cause smooth muscle constriction and effusion of fluid. This results in intestinal discomfort, vomiting and diarrhea.

  - mast cell degranulation along the gut can increase the permeability of mucous membranes, so that the allergen enters the blood stream cause asthmatic attack or development of edematous lesion on skin called urticaria or hives depending on the type of allergen where they deposited.

– when a food allergen is carried to sensitized mast cells in the skin causing swollen (edematous) red (erythematous) eruption. This response is called Wheal and Flare reaction.

LATE – PHASE REACTION

- Type I hypersensitivity begins to subside, mediators released during the course of the reaction often induce a localized inflammatory reaction called the late phase reaction.
- several hours after the immediate hypersensitivity reaction is over, a second inflammatory response may develop due to immigration and degranulation of neutrophils and eosinophils under the influence of mast-cell-derived chemotactic molecules.
- histamine, lysosomal enzymes, and reactive oxygen metabolites are released from these cells at this time.
- Late-phase reactions can occur in the lungs of asthmatics or in skin allergies.
- Late-phase reaction is distinct from the late response seen in asthma, begins to develop 4-6 hour after the initial type I reaction and persists for 1-2 days.
- Characterized by infiltration of neutrophils, eosinophils, macrophages, lymphocytes and basophils.

DETECTION OR DIAGNOSIS OF TYPE I HYPERSENSITIVITY

IgE-Mediated Allergies

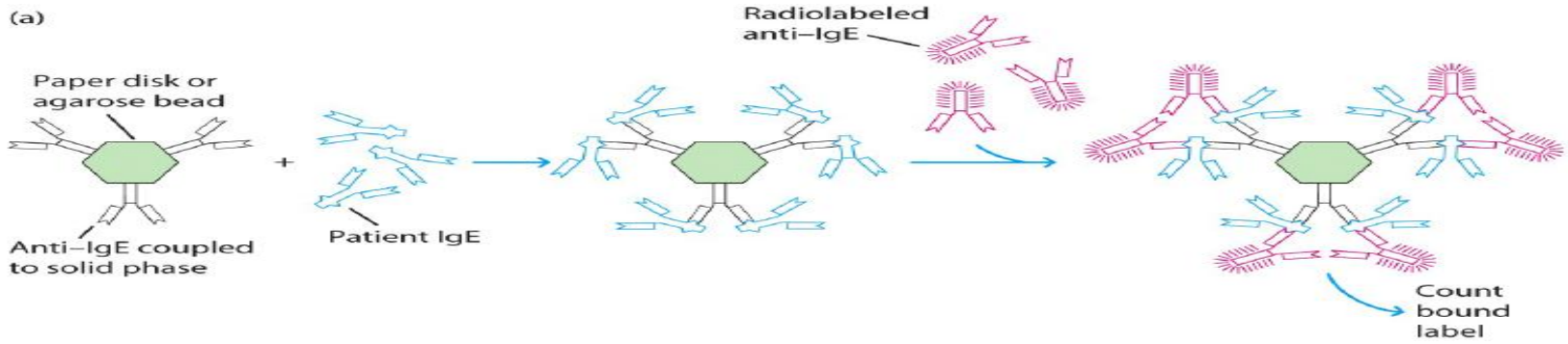
Skin Tests

Blood Tests

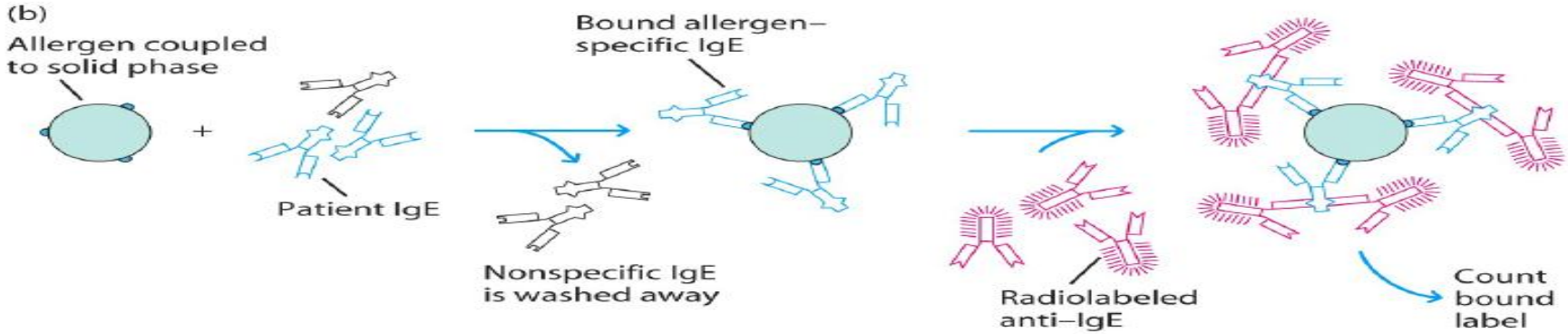
Determine the serum level of total IgE antibody by RIST & RAST

