K. J. Lee: Essential Otolaryngology and Head and Neck Surgery (IIIrd Ed)

Chapter 26: Allergy and Immunology

Immunology

Immunity refers to the body's ability to resist a particular disease, infection, or poison. Immunology is the study of inherited and acquired mechanisms necessary to accomplish that goal.

The principal organs which serve as sites for proliferation and development of cells involved in immune responses are the thymus, spleen, lymph nodes, Peyer's patches of the gastrointestinal tract, and the bone marrow. The principal cells involved in the immune response are monocytes, neutrophils, eosinophils, lymphocytes, basophils, tissue macrophages, and mast cells.

The *nonspecific immune response* refers to phagocytosis plus inflammation with the production of various mediators whereas the specific immune response refers to the functions of the humoral (B cell) and the cellular (T cell) mediated systems.

Phagocytosis

Phagocytic cells migrate from capillaries to tissues to attack foreign invaders. The attraction to the proper area is chemotaxis. The offending microorganisms are then coated with opsonins, attached to phagocytes, ingested, killed, and digested.

1. The principal phagocytes are macrophages or monocytes, neutrophils, and eosinophils. Quantitative defects of neutrophils produce neutropenia which leads to recurrent infections. Hyposplenism causes a lack of macrophages which also makes one susceptible to serious infections.

2. Chemotaxis is the nonrandom movement of cells. There is a variety of chemotactic factors such as eosinophil chemotactic factor of anaphylaxis (ECF-A), products of clot formation, and lymphokines. The in vivo test for chemotaxis is the Rebuck skin window. An area of skin is scraped, the cover slip applied, and after a certain period the cover slip is stained and the cells which have migrated to the area are identified and counted.

3. Opsonins are serum factors which interact with microorganisms to aid their digestion by phagocytic cells. The two most important are IgG (heat-stable specific antibody) and complement C3b (heat-labile component).

4. Ingestion and intracellular killing: The opsonized microorganism is attached to and ingested by the phagocyte. The particle is incorporated into a vacuole into which granules containing lysozyme and other proteolytic enzymes are released. Demonstrable metabolic activity with increased oxygen and glucose consumption occurs. The increased glucose C1 oxidation affects hexose monophosphate activity. Intracellular killing is by means of high acidity, myeloperoxidase, or hydrogen peroxide. Some organisms are virulent because of their ability to destroy hydrogen peroxide.

5. Qualitative defect of phagocytosis implies a normal number of cells but abnormal function, i.e. chronic granulomatous disease of children. Enzyme defect creates a glucose-6-phosphate deficiency allowing recurrent infections by catalase-positive, peroxide-negative organisms such as E. coli, Klebsiella and Pseudomonas. The nitroblue tetrazolium test (NBT) is a good screening test of phagocytosis since a normally functioning phagocyte reduces this dye to an intense blue pigment.

Mediator Cells

This group of cells, mainly mast cells, basophils, and neutrophils, elaborate pharmacologically active substances that produce and control the inflammatory response. Primary mediators such as histamine are released early in the inflammatory response, whereas secondary mediators such as prostaglandins are released later. Examples of some of these mediators include the following.

Histamine

Histamine is a low-molecular-weight substance stored in the granules of circulating basophils and tissue-fixed mast cells. Histamine when released stimulates two distinct receptors. H1 receptors, inhibited by standard antihistamines, contract bronchial smooth muscle while H2 receptors, affected only by specific antihistamines, exist on stomach cells and stimulate gastric acid secretion.

Eosinophil Chemotactic Factor of Anaphylaxis (ECF-A)

This factor is a tetrapeptide with a molecular weight of about 500 that attracts eosinophils to the area of inflammation.

Slow Reacting Substance of Anaphylaxis (SRS-A)

This substance is an acid sulfur ester with a molecular weight less than 500. Like histamine, this is produced by mast cells and basophils. Although, initially, a greater percentage of histamine is produced, the ratio is reversed in a few minutes. Antihistamine block histamine but not SRS-A.

Kinins

Kinins act as secondary mediators of immediate hypersensitivity by causing contraction of bronchiolar smooth muscle, vasodilatation, and increased vascular permeability. The best known is bradykinin, a nine-amino acid peptide. Kinins are formed from kininogens in the presence of enzymes called kallikreins.

