16.1 The Immune Response

**Immunopathology:** the study of disease states associated with underactivity and overactivity of the immune response

- Allergy, hypersensitivity – an exaggerated, misdirected expression of immune responses to an allergen (antigen)
- Autoimmunity – abnormal responses to self Ag
- Immunodeficiency – deficiency or loss of immunity
- Cancer – both a cause and effect of immune dysfunction
Figure 16.1 Overview of disease of the immune system
# TABLE 16.1

## Hypersensitivity States

<table>
<thead>
<tr>
<th>Type</th>
<th>Systems and Mechanisms Involved</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Immediate</td>
<td>IgE-mediated; involves mast cells, basophils, and allergic mediators</td>
<td>Anaphylaxis, allergies such as hay fever, asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Antibody</td>
<td>IgG, IgM antibodies act upon cells with complement and cause cell lysis; includes some autoimmune diseases</td>
<td>Blood group incompatibility, pernicious anemia; myasthenia gravis</td>
</tr>
<tr>
<td>mediated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Immune</td>
<td>Antibody-mediated inflammation; circulating IgG complexes deposited in basement membranes of target organs; includes some autoimmune diseases</td>
<td>Systemic lupus erythematosus; rheumatoid arthritis; serum sickness; rheumatic fever</td>
</tr>
<tr>
<td>complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mediated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV. T-cell</td>
<td>Delayed hypersensitivity and cytotoxic reactions in tissues</td>
<td>Infection reactions; contact dermatitis; graft rejection; some types of autoimmunity</td>
</tr>
<tr>
<td>mediated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
16.2 Type I Allergic Reactions

Two levels of severity:

- **Atopy** – any chronic local allergy such as hay fever or asthma

- **Anaphylaxis** – a systemic, often explosive reaction that involves airway obstruction and circulatory collapse
Contact with Allergens

- Generalized predisposition to allergies is familial – not to a specific allergy
- Allergy can be affected by age, infection, and geographic area
- Atopic allergies may be lifelong or may be “outgrown”; may also develop later in life
Nature of Allergens and Their Portals of Entry

- Allergens have immunogenic characteristics
- Typically enter through epithelial portals – respiratory, gastrointestinal, skin
- Organ of allergic expression may or may not be the same as the portal of entry
**TABLE 16.2**  Common Allergens, Classified by Portal of Entry

<table>
<thead>
<tr>
<th>Inhalants</th>
<th>Ingestants</th>
<th>Injectants</th>
<th>Contactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollen</td>
<td>Food (milk, peanuts, wheat, shellfish, soybeans, nuts, eggs, fruits)</td>
<td>Hymenopteran venom (bee, wasp)</td>
<td>Drugs</td>
</tr>
<tr>
<td>Dust</td>
<td></td>
<td>Drugs</td>
<td>Cosmetics</td>
</tr>
<tr>
<td>Mold spores</td>
<td></td>
<td>Vaccines</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Dander</td>
<td></td>
<td>Serum</td>
<td>Detergents</td>
</tr>
<tr>
<td>Animal hair</td>
<td></td>
<td>Enzymes</td>
<td>Formalin</td>
</tr>
<tr>
<td>Insect parts</td>
<td>Food additives</td>
<td>Hormones</td>
<td>Rubber</td>
</tr>
<tr>
<td>Formalin</td>
<td>Drugs (aspirin, penicillin)</td>
<td></td>
<td>Solvents</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td>Dyes</td>
</tr>
</tbody>
</table>
Figure 16.2 (b) and (c)
Mechanism of Type I Allergy

Develop in stages:

- **Sensitizing dose** – on first contact with allergen, specific B cells form IgE which attaches to mast cells and basophils; generally no signs or symptoms

- **Provocative dose** – subsequent exposure with the same allergen binds to the IgE-mast cell complex

- **Degranulation** releases mediators with physiological effects such as vasodilation and bronchoconstriction

- **Symptoms** are rash, itching, redness, increased mucous discharge, pain, swelling, and difficulty breathing
Figure 16.3

**Sensitization/IgE Production**

1. Allergen particles enter mucous membrane.
2. Lymphatic vessel carries them to lymph node.
3. B cell recognizes allergen with help of T cell.
4. Proliferates into plasma cells.
5. Synthesizes IgE.
6. IgE binds to mast cell surface receptors.
7. Allergen is encountered again.
8. Allergen attaches to IgE on mast cells and triggers degranulation and release of allergic mediators.
10. Mast cell in tissue primed with IgE.

**End result: Symptoms in various organs**

- Red, itchy eyes
- Hives
- Runny nose
Role of Mast Cells and Basophils

- **Mast cells** are located in the connective tissue of virtually all organs; high concentration in lungs, skin, GI, and genital tract.

- **Basophils** circulate in blood and migrate into tissues.

- Each cell can bind 10,000-40,000 IgE.

- Cytoplasmic granules contain physiologically active cytokines, histamine, etc.