Immunoassays for IgE

RIST (Radioimmunosorbent Test)



RAST (Radioallergosorbent Test)



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PREVENTION & TREATMENT OF TYPE I HYPERSENSITIVITY

- Food allergy is prevented by change of diet.
- Allergic rhinitis is treated by using antihistamine drugs.
- Asthma is treated by using bronchodilators, anti-inflammatory drugs such as corticosteroids.
- Type I hypersensitivity is also treated by using epinephrine (adrenalin), cortisone, theophylline, cromolyn sodium etc.

TYPE II HYPERSENSITIVITY

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Type II Hypersensitivity (Cytotoxic) Reactions/antibody-dependent

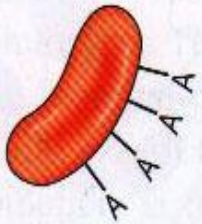
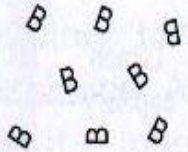
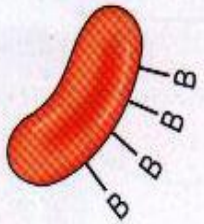
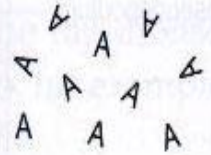
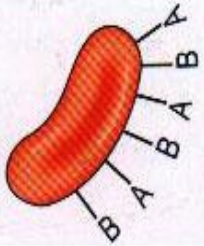
- Type II hypersensitivity reactions involve antibody-mediated destruction of cell.
- Involve activation of complement by IgG or IgM binding to an antigenic cell.
- Type II hypersensitivity reactions are those in which tissue or cell damage is the direct result of the action of antibody and complement. Antibodies directed against antigens on the surface of nucleated cells or RBC will cause their lysis in the presence of complement.

EXAMPLE

Transfusion reactions:

- **ABO Blood group system:**

  - The cell surface proteins found on RBCs are called blood group antigens.

Blood group	Antigen + antibody(ies) present	As donor, is	As recipient, is
A	 Antigen A  Makes anti-B	Compatible with: A and AB Incompatible with: B and O, because both make anti-A antibodies that will react with A antigens	Compatible with: A and O Incompatible with: B and AB, because type A makes anti-B antibodies that will react with B antigens
B	 Antigen B  Makes anti-A	Compatible with: B and AB Incompatible with: A and O, because both make anti-B antibodies that will react with B antigens	Compatible with: B and O Incompatible with: A and AB, because type B makes anti-A antibodies that will react with A antigens
AB	 Antigens A and B Makes neither anti-A nor anti-B	Compatible with: AB only Incompatible with: A, B and O, because all three make antibodies that will react with AB antigens	Compatible with all groups **UNIVERSAL RECIPIENT** AB makes no antibodies and therefore will not react with any type of donated blood
O	 Neither A nor B antigen  Makes both anti-A and anti-B	Compatible with all groups **UNIVERSAL DONOR** O red cells have no antigens, and will therefore not stimulate anti-A or anti-B antibodies	Compatible with: O only Incompatible with: A, AB and B, because type O makes anti-A and anti-B antibodies

- In blood transfusion reaction, host antibodies react with foreign antigens on the incompatible transfused blood cells and mediate destruction of these cells. Antibody can mediate cell destruction by activating the complement system to creat pores in the membrane of the foreign ceee.

- When blood is transfused into an individual, those cell surface proteins that are foreign to the recipient trigger an antibody response.

- If a type A individual is accidentlly transfused with blood containing type B cells, the anti-B isobemagglutinins will bind to the B blood cells and mediate their destruction by means of complement-mediated lysis.

