Chapter 16: Disorders in Immunity
16.1 The Immune Response: A Two-Sided Coin

- The Immune Response: A Two-Sided Coin
- **Immunopathology**: the study of disease states associated with overactivity or underactivity of the immune response
  - Allergies
  - Autoimmunity
  - Grafts and transfusions
  - Immunodeficiency
Overreactions to Antigens: Allergy/Hypersensitivity

- **Allergy**: altered reactivity or exaggerated immune response manifested by inflammation
- **Hypersensitivity**: sometimes used interchangeably with allergy, but some consider this to be delayed reaction (while allergies are immediate)
- **Allergens**: the antigen to which allergic individuals are sensitive
- **Four major categories of allergies**
<table>
<thead>
<tr>
<th>Type</th>
<th>Systems and Mechanisms Involved</th>
<th>Examples</th>
</tr>
</thead>
</table>
| I       | Immediate hypersensitivity
IgE-mediated; involves mast cells, basophils, and allergic mediators | Anaphylaxis, allergies such as hay fever, asthma               |
| II      | Antibody-mediated
IgG, IgM antibodies act upon cells with complement and cause cell lysis; includes some autoimmune diseases | Blood group incompatibility, pernicious anemia; myasthenia gravis |
| III     | Immune complex-mediated
Antibody-mediated inflammation; circulating IgG complexes deposited in basement membranes of target organs; includes some autoimmune diseases | Systemic lupus erythematosus; rheumatoid arthritis; serum sickness; rheumatic fever |
| IV      | T-cell-mediated
Delayed hypersensitivity and cytotoxic reactions in tissues | Infection reactions; contact dermatitis; graft rejection; some types of autoimmunity |
16.2 Type I Allergic Reactions: Atopy and Anaphylaxis

• Two levels of severity of type I allergies
  – **Atopy**: chronic local allergy (hay fever, asthma, etc.)
  – **Anaphylaxis**: systemic, sometimes fatal reaction
Epidemiology and Modes of Contact with Allergens

• 10% to 30% of the population prone to atopic allergy
  – Likely an underestimation because of the numbers of patients who self-treat
  – Half a billion dollars spent annually on treatment
• Genetic program that favors allergic antibody (IgE) production, increased reactivity of mast cells, and increased susceptibility of target tissue to allergic mediators
• Also affected by age, infection and geographic locale
The Nature of Allergens and Their Portals of Entry

- Proteins are more allergenic than carbohydrates, fats, or nucleic acids
- Some allergens are haptens
- Typically enter through epithelial portals in the respiratory tract, gastrointestinal tract, and skin
- Inhalants: airborne environmental allergens
- Ingestants: allergens that enter by mouth
- Injectant allergies: side effect of drugs or other substances used in diagnosing, treating, or preventing disease; or naturally through venom from stings
- Contactants: allergens that enter through the skin
<table>
<thead>
<tr>
<th><strong>Inhalants</strong></th>
<th><strong>Ingestants</strong></th>
<th><strong>Injectants</strong></th>
<th><strong>Contactants</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen</td>
<td>Food</td>
<td>Hymenopteran venom (bee, wasp)</td>
<td>Drugs</td>
</tr>
<tr>
<td>Dust</td>
<td>(milk, peanuts, wheat, shellfish, soybeans, nuts, eggs, fruits)</td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Mold spores</td>
<td>Food additives</td>
<td>Vaccines</td>
<td>Cosmetics</td>
</tr>
<tr>
<td>Dander</td>
<td></td>
<td>Serum</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Animal hair</td>
<td></td>
<td>Enzymes</td>
<td>Detergents</td>
</tr>
<tr>
<td>Insect parts</td>
<td></td>
<td>Hormones</td>
<td>Formalin</td>
</tr>
<tr>
<td>Formalin</td>
<td></td>
<td></td>
<td>Rubber</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td>Glue</td>
</tr>
<tr>
<td>Enzymes</td>
<td></td>
<td></td>
<td>Solvents</td>
</tr>
<tr>
<td></td>
<td>Food</td>
<td></td>
<td>Dyes</td>
</tr>
<tr>
<td></td>
<td>(aspirin, penicillin)</td>
<td></td>
<td></td>
</tr>
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</table>
# National Allergy Bureau Pollen and Mold Report