Prostaglandins

Prostaglandins are 20-carbon unsaturated aliphatic cells. These compounds potentiate the function of other mediators. Important in asthmatic patients.

Complement

Complements are the heat-labile portion of serum with bactericidal activity which are labeled in order of their discovery (i.e. C1, C2). Subunits or fragments are labeled with letters (i.e. C3a).

Activation

The classic complement pathway is activated by antigen-antibody complexes. Nine components are activated enzymatically in a cascadelike pattern. The alternative complement pathway can be activated by nonimmune means such as by the coagulation system.

Function

Their role is in host defense against infection, anaphylactic function, increasing vascular permeability, and chemotactic function atracting to the area of injury. Lytic function produces structural membrane damage. Component C3b acts as an opsonin to aid in ingestion by phagocytic cells.

Test of Complement Function

Complement function is tested by determination of the whole complement titer and measurement of the C3 level.

Clinical Findings

Deficiencies of the components of the complement cascade have been described. Clinical findings reveal a susceptibility to severe infections and autoimmune diseases. Hereditary angioneurotic edema (HANE) is due to the deficiency of a factor which controls the complement cascade C1-esterase inhibitor. Following light trauma there is an overproduction of CIE followed by anaphylatoxins which produce life-threatening edema.

Specific Antigen Recognition Cells

Lymphocytes have the ability to recognize very specific environmental materials called antigens and to produce a very specific response. Although all lymphocytes look alike under the microscope they are classified as T cells and B cells on the basis of very different functions; cell mediated immunity or humoral immunity.

T Lymphocyte Antigen Recognition System

These special lymphocytes named from their origin in the thymus gland comprise aboute 65% of the circulating lymphocytes and the cells of the subcortical regions of the lymph nodes. When special antigen receptors on the sensitized cell surface are triggered, morphologic changes such as mitosis and blast formation plus the release of lymphokines occurs. Some examples of lymphokines are macrophage inhibition factor (MIF), which inhibits outward migration of accumulated macrophages, and interferon, which protects cells against virus infection. T lymphocytes are responsible for delayed hypersensitivity skin

reactions, tumor immunity, transplant rejection, and immunity to facultative intracellular organisms (viruses).

Tests of T Cell Function

a. Lymphocyte count and morphology (remember 65% of peripheral lymphocytes are T cells).

b. E rosette assay: Human T lymphocytes spontaneously bind sheep red blood cells forming rosettes.

c. Delayed hypersensitivity skin tests: Positive delayed reactions of erythema and induration to previously encountered antigens.

d. Allogeneic skin graft rejection.

e. Special in vitro tests of lymphocyte proliferation and lymphokine production.

T Cell Deficiencies. Characteristic of T lympocyte disorders are recurrent infections by viruses, fungi, and mycobacteria. Live virus vaccination may lead to overwhelming infection. DiGeorge's syndroem, congenital aplasia of the thymus, is due to the failure of development of the third and fourth branchial pouches. Life-threatening infections are associated with hypoparathyroid disease.

B Lymphocyte Antigen Recognition System

The B lymphocytes differentiate in the bone marrow although the "B" stands for the bursa of Fabricius where these cells originate in the chicken. Antigen stimulated B lymphocytes proliferate or clone, migrate to the germinal centers of lymph nodes, mature into plasma cells, and when rechallenged form antigen specific humoral antibodies. The immunoglobulins (Ig) represent 20% of the plasma proteins (Table 26-1).

IgG. This is the major immunoglobulin in normal serum. It has a biologic half-life of 20-30 days, is located in intra- and extra-vascular spaces, functions as an opsonin, activates complement, neutralizes antigens, and is the only immunoglobulin transferred to the fetus. There are four subclasses (IgG1 through IgG4).

IgA. IgA is the second most abundant serum immunoglobulin. High concentrations occur in external secretions such as saliva, tears, and colostrum. Though synthesized as a monomer, IgA is secreted by the plasma cell as a dymer linked by a J chain. When in conjunction with the epithelial cell the secretory component is added. Two subclasses exist (IgA1 and IgA2).

