IMMUNOLOGY

HYPERSENSITIVITY

Presented By
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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 dysfunction.

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.
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
<table>
<thead>
<tr>
<th>Type</th>
<th>Allergen</th>
<th>Fc receptor for IgE</th>
<th>Allergen-specific IgE</th>
<th>Degranulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td></td>
<td></td>
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<tr>
<td>IgE-Mediated Hypersensitivity</td>
<td>Allergen bound to mast cells and basophils with release of vasoactive mediators.</td>
<td>IgE-Mediated Hypersensitivity</td>
<td>Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.</td>
<td>Cell-Mediated Hypersensitivity</td>
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<tr>
<td>Type II</td>
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<tr>
<td>IgG- or IgM-Mediated Cytotoxic Hypersensitivity</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.</td>
<td>IgM-Mediated Cytotoxic Hypersensitivity</td>
<td>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.</td>
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<tr>
<td>Type III</td>
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<td></td>
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</tr>
<tr>
<td>Immune Complex–Mediated Hypersensitivity</td>
<td>Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</td>
<td>Cell-Mediated Hypersensitivity</td>
<td>Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.</td>
<td></td>
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<tr>
<td>Type IV</td>
<td></td>
<td></td>
<td></td>
<td>Activated macrophage</td>
</tr>
<tr>
<td>Antigen</td>
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</tbody>
</table>
TYPE I HYPERSENSITIVITY
 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, the 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

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign serum</td>
<td>Nuts</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Seafood</td>
</tr>
<tr>
<td>Plant pollens</td>
<td>Eggs</td>
</tr>
<tr>
<td>Rye grass</td>
<td>Peas, beans</td>
</tr>
<tr>
<td>Ragweed</td>
<td>Milk</td>
</tr>
<tr>
<td>Timothy grass</td>
<td>Insect products</td>
</tr>
<tr>
<td>Birch trees</td>
<td>Bee venom</td>
</tr>
<tr>
<td>Drugs</td>
<td>Wasp venom</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Ant venom</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Cockroach calyx</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>Dust mites</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Mold spores</td>
</tr>
<tr>
<td></td>
<td>Animal hair and dander</td>
</tr>
<tr>
<td></td>
<td>Latex</td>
</tr>
</tbody>
</table>
MECHANISM OF TYPE 1 HYPERSENSITIVITY

1. Allergen binds to CD4+ T cell and induces IL-4 production.
2. IL-4 stimulates B cell differentiation into plasma cells that produce allergen-specific IgE.
3. IgE binds to mast cell Fc receptor.
4. Exposure to allergen triggers degranulation of mast cells, releasing vasoactive amines.
5. Vasoactive amines cause smooth muscle contraction, vascular dilation, and mucus gland secretion.

"HEAL US TO HEAL OTHERS"
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 pharmacologically 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.
### TABLE 15-3 Principal mediators involved in type 1 hypersensitivity

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRIMARY</strong></td>
<td></td>
</tr>
<tr>
<td>Histamine, heparin</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Serotonin (rodents)</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Eosinophil chemotactic factor (ECF-A)</td>
<td>Eosinophil chemotaxis</td>
</tr>
<tr>
<td>Neutrophil chemotactic factor (NCF-A)</td>
<td>Neutrophil chemotaxis</td>
</tr>
<tr>
<td>Proteases (tryptase, chymase)</td>
<td>Bronchial mucus secretion; degradation of blood vessel basement membrane generation of complement split products</td>
</tr>
<tr>
<td><strong>SECONDARY</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Platelet aggregation and degranulation; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)</td>
<td>Increased vascular permeability; contraction of pulmonary smooth muscles</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Increased vascular permeability; smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
<tr>
<td>IL-1 and TNF-α</td>
<td>Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells</td>
</tr>
<tr>
<td>IL-4 and IL-13</td>
<td>Increased IgE production</td>
</tr>
<tr>
<td>IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF</td>
<td>Various effects (see Table 12-1)</td>
</tr>
</tbody>
</table>
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