<table>
<thead>
<tr>
<th>Pollen Type</th>
<th>Count Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trees</td>
<td>Moderate</td>
<td>41 / m³</td>
</tr>
<tr>
<td>Weeds</td>
<td>High</td>
<td>64 / m³</td>
</tr>
<tr>
<td>Grass</td>
<td>High</td>
<td>60 / m³</td>
</tr>
<tr>
<td>Mold</td>
<td>Low</td>
<td>4,219 / m³</td>
</tr>
</tbody>
</table>

- **Location:** Sacramento, California  
- **Date:** June 04, 2003  
- **Counting Station:** Allergy Medical Group of the North Area

(c) SPL/Photo Researchers, David M. Phillips/Visuals Unlimited
Mechanisms of Type I Allergy: Sensitization and Provocation

• Type I allergies occur in stages
• Initial encounter- sensitizing dose
• Next encounter- memory cells and immunoglobulin are ready to react
The Physiology of IgE-Mediated Allergies

- Allergen penetrates portal of entry
- Encounter a moist membrane, release molecules of allergen that pass into tissue fluids and lymphatics
- Lymphatics carry allergen to the lymph nodes
- Clones of B cells recognize the allergen, are activated, and proliferate into plasma cells
- Plasma cells produce IgE, the antibody of allergy
  - IgE has an Fc region with great affinity for mast cells and basophils
  - The binding of IgE to these cells causes the reactions that occur upon repeat exposure to the allergen
The Role of Mast Cells and Basophils

- Ubiquitous location in tissues
- Capacity to bind IgE during sensitization
- Cytoplasmic granules which contain physiologically active cytokines
- Tendency to **degranulate**
The Second Contact with Allergen

- IgE-primed mast cells can remain in the tissues for years
- A person retains the capacity to react immediately upon reexposure
- Next time allergen molecules contact the mast cells, they bind across adjacent receptors and stimulate degranulation
- Chemical mediators are released and diffuse into tissues and bloodstream
- Cytokines give rise to local and systemic reactions
Cytokines, Target Organs, and Allergic Symptoms

• Principal chemical mediators produced by mast cells and basophils
  – Histamine- stimulates smooth muscle, glands, and eosinophils; responsible for wheal and flare reaction, pruritis, and headache
  – Serotonin- effects appear to complement those of histamine
  – Leukotriene- induces gradual contraction of smooth muscle
  – Platelet-activating factor- lipid with similar effects as histamine
  – Prostaglandins- inflammatory agents responsible for vasodilation, increased vascular permeability, increased sensitivity to pain, bronchoconstriction
  – Bradykinin- prolonged smooth muscle contraction of the bronchioles, dilation of peripheral arterioles, increased capillary permeability, increased mucus secretion

• Account for the wide range of allergic symptoms
Figure 16.4
Specific Diseases Associated with IgE- and Mast-Cell-Mediated Allergy

- Hay fever
- Allergic asthma
- Food allergy
- Drug allergy
- Eczema
- Anaphylaxis
Atopic Diseases

• Hay fever (allergic rhinitis)
• Asthma
• Atopic dermatitis
Hay Fever (Allergic Rhinitis)

• Targets: respiratory membranes
• Symptoms: nasal congestion, sneezing, coughing, mucus secretion, itchy, red, teary eyes, and mild bronchoconstriction
Asthma

• Episodes of impaired breathing due to severe bronchoconstriction
• Symptoms range from occasional bouts of difficult breathing to fatal suffocation
• Chronically inflamed respiratory tract
• Severely overreactive to allergy chemicals, esp. leukotrienes and serotonin
Atopic Dermatitis

• Also called eczema
• Intensely itchy inflammatory condition of the skin
• Infancy: reddened, vesicular, weeping, encrusted skin lesions
• Childhood and adulthood: dry, scaly, thickened skin condition
Figure 16.5
Food Allergy

- Mode of entry: intestinal
- Gastrointestinal symptoms: vomiting, diarrhea, abdominal pain
- Other symptoms: eczema, hives, rhinitis, asthma, and occasionally anaphylaxis
- Most common food allergens: peanuts, fish, cow’s milk, eggs, shellfish, and soybeans
- Classic food hypersensitivity involves IgE and degranulation of mast cells
Drug Allergy

- Virtually any tissue can be affected
- Reactions range from mild atopy to fatal anaphylaxis
- Actual allergen is not the drug itself but a hapten given off when the liver processes the drug
Anaphylaxis: An Overpowering Systemic Reaction

- Cutaneous anaphylaxis: wheal and flare inflammatory reaction to a local injection of allergen
- Systemic anaphylaxis: sudden respiratory and circulatory disruption that can be fatal
Diagnosis of Allergy

- Involves several levels of tests, including nonspecific, specific, *in vitro*, and *in vivo* methods.

