HYPERSENSITIVITY

**I**mmune-mediated disorders which are caused by inappropriately vigorous innate and/or adaptive response to **antigens** that pose little or no threat, called hypersensitivities, will be the main focus of this lecture.

The term hypersensitivity denotes a condition in which an immune response results in exaggerated or inappropriate reactions that are harmful to the host. In a given individual, such reactions typically occur after the **second contact** with a specific antigen (**allergen**). The **first contact** is a necessary preliminary event that induces sensitization to that allergen.

There are **four** main types of hypersensitivity reactions.

Types I, II, and III are antibody mediated, and type IV is T-cell mediated.

**Types I : OVERVIEW OF IgE-DEPENDENT ALLERGIC REACTIONS**

 All allergic reactions share common feature, **is the production of IgE antibody, which is dependent on the activation of IL-4–producing helper T cells,** allergic reactions differ greatly in the types of antigens that elicit these reactions and their clinical and pathologic manifestations.

Whereas healthy individuals either do not respond or have harmless T cell and antibody responses to common environmental antigens.Antigens that elicit immediate hypersensitivity reactions called allergens.

**🡪The typical sequence of events in immediate hypersensitivity consists of exposure to an antigen, activation of lymphocytes (TH2 cells, and B cells) specific for the antigen, production of IgE antibody, binding of the antibody to Fc receptors of mast cells, and triggering of the mast cells by re-exposure to the antigen, resulting in the release of mediators from the mast cells and the subsequent pathologic reaction**.

🡪Binding of IgE to mast cells is also called **sensitization** because IgE-coated mast cells are ready to be activated on antigen encounter (i.e., they are sensitive to the antigen).

***🡪The clinical and pathologic manifestations of allergy consist of the vascular and smooth muscle reaction that develops rapidly after repeated exposure to the allergen (immediate hypersensitivity) and a delayed late phase inflammatory reaction.***

 ***🡪Allergic reactions are manifested in different ways, depending on the tissues affected, including skin rashes, sinus congestion, bronchial constriction, abdominal pain, diarrhea, and systemic shock.***

🡪There is a genetic predisposition for the development of allergies. Many susceptibility genes have been identified. ***Atopic individuals produce high levels of IgE in response to environmental allergens, whereas normal individuals generally produce other Ig isotypes, such as IgM and IgG, and only small amounts of IgE***.

***🡪Antigens that elicit immediate hypersensitivity reactions (allergens) are proteins or chemicals bound to proteins.***Two important characteristics of allergens are that individuals are exposed to them repeatedly and, unlike microbes, they do not generally stimulate the innate immune responses that are associated with macrophage and dendritic cell secretion of TH1- and TH17-inducing cytokines. Chronic or repeated cell activation in the absence of strong innate immunity may drive CD4+ T cells preferentially toward the TH2 pathway. The chemical nature. Some features are typical of many common allergens. These include low to medium molecular weight, stability, glycosylation, and high solubility in body fluids.These structural features probably protect the antigens from denaturation and degradation in the gastrointestinal tract and allow them to be absorbed intact. Some nonprotein substances, such as the antibiotic penicillin, can elicit strong IgE responses, when react chemically with amino acid residues in self proteins to form hapten carrier conjugates, which induce IL-4–producing helper T cell responses and IgE production.

1. **Activation of IL-4–Producing Helper T Cells**

***In allergic diseases, TH 2cells are required for differentiation of IgE-producing B cells, and play a central role in the inflammatory reaction in tissues***.

 It is likely that dendritic cells in epithelia through which allergens enter capture the antigens, transport them to draining lymph nodes, process them, and present peptides to naïve CD4+ T cells. The T cells then differentiate into TH2 cells that secrete TH2 cytokines. The major factors that stimulate the development of the TH2 subset are cytokines, especially IL-4.

The differentiated TH2 cells migrate to tissue sites of allergen exposure, where they contribute to the inflammatory effector phase of allergic reactions.