IgM. With a molecular weight of 900.000, the largest immunoglobulin remains in the intravascular space. IgM is the earliest detectable immunoglobulin in the fetus, agglutinates particulate antigens, and activates complement.

IgD. Its function is unknown, but it is possibly the antigen receptor on lymphocyte surfaces.

IgE. This skin-sensitizing antibody is present only in trace amounts but is elevated in allergic and parasitic states (Table 26-2). IgE is produced by plasma cells in the paragut and pararespiratory lymphoid tissue and affixes to membrane receptors on basophils and mast cells. There is a very short serum half-life of 2.7 days but a much longer tissue half-life of about 15 days. Passively transferred IgE takes a minimum of 4 hours to attach to the basophils and mast cells. What happens next will be presented under the Allergy Type I anaphylactic reaction.

Molecular Structure of Immunoglobulins (Fig. 26-1)

Table 26-1. The Five Classes of Human Immunoglobulins

	IgG	IgA	IgM	IgD	IgE
Molecular weight	150.000	160.000	900.000	150.000	190000
Serum concentration (mg/100 mL)	1240	280	120	3	0.03
Subsets	4	2	0	0	0
Placental transfer	+	-	-	-	-
First detectable Ab	-	-	+	-	-
Complement activation	+	-	-	-	-
Riagenic activity	-	-	-	-	+
Half-life in days	21	6	6	3	2.

Two identical heavy (H) chains and two identical light (L) chains are held together by noncovalent forces and covalent disulfide bridges. The L chains have the same molecular weight (MW) of 22.500, whereas the H chain MW varies from 53.000-70.000. The H chain determines the class and subclass of immunoglobulin. The IgM immunoglobulin is a pentamer (H2L2)5 formed by the covalent association of five subunits each having a molecular weight of 180.000. Fab fragment refers to the fragment of the antibody molecule that is antigen binding. At the opposite end is the crystallizable or Fc portion with no antigen-binding activity. Proteolytic cleavage of immunoglobulins with enzymes such as papain or pepsin is what produces these fragments. The hinge region which joins the Fab arms to the Fc region contains cysteinyl residues and allows for flexibility and change of configuration from a T to Y shape.

Tests of B Cell Function

1. Measurement of serum levels of immunoglobulins by radial immunodiffusion techniques for IgG, IgA, and IgM. Serum IgE assay requires the paper radioimmunoassay test (PRIST).

2. Measurement of natural specific antibodies such as isohemagglutinins.

3. Antibody response following immunization, Schick test.

4. Presence of plasma cells.

Table 26-2. Some of the Conditions Associated with Raised Levels of Total Serum IgE

Atopic Allergic Diseases

Atopic rhinitis
Atopic asthma
Atopic dermatitis

Other Hypersensitivity Disorders

PIE syndrome
Bronchopulmonary aspergillosis
Wiskott-Aldrich syndrome

Parasitic Infestations

Visceral larva migrans (Toxocara canis)
Intestinal capillariasis (Capillaria philippinensis)
Schistosomiasis
Ascariosis
Hookworm
Echinococcosis
Trichinosis
Topical eosinophilia (filariasis)

Immunologic Deficiencies or Disorders

Thymic dysplasias or deficiencies (T-lymphocyte disorders)
Hyperimmunoglobulinemia E with recurrent pyodermas (Job-Buckley syndr)

Miscellaneous Conditions

Leprosy
Pemphigoid
Pulmonary hemosiderosis (occasionally)
Multiple myeloma
Autoimmune diseases (occasionally)
Minimal-change nephrotic syndrome (occasionally).

Disorders Affecting B Cells

Chronic or recurrent pyogenic infections with virulent extracellular bacteria such as gram-negative cocci and Haemophilus influenzae are characteristic of B cell deficiencies. Since antibodies, complement, and phagocytes work together to immobilize and destroy pathogenic organisms, the clinical manifestations of B-cell deficiencies, complement deficiencies, and phagocyte abnormalities are similar. Chronic sinopulmonary disease is

common.

Hypogammaglobulinemia can be hereditary, transient in infancy, or acquired later in life secondary to a metabolic problem, immunosuppressive agents, surgery, or systemic disease. The most common specific dysgammaglobulinemia is selective IgA deficiency.