- Manifestations of intravascular hemolysis of the transfused RBC triggered by the IgM isohemagglutinins are,

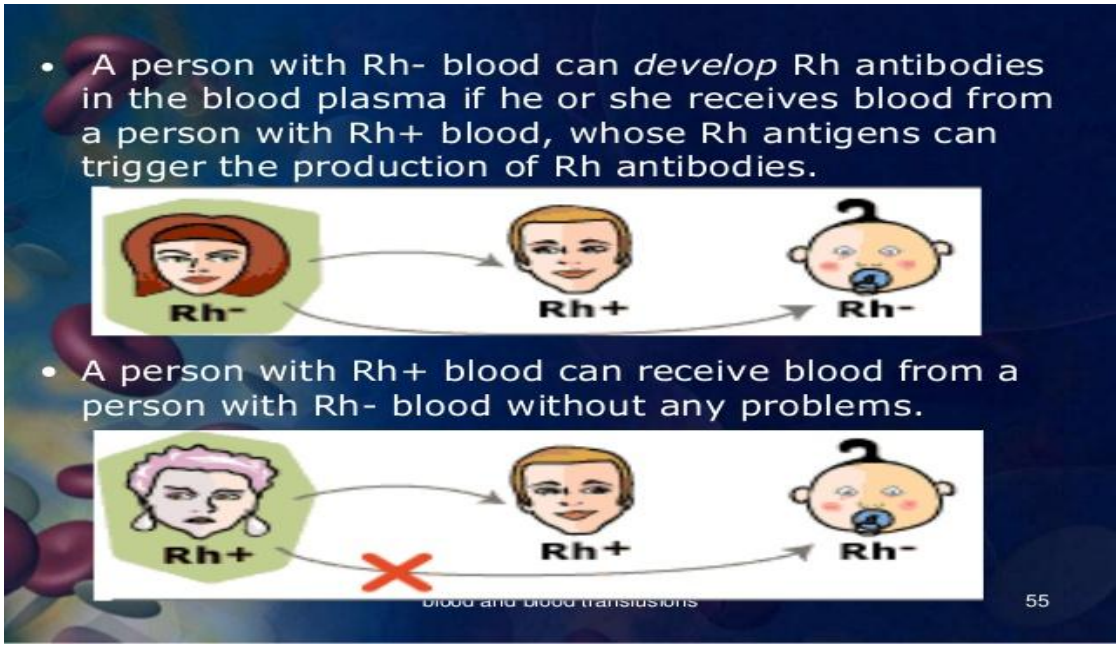
  - Some of the Hb gets converted to bilirubin, which at high levels is toxic.
  - Symptoms include fever, chills, nausea, clotting within blood vessels, pain in the lower back and Hb in urine.

- Transfusion reactions can be prevented by proper crpossmatching between the donor's and the recipient' blood.