1. **Activation of B Cells and Switching to IgE**

B cells specific for allergens are activated by TH 2 cells in lymphoid organs, as in other T cell–dependent B cell responses. In response to CD40 ligand and cytokines, mainly IL-4, the B cells undergo heavy chain isotype switching and produce IgE.

1. **ROLE OF TH2 CELLS, MAST CELLS, BASOPHILS, AND EOSINOPHILS IN ALLERGIC REACTIONS**

***TH2 cells, mast cells, basophils, and eosinophils are the major effector cells of immediate hypersensitivity reactions and allergic disease***.

+ Mast cells, basophils, and eosinophils, in distinction from TH2 cells, have cytoplasmic granules that contain preformed amines and enzymes, and all three cell types produce lipid mediators and cytokines that induce inflammation.

+ TH2 cells contribute to inflammation by secreting cytokines.

1. **Role of TH2 Cells and Innate Lymphoid Cells in Allergic Disease**

***TH2 cells secrete cytokines, including IL-4, IL-5, and IL-13, that work in combination with mast cells and eosinophils to promote inflammatory responses to allergens within tissues***.

* IL-4 secreted by TH2 cells induces expression of endothelial VCAM-1 that promotes the recruitment of eosinophils and additional TH2 cells into tissues. IL-5 secreted by TH2 cells activates eosinophils. IL-13 stimulates epithelial cells (e.g., in the airways) to secrete increased amounts of mucus, and excessive mucus production is also a common feature of these reactions. TH2 cells also contribute to the inflammation of the late-phase reaction.
1. **Binding of IgE to Mast Cells and Basophils: The Fcε Receptor**

***Mast cells and basophils express a high-affinity Fc receptor specific for*** ε ***heavy chains, called FcεRI, which binds IgE.*** The affinity of FcεRI for IgE is very high, much higher than that of any other Fc receptor for its antibody ligand. Therefore, the normal serum concentration of IgE, although low in comparison to other Ig isotypes, is sufficient to allow occupancy of FcεRI receptors. In addition to mast cells and basophils, FcεRI has been detected on eosinophils.

1. **Activation of Mast Cells**

In an individual allergic to a particular antigen, a large proportion of the IgE bound to FcεRI on the surface of mast cells is specific for that antigen. Exposure to the antigen will cross-link sufficient IgE molecules to trigger mast cell activation.

* ***Activation of mast cells results in three types of biologic response: secretion of the preformed granule contents by exocytosis (degranulation), synthesis and secretion of lipid mediators, and synthesis and secretion of cytokines***.
1. **Mediators Derived from Mast Cells:**

***Histamine***

🡪Histamine acts by binding to target cell receptors (e.g., H1, H2, H3)

🡪The actions of histamine are short-lived on binding to cellular receptors, initiates intracellular events, and products cause different changes in different cell types. Binding of histamine to endothelium causes contraction of the endothelial cells, leading to increased inter endothelial spaces, increased vascular permeability, and leakage of plasma into the tissues and other effect cause vasodilation also causes contraction of intestinal and bronchial smooth muscle.

 ***Lipid Mediators***

🡪The major arachidonic acid–derived mediator produced by the cyclooxygenase pathway in mast -cells is **prostaglandin D2** (PGD2). Acts as a vasodilator and a bronchoconstrictor. PGD2 also promotes neutrophil chemotaxis and accumulation at inflammatory sites.

🡪The major arachidonic acid–derived mediators produced by the lipoxygenase pathway are the **leukotrienes**, especially LTC4 and its degradation products LTD4 and LTE4 which cause prolonged bronchoconstriction. (slow-reacting substance of anaphylaxis and are thought to be important mediators of asthmatic bronchoconstriction.

**🡪platelet-activating factor** (PAF has direct bronchoconstricting actions. It also causes retraction of endothelial cells and can relax vascular smooth muscle.