Regulation of the immune response. What determines the degree of response or of antibody production?

1. The antigen is the first factor. A larger antigen that is aggregated or particulate produces a greater response.

2. The T cells release lymphokines which may help or suppress the immune response (antibody production. These therefore are called T cell helpers or T cell suppressors.

3. Levels of the nucleotides, cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), reflect the energy function of the principal cells involved in the immune response. Cyclic AMP is the activator of phosphorylase kinase which is important in glucose release. Increasing cytoplasmic concentration of cAMP modifies cell membrane permeability and inhibits the release of mediators. Lowering of the intracellular cAMP causes the release of mediators of anaphylaxis which then produce the pathological response.

Allergy

Allergy is defined as a hypersensitive or pathologic reaction to environmental factors or substance such as pollens, foods, dust, or microorganisms in amounts that do not affect most people. Allergy involves the release of mediators from mast cells and basophils triggered by a variety of agents and subdivided into atopic (IgE mediated) and nonatopic (non-IgE mediated)(Fig. 26-2). At least 10% of the population has some allergy-related disorder.

Historical Background

1. John Bostock 1819: Earliest description of "summer catarrh".

2. Blakeley, 1873: First skin tests for grass sensitivity.

3. Von Pirquet, 1906: Introduced the term "allergy".

4. Noon, 1911: First desensitization with pollen extract injection.

5. Prausnitz-Küstner, 1921: Passive transfer of skin sensitizing factor in serum.

6. Cooke, 1935: Blocking or inhibiting antibody in serum treated patients.

7. Rinkel, 1963: End-point intracutaneous titration (optimal dose).

8. Porter, 1959: Anatomy and functional structure of immunoglobulins.

9. Berson and Yalow, 1959: Development of radioimmunoassay techniques.

10. Wide, 1968: Assay for specific IgE antibody (RAST).

Classification of Hypersensitivity Reactions into Four Types

as Described by Gell and Coombs (Table 26-3)

Table 26-3. Gell and Coombs Classification of Hypersensitivity Reactions

I or Anaphylactic

Allergic rhinitis and conjunctivitis
Extrinsic asthma
Urticaria and angioedema (some)
Anaphylaxis (some)
Allergic bronchopulmonary aspergillosis (type III also)
Atopic eczema (?)
Drug reactions
Insect hypersensitivity.

II or Cytotoxic

&& Blood transfusion reaction (anaphylaxis)
& Hemolytic disease of the newborn
&& Isoallergic neonatal thrombocytopenia
&& Coombs positive hemolytic anemias
&& Drug-induced decreases in circulating blood cells (RBCs, WBCs, platelets)
Goodpasture's disease

III or Immune Complex or Arthus Type

Serum sickness
Lupus erythematosus
Glomerulonephritis (i.e. poststreptococcal)
Allergic bronchopulmonary aspergillosis (type I also)
Hypersensitivity pneumonitis (type IV also)
Vasculitis
Drug reactions

IV or Delayed Hypersensitivity

Contact dermatitis
Experimental allergic encephalitis
Tuberculin sensitivity
Tissue transplant rejection
Drug reactions
Hypersensitivity pneumonitis (type III also).

& Does not involve complement.
&& May or may not involve complement.

Type I Anaphylactic Reaction

The immediate type of hypersensitivity reaction occurs in about 10 minutes on introduction of an antigen into a sensitized person. This is the humoral or reaginic response. IgE antibodies attach to the membranes of mast cells and basophils, as many as 80.000 IgE molecules per cell. When two juxtaposed antigen-specific IgE molecules are attached to Fc receptors and bridged by the appropriate antigen, a series of cell surface events occurs causing the release of the vasoactive amines, primarily histamine. Relatively few specific IgE molecules thus can produce a devastatingly amplified response. Clinically this reaction is found in bronchial asthma, allergic rhinitis, urticaria, some food and drug allergies, and reactions to stinging insects.