*In vitro* methods:
- Measure elevated blood levels of tryptase
- Differential blood cell count
- Leukocyte histamine-release test
- Serological tests that use radioimmune assays

*Skin testing*:
- Patient’s skin injected, scratched, or pricked with a small amount of pure allergen extract
- Allergist maps the skin
- Each site appraised for a wheal response after approximately 20 minutes
Figure 16.6
Treatment and Prevention of Allergy

• Treatment and Prevention of Allergy
  – Avoid the allergen
  – Take drugs that block the action of lymphocytes, mast cells, or chemical mediators
  – Undergo desensitization therapy
Therapy to Counteract Allergies

Figure 16.7

Corticosteroids keep the plasma cell from synthesizing IgE and inhibit T cells.

Cromolyn acts on the surface of mast cell; no degranulation

Antihistamines, aspirin, epinephrine, theophylline counteract the effects of cytokines on targets.

Avoidance of allergen

Allergen

IgE

Monoclonal drugs that inactivate IgE

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16.3 Type II Hypersensitivities: Reactions that Lyse Foreign Cells

• Complex group of syndromes that involve complement-assisted lysis of cells by IgG and IgM directed against those cells’ surface antigens

• Includes transfusion reactions and some types of autoimmunities
The Basis of Human ABO Antigens and Blood Types

- **ABO blood groups**
- ABO antigen markers on RBCs are genetically determined and composed of glycoproteins
- Three alternative **alleles**: A, B, or O
- Results in four blood types
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Blood Type</th>
<th>Antigen Present on Erythrocyte Membranes</th>
<th>Antibody in Plasma</th>
<th>Among Whites (%)</th>
<th>Among Asians (%)</th>
<th>Among Those of African and Caribbean Descent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA, AO</td>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
<td>41</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>BB, BO</td>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
<td>10</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>A and B</td>
<td>Neither anti-A nor anti-B</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>OO</td>
<td>O</td>
<td>Neither A nor B</td>
<td>Anti-A and anti-B</td>
<td>45</td>
<td>40</td>
<td>46</td>
</tr>
</tbody>
</table>
Important Points about Blood Types

• They are named for the dominant antigen
• The RBCs of type O persons have antigens but not A and B antigens
• Tissues other than RBCs carry A and B antigens
Antibodies Against A and B Antigens

- Preformed antibodies
- Develop in early infancy
Clinical Concerns in Transfusions

Figure 16.10
Universal Transfusions

• Under certain circumstances
• Type O- universal donor
• Type AB- universal recipient
Transfusion Reactions

- Severest: massive hemolysis leading to systemic shock and kidney failure
- Fever, anemia, jaundice
- Managed by immediately halting the transfusion, administering drugs to remove hemoglobin from the blood, and beginning another transfusion with RBCs of the correct type
The Rh Factor and Its Clinical Importance

• Rh Factor (D antigen)
• Rh type results from a combination of two possible alleles
  – Inherit one Rh gene is Rh⁺
  – Inherit two recessive genes is Rh⁻
• The only ways one can develop antibodies against this factor are through placental sensitization or transfusion
Figure 16.12

(a) The development and aftermath of Rh sensitization
Initial sensitization of the maternal immune system to fetal Rh\(^+\) factor occurs when fetal cells leak into the Rh\(^-\) mother’s circulation late in pregnancy or during delivery when the placenta tears away. The child will escape hemolytic disease in most instances, but the mother, now sensitized, will be capable of an immediate reaction to a second Rh\(^+\) fetus and its Rh-factor antigen. At that time, the mother’s anti-Rh antibodies pass into the fetal circulation and elicit severe hemolysis in the fetus and neonate.

(b) Prevention of erythroblastosis fetalis with anti-Rh immune globulin (RhoGAM)
Injecting a mother who is at risk with RhoGAM during her first Rh\(^+\) pregnancy helps to inactivate and remove the fetal Rh\(^+\) cells before her immune system can react and develop sensitivity.
Other RBC Antigens

• About 20 other RBC antigen groups
• Examples: MN, Ss, Kell, and P blood groups
• Transfused blood is screened to prevent possible cross-reactions
• Useful in forensic medicine, ethnic ancestry studies, anthropology
16.4 Type III Hypersensitivities: Immune Complex Reactions

• Involves the reaction of soluble antigen with antibody and the deposition of the resulting complexes in basement membranes of epithelial tissue

• Similar to type II
  – Involves production of IgG and IgM after repeated exposure to antigens and the activation of complement