 ***Cytokines***

***Mast cells produce many different cytokines that contribute to allergic inflammation (the late-phase reaction).***

These cytokines like TNF, IL-1, IL-4, IL-6, CCL3…... and granulocyte-monocyte colony-stimulating factor (GM-CSF). The cytokines that are released from activated mast cells and TH2 cells are mainly responsible for the inflammation associated with the late-phase reaction. TNF activates endothelial expression of adhesion molecules and together with chemokines accounts for neutrophil and monocyte infiltrates.

1. **Properties of Eosinophils**

***Cytokines produced by TH2 cells promote the activation of eosinophils and their recruitment to late-phase reaction inflammatory sites***. ***Eosinophils release granule proteins that are toxic to helminthic parasites and may injure normal tissue***

**IgE- AND MAST CELL–DEPENDENT REACTIONS**

**1)The Immediate Reaction**

***The early vascular changes that occur during immediate hypersensitivity reactions are demonstrated by the wheal-and-flare reaction to the intradermal injection of an allergen*** (Fig. 20-8).

The wheal-and-flare reaction results from sensitization of dermal mast cells by IgE that binds to FcεRI, crosslinking of IgE by the antigen, and activation of mast cells with release of mediators, notably histamine. Histamine binds to histamine receptors on venular endothelial cells; the endothelial cells synthesize and release PGI2, nitric oxide, and PAF; and these mediators cause vasodilation and vascular leak. Skin mast cells appear to produce only small amounts of long-acting mediators such as leukotrienes, so the wheal-and-flare response subsides rapidly.

**2) The Late-Phase Reaction**

***The immediate wheal-and-flare reaction is followed 2 to 4 hours later by a late-phase reaction consisting of the accumulation of inflammatory leukocytes, including neutrophils, eosinophils, basophils, and helper T cells***. Cytokines produced by mast cells, including TNF, upregulate endothelial expression of leukocyte adhesion molecules and chemokines recruit blood leukocytes.Thus, mast cell activation promotes the influx of leukocytes into tissues. The types of leukocytes that are typical of late-phase reactions are eosinophils and helper T cells (TH2).Neutrophils are also often present in these reactions.

Bronchial asthma is a disease in which there may be repeated bouts of inflammation with accumulations of eosinophils and TH2 cells without the vascular changes that are characteristic of the immediate response. In such disorders, there may be little mast cell activation, and the cytokines that sustain the late-phase reaction may be produced mainly by T cells.

**ALLERGIC DISEASES IN HUMANS**

***Mast cell degranulation is a central component of many allergic diseases, and the clinical and pathologic manifestations of the diseases depend on the tissues in which the mast cell mediators have effects as well as the chronicity of the resulting inflammatory process***. Atopic individuals may have one or more manifestations of allergic disease.

The most common forms of these diseases are allergic rhinitis (hay fever), bronchial asthma, atopic dermatitis (eczema), and food allergies.

1. **Systemic Anaphylaxis**

***Anaphylaxis is a systemic immediate hypersensitivity reaction characterized by edema in many tissues and a decrease in blood pressure, secondary to vasodilation***. These effects usually result from the systemic presence of antigen introduced by injection, an insect sting, or absorption across an epithelial surface such as gut mucosa. The allergen activates mast cells in many tissues, resulting in the release of mediators that gain access to vascular beds throughout the body.

The decrease in vascular tone and leakage of plasma caused by mast cell mediators can lead to a significant decrease in blood pressure or shock, called anaphylactic shock, which is often fatal. The cardiovascular effects are accompanied by constriction of the upper and lower airways, laryngeal edema, hypermotility of the gut, outpouring of mucus in the gut and respiratory tract, and urticarial lesions (hives) in the skin. The mainstay of treatment is systemic epinephrine, which can be lifesaving by reversing the bronchoconstrictive and vasodilatory effects of mast cell mediators.

1. **Bronchial Asthma**

***Asthma is an inflammatory disease caused by repeated immediate-type hypersensitivity and late-phase allergic reactions in the lung leading to the clinic-pathologic triad of intermittent and reversible airway obstruction, chronic bronchial inflammation with eosinophils, and bronchial smooth muscle cell hypertrophy and hyperreactivity to bronchoconstrictors***. Patients suffer paroxysms of bronchoconstriction and increased production of thick mucus, which leads to bronchial obstruction and exacerbates respiratory difficulties.