1. Allergen binds to IgE and FcεRI
2. Activates PTK and Phospholipase C
3. Phospholipase C converts PIP2 to DAG and IP3
4. IP3 activating Ca2+ from the endoplasmic reticulum
5. Ca2+ activates PKC, leading to the release of arachidonic acid
6. Arachidonic acid is converted to leukotriene A4, LTC4, LTD4, LTE4, PGD2, and SRS-A
7. These compounds trigger degranulation and secretion from the mast cell granules
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 venom 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**

![Diagram of predisposing factors to atopic phenotype]

- **Genetic Determinants**
  - Certain alleles: HLA, Pro-Th2, Pro-inflammation

- **Environmental Determinants**
  - Hygiene hypothesis: Allergen exposures, childhood route dosage

- **Triggering Events**
  - Cause sensitization: infections, stress, nutrition, pollutants

- **Clinical Atopy upon Exposure to Allergen**
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 conjunctivae 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)**
- Histamine
- PGD₂
- LTC₄
- Vasodilation
- Mucus secretion

**Late Response (hours)**
- IL-4, TNF-α, LTC₄
- PAF, IL-5, ECF
- Increased endothelial cell adhesion
- Leukocyte migration
- Leukocyte activation

**Phases**
- Early response
- Late response

**Evidence**
- Recruitment of inflammatory cells (eosinophils; neutrophils)
- Thickened basement membrane
- Curshmann’s spirals
- Epithelial injury
- Bronchoconstriction
- Mucus glands

** cited source**
“HEAL US TO HEAL OTHERS”
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 develop 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

Skin Tests

Blood Tests

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

IgE-Mediated Allergies
Immunoassays for IgE

RIST (Radioimmunosorbent Test)

(a) Paper disk or agarose bead

Anti-IgE coupled to solid phase

Radiolabeled anti-IgE

Patient IgE

Count bound label

RAST (Radioallergosorbent Test)

(b) Allergen coupled to solid phase

Bound allergen–specific IgE

Nonspecific IgE is washed away

Radiolabeled anti-IgE

Count bound label

“HEAL US TO HEAL OTHERS”
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
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.
<table>
<thead>
<tr>
<th>Blood group</th>
<th>Antigen + antibody(ies) present</th>
<th>As donor, is</th>
<th>As recipient, is</th>
</tr>
</thead>
</table>
| 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 A 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 create pores in the membrane of the foreign cells.

- 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 accidentally transfused with blood containing type B cells, the anti-B isohemagglutinins 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 crossmatching between the donor’s and the recipient’s 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.

- A person with Rh- blood can develop Rh antibodies in the blood plasma if he or she receives blood from a person with Rh+ blood, whose Rh antigens can trigger the production of Rh antibodies.

- A person with Rh+ blood can receive blood from a person with Rh- blood without any problems.
Hemolytic disease of the newborn

**DEVELOPMENT OF ERYTHROBLASTOSIS FETALIS (WITHOUT RHOGAM)**

1st Pregnancy
- Placenta
- Maternal circulation
- RBCs with Rh antigen

Delivery
- Mother
- Plasma cells
- Rh-specific B cell
- Memory cell

2nd Pregnancy
- Memory cell
- Plasma cells
- IgG

IgG anti-Rh Ab crosses placenta and attacks fetal RBCs causing erythroblastosis fetalis

**PREVENTION (WITH RHOGAM)**

Mother (treated with Rhogam)
- B cell
- Rhogam

Prevents B-cell activation and memory cell formation
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
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 plexus 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

1. Immune complexes are deposited in wall of blood vessel.

2. Presence of immune complexes activates complement and attracts inflammatory cells such as neutrophils.

3. Enzymes released from neutrophils cause damage to endothelial cells of basement membrane.

Basement membrane of blood vessel

Endothelial cell

Ag

Neutrophils

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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 hemorrhage 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 sickness

Figure 30–10 The major mechanisms involved in the pathogenesis of serum sickness and generalized immune complex–mediated disease.
Type IV Hypersensitivity
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 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.
- Immunology by Tizard, fourth edition.
Thank you Very Much

“HEAL US TO HEAL OTHERS”