Type II Cytotoxic Reaction

This complement-dependent reaction is slower and takes a few hours to occur. The antigen attaches to a target cell which dies in the presence of antibody and fresh complement, the complement-fixing antibody being directed against cell membranes. One can have transfusion reactions due to antibody acting with red cells, white cells, or platelets. Clinical examples are the autoimmune hemolytic anemias, poststreptococcal glomerulonephritis, and the hemolytic anemias.

Type III Toxic-Complex Reactions

Consider an antigen uniting with a circulating antibody to form a "solubable complex" or "immune complex". This type of hypersensitivity, which may take 6 hours to develop, refers to the antibody aggregates which attach to the endothelial cells of small blood vessels. An inflammatory reaction follows the realease of mediators. Clinically, we have the Arthus reaction, a local response, or serum sickness, a generalized response.

Type IV Cellular Hypersensitivity

This reaction occurs 24-72 hours after antigen introduction with no mediation by the conventional circulating antibodies. Instead the antigen acts directly with the sensitized T lymphocyte which releases SRS, kinins, and proteolytic enzymes. Examples are tubercle formation and homograft rejection.

Some Common Antigens of Allergic Importance

Pollens

Pollen grains common to all flowering plants develop in the anther or the stamen. The outermost layer, the exine is quite rigid. Within is the intine composed of cellulose which enclose the protoplast. Thommen postulated that for pollen to be symptomatic it must be allergenic, be anemophilous or windborne, sufficiently buoyant to be transported long distances and widely distributed in the ambient air.

Fungi

Fungi have nonchlorophyl, branching, filamentous hyphae which generally reproduce by spore formation. The airborne spores are the major source of inhalant exposure. Fungi recovered indoors include Penicillium, Aspergillus, and Fusarium. The most common outdoor fungi are Alternaria, Heminthosporium, and Hormodendrum.

House Dust

A heterogenous mixture of human and animal danders, fungi, bacteria, insect debris, vegetable and wood fibers, foor remnants, and inorganic substrates. The mite content of house dust may be the most important antigen but the degeneration of vegetable matter particularly cotton linters is also important.

Other Nonpollen Allergens

Consider feathers, especially old decaying ones, seeds such as cottonseed found in cotton linters and flaxseed, orris root, the powdered root of the iris family, and pyrethrum found in insecticides. Symptoms caused by tobacco may be the nonspecific irritation from smoke, a specific allergy to tobacco smoke, allergy to tobacco itself, the flavoring materials such as perfumes and oils, or to tobacco dust and associated molds.

Contact Allergens

Allergic contact dermatitis is a type IV cell-mediated delayed hypersensitivity. Contact chemicals may act as haptens combining with epidermal protein to form a complete antigen-inducing sensitization. Repeat contact induces the inflammatory reaction. The most common sensitizers are Rhus sp. or poison ivy, paraphenylenediamine used in industry, nickel compounds, rubber compounds, ethylenediamine used in medications, and dichromates used in ink and paints.

Common Food Allergens

The most common foods associated with a type I anaphylactic response are fish, eggs, nuts, and cow's milk. Type III antigen-antibody complexes produce serum sickness or an Arthus reaction. Milk precipitins have been identified. A type V reaction was recently postulated to explain the oddities of many food allergies; their cyclic nature, masking effects, and additive effects that are not explained by the Gell and Coomb Classification I-IV.

Food allergens are usually glycoproteins with a molecular weight between 18.000 and 36.000. Foods also may contain pharmacologically active substances such as vasoactive amines in bananas, cheese, and wines, and methylxanthines such as caffeine found in coffee, tea, and colas.

Salicylates

This ubiquitous medicine will occasionally produce a watery nose with obstruction and polyp formation, asthma, urticaria, plus a high eosinophil count. However, this is not IgE-

mediated since there is no skin sensitivity and no passive transfer.

Salicylates may inhibit endogenous prostaglanding production causing an imbalance.

The Allergy Workup and Additional Tests

Nasal Cytogram

1. Allergy: Increased eosinophils and goblet cells plus enlarged irregular lymphoctes.

2. Bacterial infection: Increased polys and bacteria.

3. Viral infection: Exfoliated cells with granulation and fragmentation of the cytoplasm, pyknotic nuclei, and inclusion bodies.