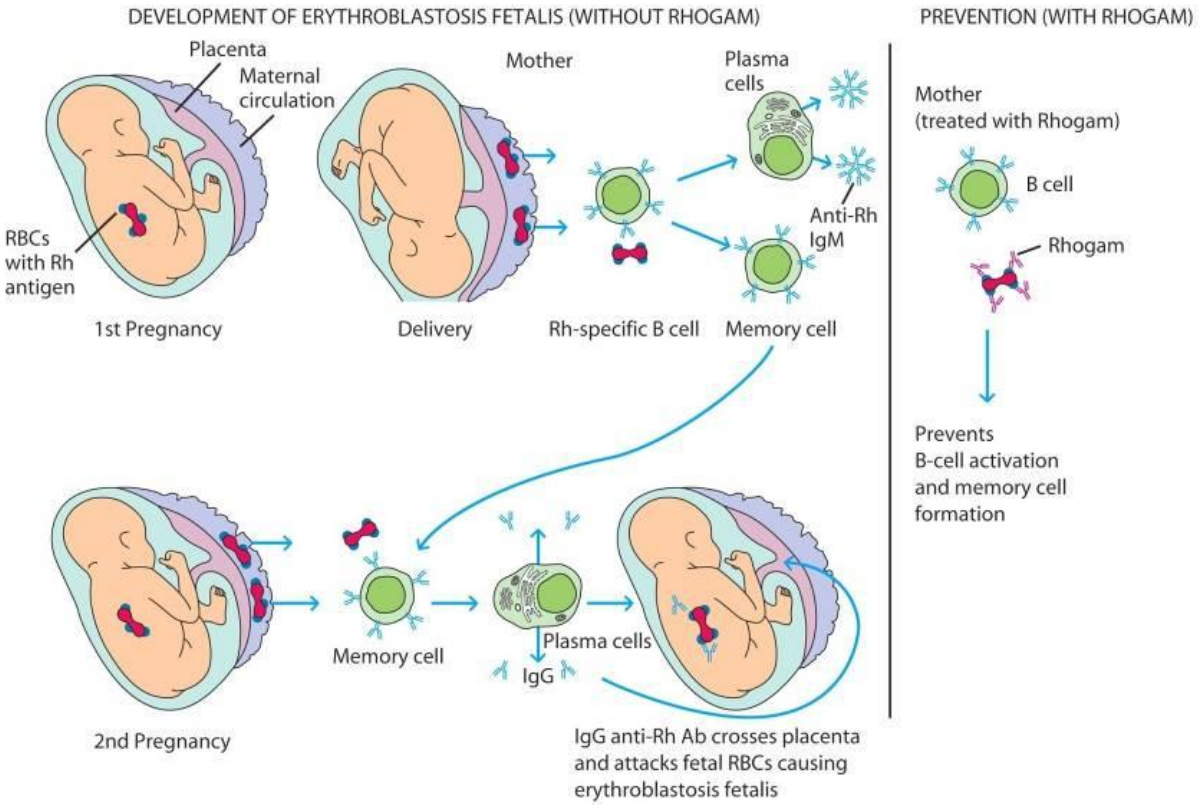
Rh (Rhesus) blood group system:

- In 1940 Landsteiner and Wiener showed that antibodies produced against rhesus monkey RBCs agglutinated the RBCs of 85% of human population.

- The antibodies were directed against a molecule called the rhesus (Rh) antigen ie, D antigen and individuals possessing it were called Rh positive. The remaining 15% who do not carry it were called Rh negative.



Hemolytic disease of the newborn



- HDN is called as erythroblastosis fetalis.
- HDN occurs as a result of Rh incompatibility.
- Develops when an Rh-negative mother carries an Rh-positive fetus.
- Normally, during pregnancy the fetal RBCs are separated from the mother's circulation by the layer of cells in the placenta called the trophoblast.
- During her first pregnancy with an Rh+ fetus, an Rh- woman is usually not exposed to enough fetal RBCs to activate her Rh-specific B cells.
- At the time of delivery, separation of the placenta from the uterine wall allows larger amounts of fetal umbilical-cord blood to enter the mother's circulation. These fetal RBCs activate Rh-specific B cells, resulting in production of Rh-specific plasma cells and memory B cells in the mother.
- The secreted IgM antibody clears the Rh+ fetal RBCs from the mother's circulation, but the memory cells remain, a threat to any subsequent pregnancy with an Rh+ fetus.

- Activation of these memory cells in a subsequent pregnancy results in the formation of IgG anti-Rh antibodies.
- Maternal IgG antibodies can cross the placenta and reach the fetal circulation where they react with the fetal RBCs and damage the fetal RBCs.
- This RBC destruction results in the death of the fetus. The fetus may survive to be born in a jaundiced or anemic state.

DIAGNOSIS

- Detected by testing maternal serum.
- Presence of maternal IgG on the surface of fetal RBCs can be detected by Coombs test.

PREVENTION AND TREATMENT

- **Prevented by administering antibodies against the Rh antigen to mother within 24-48 hours after the first delivery. These antibodies called Rhogam, bind to any fetal RBCs that enter the mother's circulation at the time of delivery and facilitate their clearance before B-cell activation and ensuing memory-cell production can take place.**
- **For a severe reaction, the fetus can be given an intrauterine blood-exchange transfusion to replace fetal Rh+ RBCs with Rh- cells. These transfusions are given every 10-21 days until delivery.**