- Cells degranulate when stimulated by allergen.
Cellular reactions

1. Allergen particles enter the mucous membrane.
2. Carries them to the lymphatic vessel and lymph node.
3. B cell recognizes the allergen with the help of T cell.
4. Proliferates into plasma cells.
5. Synthesizes IgE.
6. IgE binds to mast cell surface receptors.
7. Allergen is encountered again.
8. Allergen attaches to IgE on mast cells and triggers degranulation and release of allergic mediators.
10. End result: Symptoms in various organs.
Cytokines, Target Organs, Allergic Symptoms

Act alone or in combination; account for scope of allergic symptoms

Histamine, serotonin, leukotriene, platelet-activating factor, prostaglandins, bradykinin

General targets include: skin, upper respiratory tract, GI tract, and conjunctiva

Responses: rashes, itching, redness, rhinitis, sneezing, diarrhea, shedding tears

Systemic targets: smooth muscles, mucous glands, and nervous tissue

Responses: vascular dilation and constriction resulting in change in blood pressure and respiration
Histamine – most profuse and fastest acting; stimulator of smooth muscle, glands, and eosinophils

- Response to chemical depends on the muscle location: constricts smooth muscles of small bronchi, intestines; relaxes vascular smooth muscles

- Serotonin, leukotrienes, prostaglandins, bradykinin are additional allergic mediators
Figure 16.4 Reactions to inflammatory cytokines
Specific Diseases

**Atopic disease** – hay fever, rhinitis; seasonal, inhaled plant pollen or mold

- Asthma – severe bronchoconstriction; inhaled allergen
- Eczema – dermatitis; ingestion, inhalation, skin contact

**Food allergy** – intestinal portal can affect skin and respiratory tract

- Vomiting, diarrhea, abdominal pain; possibly severe
- Eczema, hives, rhinitis, asthma, occasionally anaphylaxis

**Drug allergy** – common side effect of treatment; any tissue can be affected; reaction from mild atopy to fatal anaphylaxis
Figure 16.5 Skin manifestations in atopic allergies
Anaphylaxis

Anaphylaxis – a reaction of animals injected with a foreign protein

Systemic anaphylaxis – sudden respiratory and circulatory disruption that can be fatal in a few minutes

Allergen and route are variable

Bee stings, antibiotics, or serum injection
Diagnosis of Allergy

- Important to determine if a person is experiencing allergy or infection
- Skin testing

Figure 16.6
Treatment and Prevention

General methods include:

1. Avoiding allergen

2. Use drugs that block the action of the lymphocytes, mast cells, or chemical mediators (antihistamines)

3. Desensitization therapy – injected allergens may stimulate the formation of high-levels of allergen-specific IgG that act to block IgE; mast cells don’t degranulate
Figure 16.7 Strategies for circumventing allergic attacks

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

Avoidance of allergen

IgE

Cromolyn acts on the surface of mast cell; no degranulation

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

Monoclonal drugs that inactivate IgE
Figure 16.8 The blocking antibody theory for allergic desensitization

B Cell / Plasma Cell

IgG “blocking antibodies”

Mast Cell
with previous IgE

Allergen

IgG binds allergens

No reaction with mast cell

No degranulation
16.3 Type II Hypersensitivity

- Reactions that **lyse foreign cells**
- Involve antibodies, complement, leading to lysis of foreign cells
- Transfusion reactions
  - ABO blood groups
  - Rh factor – hemolytic disease of the newborn
Human ABO Antigens and Blood Types

- 4 distinct ABO blood groups
- Genetically determined RBC glycoproteins; inherited as 2 alleles of A, B, or O
- 4 blood types: A, B, AB, or O
  - Named for dominant antigen(s)
  - Type O persons lack both A and B antigens
  - Tissues other than RBCs also carry A and B antigens
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Blood Type</th>
<th>Antigen Present on Erythrocyte Membranes</th>
<th>Antibody in Plasma</th>
<th>Incidence of Type in United States</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></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></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></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></td>
<td>45</td>
<td>40</td>
<td>46</td>
</tr>
</tbody>
</table>
Figure 16.9 Genetic basis for the A and B antigens
Antibodies Against A and B Antigens

- Serum contains pre-formed antibodies that react with blood of another antigenic type-agglutination; potential transfusion complication
- **Type A** contains Abs that react against **B** antigens
- **Type B** contains Abs that react against **A** antigens
- **Type O** contains Abs that react against **A and B** antigens
- **Type AB** contains no Abs that react against **A or B** antigens
Figure 16.10 Interpretation of blood typing
Figure 16.11 Microscopic view of a transfusion reaction
Rh Factor and Hemolytic Disease of the Newborn

Hemolytic Disease of the Newborn (HDN) – an Rh- mother forms antibodies to her Rh+ fetus; usually requires subsequent exposure to the antigen to be hemolytic

Prevention requires the use of passive immunization with antibodies against the Rh antigen; prevents sensitization of mother
Figure 16.12 Rh factor incompatibility can result in RBC lysis
16.4 Type III Hypersensitivity

- Reaction of soluble antigen with antibody and the deposition of the resulting complexes in basement membranes of epithelial tissues

- Immune complexes become trapped in tissues and incite a damaging inflammatory response

  - **Arthus reaction** – localized dermal injury due to inflamed blood vessels
  
  - **Serum sickness** – systemic injury initiated by antigen-antibody complexes that circulate in the blood
Figure 16.13 Pathogenesis of immune complex disease

Steps:
1. Antibody combines with excess soluble antigen, forming large quantities of Ab/Ag complexes.
2. Circulating immune complexes become lodged in the basement membrane of epithelia in sites such as kidney, lungs, joints, skin.
3. Fragments of complement cause release of histamine and other mediator substances.
4. Neutrophils migrate to the site of immune complex deposition and release enzymes that cause severe damage in the tissues and organs involved.