RAST (Table 26-4)

Table 26-4. Indications and Contraindications for Use of RAST

Indicated

In patients not responding to environmental control and conservativew medical management.

In apprehensive children and infants in whom atopic sensitization seems likely.

In symptomatic patients with conditions in which in vivo skin testing is contraindicated (dermatographism, eczema, etc.).

In patients unable to stop medication adversely affecting skin testing.

In patients doing poorly on immunotherapy.

In evaluating individual sensitivities when initiating specific immunotherapy in atopid patients.

In transfer allergic patients on immunotherapy.

In venom sensitivity.

In the diagnosis of IgE-mediated food sensitivity.

Contraindicated

In patients with positive histories of sensitivity in whom nonspecific therapy is effective in alleviating symptoms.

In asymptomatic atopic patients currently on immunotherapy.

In symptomatic patients with negative skin tests.&

In patients with total IgE levels below 10 U/mL.

In the diagnosis of non-IgE-mediated disorders.

& Properly performed at adequate concentrations with potent extracts.

This test is a unique way of measuring the IgE response to an individual antigen. There are three steps to this assay:

1. Antigen is coupled to solid phase material such as a cellulose paper disc.

2. Specific IgE antibody can react and bind to the immobilized antigens.

3. The above molecule is now the antigen for radioactive labeled antibody specific to IgE.

Skin Tests

An in vivo bioassay challenges specific IgE-sensitized mast cells in the skin. Variables are the potency and purity of the extracts, skin reactivity, age, site of application, and prior medications. Scratch and prick tests are less sensitive than intradermal tests. Serial dilution titration is an intradermal method that uses 1:5 serial dilutions of the allergen for a more accurate response.

Treatment of Allergic Problems

Although environmental control and food management play a major role in the treatment of allergic problems I have limited this chapter to the pharmacologic and immunologic approach.

Sympathomimetics

Sympathomimetics or adrenergics are classified into alpha or beta depending on their action, excitatory or inhibitory, on target organs. If we know the activity of a particular adrenergic agent we can predict its actions.

Alpha Receptors

Excitatory action constricting the vascular smooth muscles especially of the skin and mucous membranes. This action raises blood pressure, reduces edema, help hemostasis. Action on viscera is inhibitory.

Beta Receptors

Inhibitory except for the heart which is excitatory. Further classification into beta-1 and beta-2.

Beta-1 Receptors

In the heart and small intestine.

Beta-2 Receptors

In the bronchi, blood vessels and uterus.

Alpha-adrenergic agents such as phenylephrine are potent vasoconstrictors. They have no therapeutic use for asthma, but are used most often as topical or oral decongestants for the nose and eyes.

Beta-2 receptors in the bronchi are of importance for the treatment of asthma. Stimulation of the beta receptors leads to activation of adenylcyclase and an increase in cAMP. Isoproterenol is a beta-2 receptor stimulator (beta agonist) that has some beta-1 stimulation of the heart causing side effects of tachycardia, palpitations, and hypertension. Terbutaline and metaproterenol are newer beta-2 agonists with less beta-1 activity that can be given orally or by inhalation.

Epinephrine with both alpha and beta activity is the sympathomimetic of choice in an acute anaphylactic reaction. Alpha activity causes vasoconstriction with elevation of blood pressure, beta-1 activity increases heart rate and output and beta-2 activity dilates the bronchioles.

Antihistamines

Once the structure and function of histamine in inflammation and allergy was determined along came a group of compounds with a core of ethylamine (CH2-CH2N+) which competes with a similar core on the histamine molecule. Thus antihistamines block histamine at the H1 receptor site, they do not block histamine production or destroy liberated histamine.

Ethylamine Core (CH2-CH2N=X)

Six Families	X=	Example
Ethanolamines	Oxygen link	Diphenhydramine
Alkylamines	Carbon link	Chlorpheniramine
Ethylendiamines	Nitrogen link	Tripelenamine
Piperazines	Piperazine link	Hydroxyzine
Phenothiazines	Phenothiazine	Promethazine
Miscellaneous		Clemastine.

Antihistamines are of value in the treatment of urticaria, anaphylaxis, allergic angioedema, pruritus, rhinitis, and the common cold. Adverse reactions are diverse and include sedation, dizziness, nervousness, anorexia, dryness of mouth, and hypotension.