TYPE III HYPERSENSITIVITY

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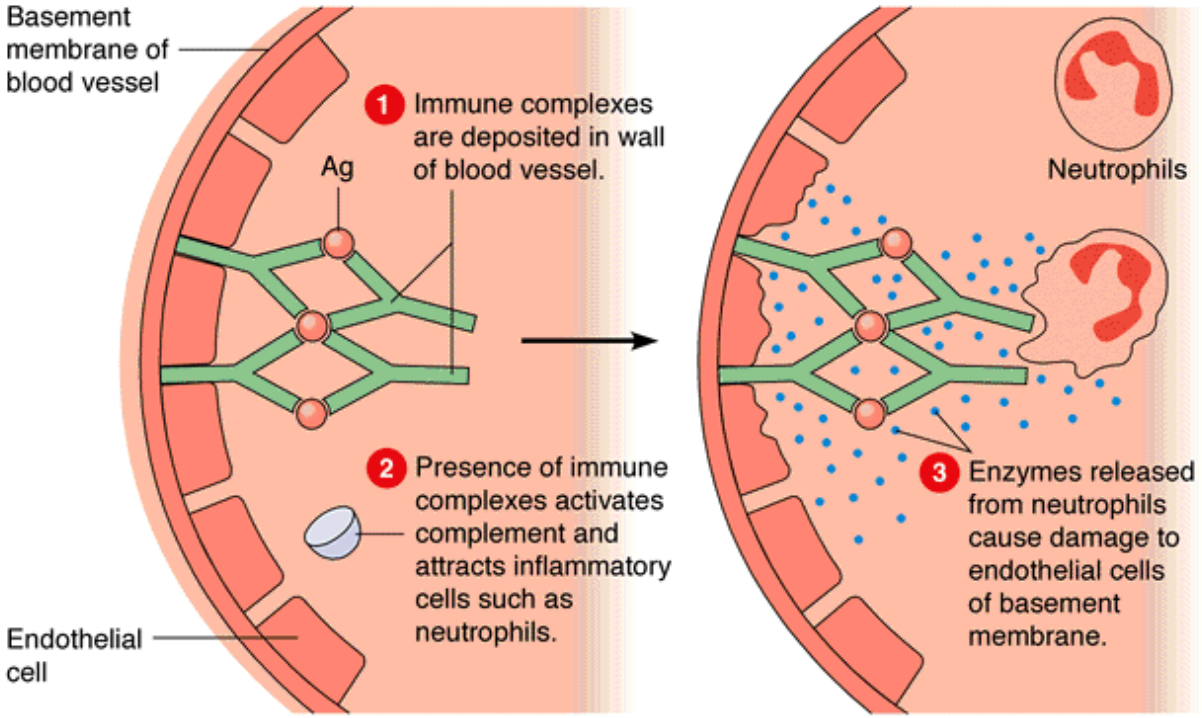
Type III Hypersensitivity (Immune Complex) Reactions

INTRODUCTION

- The reaction of antibody with antigen generates immune complexes. Generally this complexing of antigen with antibody facilitates the clearance of antigen by phagocytic cells.
- In some cases large amounts of immune complexes can lead to tissue-damaging type III hypersensitive reactions.
- The reaction depends on the quantity of immune complexes as well as their distribution within the body.
- When the complexes are deposited in tissue very near the site of antigen entry, a localized reaction develops.

- When the complexes are formed in the blood, a reaction can develop wherever the complexes are deposited.
- Complex deposition is observed on blood-vessel walls, in the synovial membrane joints, on the glomerular basement membrane of the kidney and on the choroid plexes of the brain.
- Type III hypersensitive reactions develop when immune complexes activate the complement system.
- When complement-activating immune complexes are deposited in tissues, chemotactic factors are produced and lead to a local accumulation of neutrophils. These neutrophils release their lysosomal enzymes and oxidizing radicals and these in turn cause local tissue destruction. Lesions generated in this fashion are called type III or immune complex-mediated hypersensitivity reactions.