The pathophysiologic sequence in atopic asthma is probably initiated by mast cell activation in response to allergen binding to IgE as well as by TH2 cells reacting to allergens. The lipid mediators and cytokines produced by the mast cells and T cells lead to the recruitment of eosinophils, basophils, and more TH2 cells. The chronic inflammation in this disease may continue without mast cell activation.

Smooth muscle cell hypertrophy and hyperreactivity are thought to result from leukocyte-derived mediators and cytokines. Mast cells, basophils, and eosinophils all produce mediators that constrict airway smooth muscle. The most important of the bronchoconstricting mediators are LTC4, LTD4, and LTE4. Increased mucus secretion results from the action of cytokines, on bronchial epithelial cells.

Corticosteroids may also be given systemically, especially once an attack is under way, to reduce inflammation and bronchial smooth muscle cell relaxants

1. **Immediate Hypersensitivity Reactions in the Upper Respiratory Tract, Gastrointestinal Tract, and Skin**
* **Allergic rhinitis**, also called hay fever, is perhaps the most common allergic disease and is a consequence of immediate hypersensitivity reactions to common allergens such as plant pollen or house dust mites localized to the upper respiratory tract by inhalation. The pathologic and clinical manifestations include mucosal edema, leukocyte infiltration with abundant eosinophils, mucus secretion, coughing, sneezing, and difficulty in breathing.

Allergic conjunctivitis with itchy eyes is commonly associated with the rhinitis. Focal

* **Food allergies** are immediate hypersensitivity reactions to ingested foods that lead to the release of mediators from intestinal mucosal and submucosal mast cells of the GI tract, including the oropharynx. The resulting clinical manifestations include pruritis, tissue edema, enhanced peristalsis, increased epithelial fluid secretion, and associated symptoms of oropharyngeal swelling, vomiting and diarrhea. Rhinitis, urticaria and mild bronchospasm are also often associated with allergic reactions to food, suggestive of systemic antigen circulation, and systemic anaphylaxis may occasionally occur. Allergic reactions to many different types of food most common are peanuts and shellfish.
* Common allergic reactions in the skin include **urticaria** and **atopic dermatitis**. Urticaria, or hives, is an acute wheal-and-flare reaction induced by mast cell mediators and occurs in response to direct local contact with an allergen or after an allergen enters the circulation.

Atopic dermatitis (also commonly referred to as eczema) . It is a common skin disorder that may be caused by a late-phase reaction to an allergen in the skin. In the cutaneous late-phase reaction, TNF, IL-4, and other cytokines, probably derived from TH2 cells and mast cells, act on endothelial cells to promote inflammation.

**Type II: Hypersensitivity (**Antibody–mediated: type II**)**

Type II hypersensitivity involves the binding of IgG antibodies to:[**cell surface antigens or extracellular matrix molecules]**. Antibody bound to a cell-surface antigen can induce death of the antibody-bound cell by three distinct mechanisms.

1. First, certain immunoglobulin subclasses can activate the complement system, creating pores in the membrane of a foreign cell.
2. Secondly, antibodies can mediate cell destruction by antibody dependent cell-mediated cytotoxicity (ADCC), in which cytotoxic cells bearing Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells.
3. Finally, antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell

**1: Transfusion Reactions Are an Example of Type II Hypersensitivity**

Blood types are referred to as A, B, or O, and the **antigens** that are associated with the blood types are identified as **A, B, and H**, respectively and are carbohydrates, rather than proteins. Note that the H antigen is present in all blood types.

***Antibodies*** directed toward ABH antigens are termed ***isohemagglutinins*** .

***The clinical manifestations*** of transfusion reactions result from massive intravascular hemolysis of the transfused red blood cells by antibody plus complement. These manifestations may be either immediate or delayed.