• Differs from type II
  – Its antigens are not attached to the surface of a cell
  – Free-floating complexes that can be deposited in the tissue
  – Causes an immune complex reaction
Mechanisms of Immune Complex Disease

Figure 16.13
Types of Immune Complex Disease

• **Arthus reaction**
  – Local dermal injury due to inflamed blood vessels in the vicinity of any injected antigen

• **Serum sickness**
  – A systemic injury initiated by antigen-antibody complexes that circulate in the blood and settle into membranes at various sites

• **Different from anaphylaxis because**
  – They depend upon IgG, IgM, or IgA rather than IgE
  – They require large doses of antigen
  – Their symptoms are delayed
16.5 Type IV Hypersensitivities: Cell-Mediated (Delayed) Reactions

- Involve primarily the T-cell branch of the immune system
- Symptoms arise one to several days following the second contact with an antigen
- Result when T cells respond to antigens displayed on self tissues or transplanted foreign cells
- Infectious Allergy
  - Example: tuberculin reaction
Contact Dermatitis

• Caused by exposure to resins in poison ivy or poison oak, for example

Figure 16.15
T Cells and Their Role in Organ Transplantation

• The genetic and biochemical basis for graft rejection
  – MHC genes- the cells of each person can exhibit variability in the pattern of cell surface molecules

• When the donor tissue displays surface molecules of a different MHC class, the T cells of the recipient will recognize its foreignness and react against it
T-Cell Mediated Recognition of MHC Receptors

• Host rejection of graft
• Graft rejection of host
Host Rejection of Graft

- Cytotoxic T cells of host release interleukin-2
- Amplifies helper and cytotoxic T cells specific to the foreign antigens on the donated cells
- The cytotoxic cells bind to the grafted tissue and secrete lymphokines that begin the rejection process
Graft Rejection of Host

• Some grafted tissues contain passenger lymphocytes
• **Graft versus host disease (GVHD)**
• Any host tissue bearing MHC markers foreign to the graft can be attacked
Classes of Grafts

- **Autograft**: tissue transplanted from one site on an individual’s body to another site on his or her body
- **Isograft**: tissue from an identical twin is used
- **Allografts**: exchanges between genetically different individuals belonging to the same species
- **Xenograft**: a tissue exchange between individuals of different species
Avoiding and Controlling Graft Incompatibility

• Directly compare the tissue of the recipient with that of potential donors
• Tissue matching procedures
  – Mixed lymphocyte reaction (MLR)
  – Tissue typing
Types of Transplants

• Has been performed on every major organ
• Most frequent: skin, liver, heart, kidney, coronary artery, cornea, and bone marrow
• Sources of organs and tissues- live donors and fetal tissues
16.6 An Inappropriate Response Against Self, or Autoimmunity

• Autoimmunity: an individual develops hypersensitivity to him or herself

• **Autoimmune diseases:** autoantibodies and/or T cells mount an abnormal attack against self antigens

• Systemic: involve several major organs

• Organ-specific: involve only one organ or tissue

• Usually fall under type II or type III hypersensitivity
<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
<th>Type of Hypersensitivity</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Systemic</td>
<td>III</td>
<td>Inflammation of many organs; antibodies against red and white blood cells, platelets, clotting factors, nucleus DNA.</td>
</tr>
<tr>
<td>Rheumatoid arthritis and ankylosing spondylitis</td>
<td>Systemic</td>
<td>III and IV</td>
<td>Vasculitis; frequent target is joint lining; antibodies against other antibodies (rheumatoid factor)</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Systemic</td>
<td>II</td>
<td>Excess collagen deposition in organs; antibodies formed against many intracellular organelles.</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroid</td>
<td>II</td>
<td>Destruction of the thyroid follicles.</td>
</tr>
<tr>
<td>Graves disease</td>
<td>Thyroid</td>
<td>II</td>
<td>Antibodies against thyroid-stimulating hormone receptors.</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Stomach lining</td>
<td>II</td>
<td>Antibodies against receptors prevent transport of vitamin B\textsubscript{12}.</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscle</td>
<td>II</td>
<td>Antibodies against the acetylcholine receptors on the nerve-muscle junction alter function.</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Pancreas</td>
<td>IV</td>
<td>T cells attack insulin-producing cells.</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Myelin</td>
<td>II and IV</td>
<td>T cells and antibodies sensitized to myelin sheath destroy neurons.</td>
</tr>
<tr>
<td>Goodpasture syndrome (glomerulonephritis)</td>
<td>Kidney</td>
<td>II</td>
<td>Antibodies to basement membrane of the glomerulus damage kidneys.</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Heart</td>
<td>II</td>
<td>Antibodies to group A Streptococcus cross-react with heart tissue.</td>
</tr>
</tbody>
</table>
Genetic and Gender Correlation in Autoimmune Disease