Immune Complex Mediated Hypersensitivity



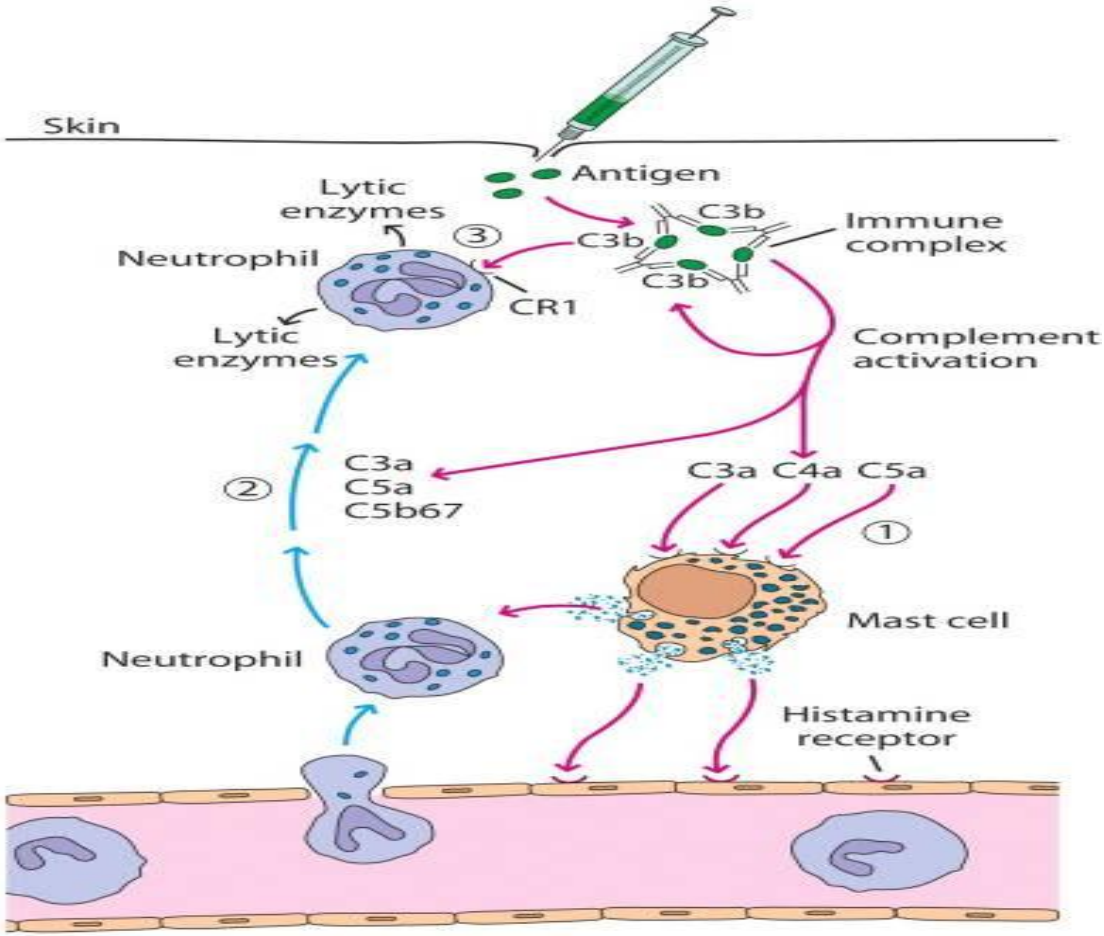
Classification of Type III Hypersensitivity Reactions

- Localized Type III Reaction
- Generalized Type III Reaction

Localized Type III Reaction

- Local reaction known as Arthus reaction
- Arthus reaction occurs when immune complexes are deposited in tissues.

Arthus Reaction



✓ **If** antigen is injected intradermally or subcutaneously into an animal that has been hyperimmunized and possesses circulating antibody able to precipitate that antigen, leads to formation of localized immune complexes. Complement activation is initiated by immune complexes and produces complement intermediates. This causes mast cell degranulation, chemotactically attract neutrophils, and stimulate release of lytic enzymes from neutrophils.

✓As a result an acute inflammatory reaction will develop within 4-8 hours at the site of injection. This type of reaction is known as Arthus Reaction.

✓ The reaction starts as a reddened, edematous swelling, local hemarrhage and thrombosis.

✓ Microscopic examination of the tissue reveals neutrophils adhering to the vascular endothelium and then migration into the tissues at the site of immune complex deposition.

✓ As the reaction develops, localized tissue damage results in an accumulation of fluid (edema) and RBC (erythema) at the site.

Generalized Type III Reaction

- When large amounts of antigen enter the bloodstream and bind to antibody, circulating immune complexes can form. These soluble complexes may activate complement and so stimulate platelet aggregation and the release of vasoactive amines.
- They will therefore affect the permeability of the vascular endothelium.
- As a result, immune complexes may be deposited in the walls of blood vessels.
- They may also be deposited in glomeruli, synovial and choroid plexus of the brain.