Heparin

When dealing with an acute anaphylactic emergency type I such as acute asthma or angioneurotic edema that is not responding to epinephrine and antihistamines it is worthwhile having heparin in your armamentarium.

An acid polysaccharide, heparin combines with alkaline histamine to form a neutral salt. In fact, histamine is naturally stored in the mast cell granules as a heparin-histamine salt. Heparin also may inhibit the early stages of the complement cascade. Apparently heparin does not neutralize the effect of slower-acting serotonin or the kinins and therefore is only effective very early in an allergic emergency.

Cromolyn

Cromolyn acts directly on mast cells and basophils in same manner to prevent degranulation and release of mediator histamine and SRS in atopy and anaphylaxis. Cromolyn stabilizes the mast cell membrane. Available as a powder administered by a "spinhaler", cromolyn is of value in preventing an asthmatic attach but is of no use once an attach has begun.

Corticosteroids

These drugs, so useful in medicine, have the ability to control inflammation temporarily and therefore have an important role in immunology and allergy. The exact mode of action is unknown but the following beneficial effects occur.

1. Affect the sodium and potassium pump reducing water uptake and edema.

2. Reduction of capillary permeability.

3. Stabilization of lysosomal membranes preventing release of mediators.

4. Possibly augment adrenergic stimulation of adenylcyclase increasing cAMP.

Unfortunately there are several complications to consider when prescribing corticosteroids for any length of time, including sodium retention and potassium loss, creating fluid and electrolyte imbalance, gastrointestinal irritation, muscle weakness, osteoporosis, growth suppression, adrenal suppression, diabetes, glaucome, cataracts, and increased susceptibility to infection.

The steroids dexamethasone, beclomethasone, and flunisolide have been developed as aerosol medications for asthma or rhinitis therapy. There is an active topical effect to control local symptoms of allergy without the usual systemic effects mentioned above.

Theophylline

The methylxanthines, of which theophylline is the most important, are competitive inhibitors of phosphodiesterase that catalyzes the conversion of cAMP to inactive 5-AMP.

Since methylxanthines prevent the destruction of cAMP while the beta agonists (i.e. metaproterenol) increase cAMP production via the enzyme adenylcyclase, there is a complementary effect when used together.

To relax bronchial smooth muscle by the above means the theophylline serum level must reach 10-20 microg/mL. Toxic effects to consider are central nervous system and cardiovascular stimulation, gastrointestinal irritation, renal albuminuria and hematuria, and diuresis causing dehydration.

Immunotherapy

Although there has been controversy over the efficacy of immunotherapy there is mounting evidence that a number of beneficial immune changes do occur.

1. Increase of IgG blocking antibodies in the serum.

2. Stimulation of IgA- and IgG-blocking antibodies in secretions.

3. Suppression of antigen-specific IgE antibodies.

4. Decrease in proliferative response of T cells.

Immunotherapy should be considered an adjunct to total allergic management that can help control but not cure symptoms (Table 26-5). In the future we may be dealing with allergoids (formalin-modified antigens); urea-denatured antigens, or polymerized antigens now being designed to reduce their allergenic properties while stimulating protective antibodies.

Table 26-5. Indications and Contraindications for Immunotherapy

Indications

Symptoms initiated by IgE antibodies.
Respiratory allergy: perennial nasal allergy, seasonal hay fever, bronchial asthma.
Severe symptoms - not controlled by mediaations and avoidance.
Long seasons.
Multiple seasons.
Perennial symptoms.

Complications:

Recurrent infections.
Serous otitis media or hearing loss.
Asthma.
Increased morbidity.
Increased absenteeism.
Decreased quality of life.
Intolerance to antiallergic drugs.

Contraindications

Nonimmune mechanisms responsible for symptoms.

IgE-mediated mechanism:

Mild symptoms - readily controlled by simple methods.
Easily avoidable allergen.
Atopic dermatitis.
Gastrointestinal food allergies.
Very short seasons.
Noncompliant patients.
Food allergy.

Relative Contraindications:

Infants and children under 2 years of age.
IgE-mediated drug and chemical sensitivity.