- Susceptibility is determined by genetics and influenced by gender
- Particular genes in the class I and II MHC coincide with certain autoimmune diseases
The Origins of Autoimmune Disease

- Sequestered antigen theory
- **Clonal selection theory**
- Theory of immune deficiency
- Inappropriate expression of MHC II markers - the bystander effect
- Molecular mimicry
- Viral infection
- **Autoimmune regulator (AIRE)**
Examples of Autoimmune Disease

- Systemic autoimmunities
- Autoimmunities of the endocrine glands
- Neuromuscular autoimmunities
Systemic Autoimmunities

• Systemic lupus erythematosus (SLE, or lupus)
• Rheumatoid arthritis
Autoimmunities of the Endocrine Glands

- Graves’ disease
- Hashimoto’s thyroiditis
- Diabetes mellitus
Neuromuscular Autoimmunities

• Myasthenia gravis
• Multiple sclerosis
16.7 Immunodeficiency Diseases: Hyposensitivity of the Immune System

- Primary diseases: present at birth (congenital) and usually stemming from genetic errors
- Secondary diseases: acquired after birth and caused by natural or artificial agents
### General Categories of Immunodeficiency Diseases with Selected Examples

#### PRIMARY IMMUNE DEFICIENCIES (GENETIC)

- **B-cell defects (low levels of B cells and antibodies)**
  - Agammaglobulinemia (X-linked, non-sex-linked)
  - Hypogammaglobulinemia
  - Selective immunoglobulin deficiencies

- **T-cell defects (lack of all classes of T cells)**
  - Thymic aplasia (DiGeorge syndrome)
  - Chronic mucocutaneous candidiasis

- **Combined B-cell and T-cell defects (usually caused by lack or abnormality of lymphoid stem cell)**
  - Severe combined immunodeficiency disease (SCID)
  - X-SCID due to an interleukin defect
  - Adenosine deaminase (ADA) deficiency
  - Wiskott-Aldrich syndrome
  - Ataxia-telangiectasia

- **Phagocyte defects**
  - Chédiak-Higashi syndrome
  - Chronic granulomatous disease of children (see Case File 14, chapter 14)
  - Lack of surface adhesion molecules

- **Complement defects**
  - Lacking one of C components
  - Hereditary angioedema
  - Associated with rheumatoid diseases

#### SECONDARY IMMUNE DEFICIENCIES (ACQUIRED)

- **From natural causes**
  - Infections (AIDS) or cancers
  - Nutrition deficiencies
  - Stress
  - Pregnancy
  - Aging

- **From immunosuppressive agents**
  - Irradiation
  - Severe burns
  - Steroids (cortisones)
  - Drugs to treat graft rejection and cancer
  - Removal of spleen
Primary Immunodeficiency Diseases

• In many cases the deficiency is due to an inherited abnormality
• An individual can lack one or both cell line (B cells and T cells)
• Some deficiencies affect other cell functions
Figure 16.18
Clinical Deficiencies in B-Cell Development or Expression

• Usually appear as an abnormality in immunoglobulin expression

• **Agammaglobulinemia** - the absence of gamma globulin (rare)

• **Hypogammaglobulinemia**
  – Symptoms: recurrent, serious bacterial infections
  – Relatively common condition
  – IgA deficiency most prevalent
Clinical Deficiencies in T-Cell Development or Expression

• Results in a broad spectrum of disease
• Deficiency can occur anywhere along the developmental spectrum
• Most severe: involve the congenital absence or immaturity of the thymus gland
  – DiGeorge syndrome
Severe Combined Immunodeficiencies: Dysfunction in B and T Cells

- **Severe combined immunodeficiencies (SCIDs):** most dire and potentially lethal
- Some due to complete absence of lymphocyte stem cell in marrow
- Other due to the dysfunction of B cells and T cells later in development
- Two most common forms: Swiss-type agammaglobulinemia and thymic alymphoplasia
- Rarer forms: adenosine deaminase (ADA) deficiency; bare lymphocyte syndrome
Secondary Immunodeficiency Diseases

• Caused by one of four general agents:
  – Infection
  – Organic disease
  – Chemotherapy
  – Radiation

• AIDS- infection-induced immunodeficiency