Serum Sickness

- Generalized type III reactions were often observed after the administration of antitoxins containing foreign serum, such as horse antitetanus or antidiphtheria serum.
- In such cases, the recipient of a foreign antiserum develops antibodies specific for the foreign serum proteins; these antibodies then form circulating immune complexes with the foreign serum antigens.
- Typically, within days or weeks after exposure to foreign serum antigens, an individual begins to manifest a combination of symptoms that are called serum sickness.
- Symptoms include fever, weakness, rashes with edema, erythema, lymphadenopathy, arthritis and glomerulonephritis.

Pathogenesis of serum sicknes

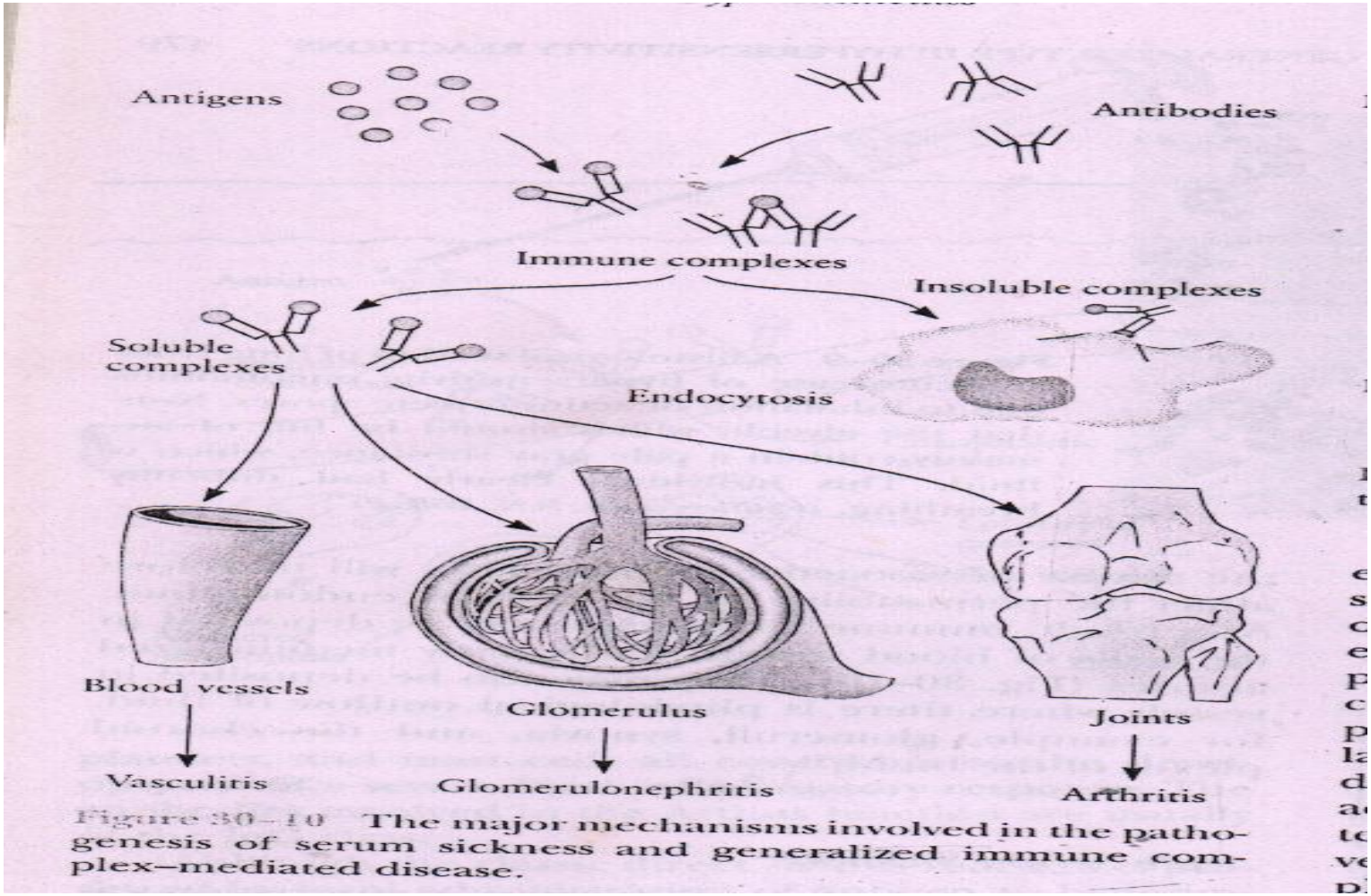


Figure 30–10 The major mechanisms involved in the pathogenesis of serum sickness and generalized immune complex–mediated disease.