* ***Reactions that begin immediately*** are most commonly associated with ABO blood-group incompatibilities, which lead to complement mediated lysis triggered by the IgM isohemagglutinins.Within hours, free hemoglobin can be detected in the plasma; it is filtered through the kidneys, resulting in hemoglobinuria. **Typical symptoms of bilirubinemia** include [fever, chills, nausea, clotting within blood vessels, pain in the lower back, and hemoglobin in the urine]. **Treatment involves** [prompt termination of the transfusion and maintenance of urine flow with a diuretic, because the accumulation of hemoglobin in the kidney can cause acute tubular necrosis].
* Antibodies to other blood-group antigens such as Rh factor may result from repeated blood transfusions .These antibodies are usually of the **IgG class**. These incompatibilities typically result in ***delayed hemolytic transfusion reactions*** that develop between 2 and 6 days after transfusion **WHY ??.** Because IgG is less effective than IgM in activating complement,

**2: Hemolytic Disease of the Newborn Is Caused by Type II Reactions**

Hemolytic disease of the newborn develops when maternal IgG antibodies specific for fetal blood-group antigens cross the placenta and destroy fetal red blood cells. The consequences of such transfer can be minor, serious, or lethal. Severe hemolytic disease of the newborn, called ***erythroblastosis fetalis*** , most commonly develops when the mother and fetus express different alleles of the **Rhesus (Rh) antigen**. individuals bearing the D allele of the Rh antigen as Rh+.

 An Rh - mother fertilized by an Rh + father is in danger of developing a response to the Rh antigen and rejecting an Rh + fetus. During pregnancy, fetal red blood cells are separated from the mother’s circulation by a 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 red blood cells to activate her Rh-specific B cells. However, 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 red blood cells stimulate Rh-specific B cells to mount an immune response, resulting in the production of Rh-specific plasma cells and memory B cells in the mother. The secreted IgM antibody clears the Rh+ fetal red cells from the mother’s circulation, but memory cells remain, a threat to any subsequent pregnancy with an Rh + fetus.

**Importantly,** since IgM antibodies do not pass through the placenta, IgM anti-Rh antigens are no threat to the fetus. Activation of IgG-secreting memory cells in a subsequent pregnancy results in the formation of IgG anti-Rh antibodies, which, however, can cross the placenta and damage the fetal red blood cells. Mild to severe anemia can develop in the fetus, sometimes with fatal consequences. In addition, conversion of hemoglobin to bilirubin can present an additional threat to the newborn because the lipid-soluble bilirubin may accumulate in the brain and cause brain damage. Fortunately, bilirubin is rapidly broken down on exposure of the skin to ultraviolet (UV) light.

Hemolytic disease of the newborn caused by Rh incompatibility in a **second or later pregnancy** can be almost entirely prevented **HOW ??** by administering antibodies against the Rh antigen to the mother at around 28 weeks of pregnancy and within 24 to 48 hours after the first delivery. These antibodies, marketed as ***Rhogam*** , bind to any fetal red blood cells that may have entered the mother’s circulation and facilitate their clearance before B-cell activation and ensuing memory-cell production can take place. In a subsequent pregnancy with an Rh +fetus, a mother who has been treated with Rhogam is unlikely to produce IgG anti-Rh antibodies; thus, the fetus is protected from the damage that would occur when these antibodies cross the placenta.

**3: Hemolytic Anemia Can Be Drug Induced**

Certain antibiotics (e.g., penicillin, cephalosporins, and streptomycin), as well as other well-known drugs can adsorb nonspecifically to proteins on red blood cell membranes, forming a drug protein complex. In some patients, such drug-protein complexes induce formation of antibodies. These antibodies then bind to the adsorbed drug on red blood cells, inducing complement-mediated lysis and thus progressive anemia.

**Type III: Immune Complex Hypersensitivity**

🡪When antibody combines with its specific antigen, immune complexes are formed. Normally, they are promptly removed, but occasionally, they persist and are deposited in tissues, resulting in several disorders.