Major organs that can be targets of immune complex deposition:
- Blood vessels
- Heart/Lungs
- Joints
- Skin
- Kidney
16.5 Immunopathologies Involving T cells

**Type IV Hypersensitivity**

- T cell-mediated
- Delayed response to Ag involving activation of and damage by T cells
- Delayed allergic response – skin response to allergens – tuberculin skin test, contact dermatitis from plants, metals, cosmetics
1. Lipid-soluble chemicals are absorbed by the skin.
2. Dendritic cells close to the epithelium pick up the allergen, process it, and display it on MHC receptors.
3. Previously sensitized $T_h1$ (CD4) cells recognize the presented allergen.
4. Sensitized $T_h1$ cells are activated to secrete cytokines (IFN, TNF) that attract macrophages and cytotoxic T cells to the site.
5. Macrophage releases mediators that stimulate a strong, local inflammatory reaction. Cytotoxic T cells directly kill cells and damage the skin. Fluid-filled blisters result.
T Cells and Organ Transplantation

Graft/transplantation rejection – host may reject graft; graft may reject host

MHC markers of donor tissue (graft) are different; T cells of the recipient recognize foreignness
Host rejection of graft

- Release interleukin-2 which amplifies helper and cytotoxic T cells which bind to donor tissue and release lymphokines that begin the rejection.

Graft rejection of host

- Graft versus host disease
- Any host tissue bearing MHC foreign to the graft are attacked.
Figure 16.16 Potential reactions in transplantation

(a) Host rejection of graft

(b) Graft rejection of host
16.6 Autoimmunity

In certain type II & III hypersensitivities, the immune system has lost tolerance to autoantigens and forms autoantibodies and sensitized T cells against them.

Disruption of function can be systemic or organ specific:

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Endocrine autoimmunities
- Myasthenia gravis
- Multiple sclerosis
The Origins of Autoimmune Disease

- **Sequestered antigen theory** – during embryonic growth some tissues are immunologically privileged

- **Forbidden clones** – some clones were not subjected to the tolerance process, and they attack tissues carrying self molecules

- **Theory of immune deficiency** – mutations in the receptor genes of some lymphocytes render them reactive to self

- **Molecular mimicry**, viral infection, microbial etiology
<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>II and 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 B₁₂</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>II</td>
<td>Antibodies stimulate destruction of insulin-secreting 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 streptococci cross-react with heart tissue</td>
</tr>
</tbody>
</table>
Figure 16.17 Common autoimmune diseases
Autoimmunities of the Endocrine Glands

- **Graves’ disease**, attachment of autoantibodies to receptors on the cells that secrete thyroxin, increases levels of thyroxin
  - Hyperthyroidism

- **Hashimoto’s thyroiditis**, autoantibodies, and T cells are reactive to the thyroid gland, reduces levels of thyroxin
  - Hypothyroidism

- **Diabetes mellitus**, a dysfunction in insulin production by cells in the pancreas
  - Reduction in insulin production
Figure 16.18 The autoimmune component in diabetes, type I

Type I Diabetes

- Destroyed islet cell
- Autoantibody specific for islets
- Insulin
- Damaged islet cell
Neuromuscular Autoimmunities

- **Myasthenia gravis**, autoantibodies bind to receptors for acetylcholine
  - Pronounced muscle weakness

- **Multiple sclerosis**, myelin sheath of nerve cells is damaged by both T cells and autoantibodies
  - Paralyzing neuromuscular disease
Figure 16.19 Myasthenia gravis
16.7 Immunodeficiency Diseases

Components of the immune response system are absent. Deficiencies involve B and T cells, phagocytes, and complement.

2 general categories:

- Primary immunodeficiency – congenital; usually genetic errors
- Secondary diseases – acquired after birth; caused by natural or artificial agents
Figure 16.20 The stages of development
Secondary diseases – due to damage after birth

Caused by: infection, organic disease, chemotherapy, or radiation

AIDS most common – T helper cells are targeted; numerous opportunistic infections and cancers
16.8 The Immune System and Cancer

- New growth of abnormal cells
- Tumors may be benign (nonspreading) self-contained; or malignant that spreads from tissue of origin to other sites
- Appear to have genetic alterations that disrupt the normal cell division cycle
- Possible causes include: errors in mitosis, genetic damage, activation of oncogenes, or retroviruses
- Immune surveillance, immune system keeps cancer “in check”