Type IV Hypersensitivity

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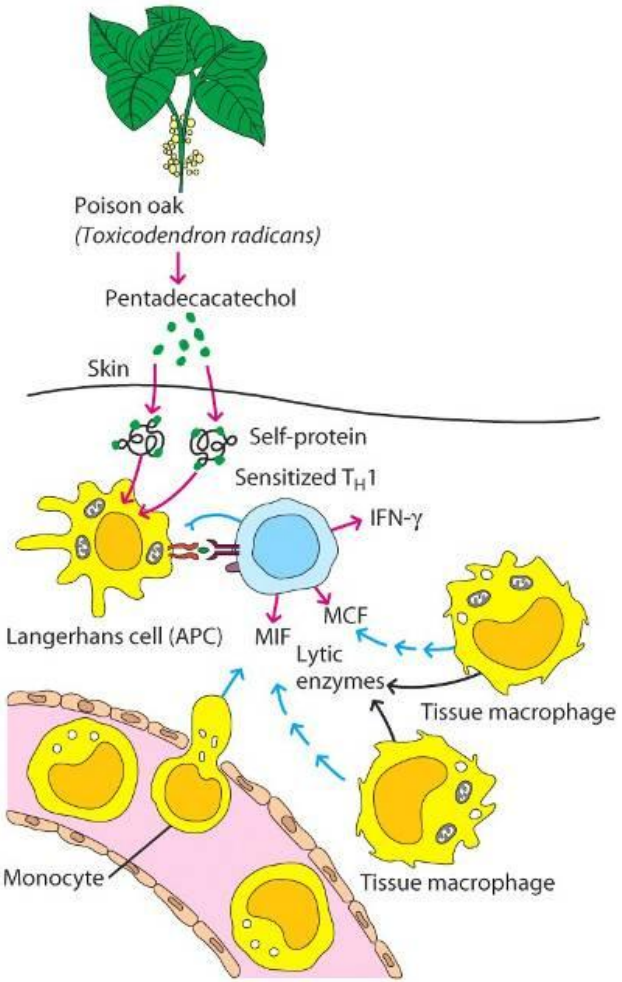
Type IV (Cell-Mediated) Reactions/Delayed-type hypersensitivity/antibody-independent

- Type IV hypersensitivity reactions result from a T-cell mediated response to antigen.
- Migration of T cells to the site of antigen deposition, the reactions usually take more than 24 hours to develop and therefore called delayed hypersensitivity reaction.
- The continued presence of antigens can provoke a chronic DTH reaction, which is characterized by excessive number of macrophages, continual release of lytic enzymes and consequent tissue destruction.
- The granulomatous skin lesions seen with *Mycobacterium leprae* and the lung cavitation Seen with *Mycobacterium tuberculosis*
- **EXAMPLE :**
  - Tuberculin Reaction – This is an inflammatory response produced in skin in response to intradermal inoculation of an extract of the tubercle bacillus.

DEVELOPMENT OF DELAYED HYPERSENSITIVITY REACTION AFTER A SECOND EXPOSURE TO POISON OAK



- Many contact dermatitis reactions are mediated by TH1 cells.
- The substances such as cosmetics, hair dye, turpentine, poison oak (pentadecacatechol compound from the leaves of oak plant) are small molecules that can complex with skin proteins. This complex is then internalized by antigen presenting cells in the skin, then processed and presented together with Class II MHC molecules causing activation of sensitized TDTH cells and **and which are now "sensitized" to these compounds.**
- Subsequent exposure to these compounds, for example, pentadecacatechol will activate these TH1 cells and induce cytokine production; approximately 48 to 72 hours after this second exposure, the secreted cytokins cause macrophages to accumulate at the site and release lytic enzymes that cause the redness and pustule formation that characterize a reaction to poison oak exposure.

REFERENCES

- Immunology by Kuby, fourth edition.
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