🡪 In persistent microbial or viral infections, immune complexes may be deposited in organs (eg, the kidneys), resulting in dysfunction.

🡪In autoimmune disorders, “self” antigens may elicit antibodies that bind to organ antigens or are deposited in organs and tissues as complexes, especially in joints (arthritis), kidneys (nephritis), and blood vessels (vasculitis).

🡪Finally, environmental antigens such as fungal spores and certain drugs can cause immune complex formation with disease.

Wherever immune complexes are deposited, they activate the complement system, and macrophages and neutrophils are attracted to the site, where they cause inflammation and tissue injury.

There are two major forms of immune complex-mediated hypersensitivity.

**Local (Arthus reaction)** and typically elicited in the skin when a low dose of antigen is injected and immune complexes form locally. IgG antibodies are involved, and the resulting activation of complement leads to activation of mast cells and neutrophils, mediator release, and enhanced vascular permeability. This typically occurs in about 12 hours.

 **Systemic immune complex disease.**There are several examples, including diseases such as acute poststreptococcal glomerulonephritis is a well known immune complex disease. Its onset occurs several weeks after a group A β-hemolytic streptococcal infection, particularly of the skin, and often occurs with infection due to nephritogenic types of streptococci. It is likely that streptococcal antigen– antibody complexes are filtered out by glomeruli, fix complement, and attract neutrophils. This series of events results in an inflammatory process that damages the kidney.

**Type IV: Cell-Mediated (Delayed) Hypersensitivity**

Cell-mediated hypersensitivity is a function not of antibody but of specifically sensitized T lymphocytes that activate macrophages to cause an inflammatory response. The response is delayed— it usually starts 2 or 3 days after contact with the antigen and often lasts for days.

**Contact Hypersensitivity**

* Contact hypersensitivity occurs after sensitization with simple chemicals (eg, nickel, formaldehyde), plant materials (poison ivy, poison oak), topically applied drugs (eg, sulfonamides, neomycin), some cosmetics, soaps, and other substances. In all cases, small molecules enter the skin and then, acting as **haptens**, attach to body proteins to serve as complete antigens.
* Cell-mediated hypersensitivity is induced, particularly in the skin. When the skin again comes in contact with the offending agent, the sensitized person develops erythema, itching, eczema, or necrosis of skin within 12-48 hours.
* Subsequent avoidance of the material will prevent recurrences.
* The APC in contact sensitivity is probably the Langerhans cell in the epidermis, which interacts with **CD4 Th1** cells that drive the response.
* T H 1 cells are important initiators of DTH, but the principal effector cells of the DTH response are activated macrophages.

Cytokines elaborated by helper T cells, including IFN- γ and Lymphotoxin- α , induce **what** ??

* blood monocytes to adhere to vascular endothelial cells,
* migrate from the blood into the surrounding tissues,
* and differentiate into activated macrophages. **Activated macrophages exhibit** **WHAT** ??enhanced phagocytosis and an increased ability to kill microorganisms. They produce cytokines that recruit more monocytes and neutrophils, and enhance the activity of T H 1 cells, amplifying the response. A prolonged DTH response can develop, which becomes destructive to the host, causing a visible granulomatous reaction. ***Granulomas*** develop when continuous activation of macrophages induces them to adhere closely to one another. and the buildup of lytic enzymes from macrophages in the area of infection lead to nonspecific destruction of cells.

**The DTH Reaction Can be Detected by a Skin Test**

The presence of a DTH reaction can be measured experimentally observing whether a characteristic skin lesion develops days later at the injection site. A positive skin-test reaction indicates that the individual has a population of sensitized T H 1 cells specific for the test antigen. For example, to determine whether an individual has been exposed to *M. tuberculosis* a protein derived from the cell wall of this mycobacterium, is injected intradermally. Development of a red, slightly swollen, firm lesion at the site between 48 and 72 hours later indicates previous exposure. Note, however, that a positive test does not allow one to conclude whether the exposure was due to a pathogenic form of M. tuberculosis or to a vaccine antigen, which is used in some parts of the world.