Fig. 19.5 IgE-mediated reactions to extrinsic antigens. All IgE-mediated responses involve mast-cell degranulation, but the symptoms experienced by the patient can be very different depending on whether the allergen is injected, inhaled, or eaten, and depending on the dose of the allergen.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common allergens</th>
<th>Route of entry</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic anaphylaxis</td>
<td>Drugs, Serum, Venoms, Peanuts</td>
<td>Intravenous (either direct or following rapid absorption)</td>
<td>Edema, Increased vascular permeability, Tracheal occlusion, Circulatory collapse, Death</td>
</tr>
<tr>
<td>Acute urticaria</td>
<td>Insect bites, Allergy testing</td>
<td>Subcutaneous</td>
<td>Local increase in blood flow and vascular permeability</td>
</tr>
<tr>
<td>(wheat-and-flare)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Pollens (ragweed, timothy, birch), Dust-mite feces</td>
<td>Inhaled</td>
<td>Edema of nasal mucosa, Irritation of nasal mucosa</td>
</tr>
<tr>
<td>(hay fever)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Danders (cat), Pollens, Dust-mite feces</td>
<td>Inhaled</td>
<td>Bronchial constriction, Increased mucus production, Airway inflammation</td>
</tr>
<tr>
<td>Food allergy</td>
<td>Tree nuts, Peanuts, Shellfish, Milk, Eggs, Fish, Wheat</td>
<td>Oral</td>
<td>Vomiting, Diarrhea, Pruritis (itching), Urticaria (hives), Anaphylaxis (rarely)</td>
</tr>
</tbody>
</table>

The case of Frank Morgan: a 14-year-old boy with chronic asthma and rhinitis.

Frank Morgan was referred by his pediatrician to the allergy clinic at age 14 years because of persistent wheezing for 2 weeks. His symptoms had not responded to frequent inhalation treatment (every 2–3 hours) with a bronchodilator, the β2-adrenergic agent albuterol (salbutamol).

This was not the first time that Frank had had respiratory problems. His first attack of wheezing occurred when he was 3 years old, after a visit to his grandparents who had recently acquired a dog. He had similar attacks of varying severity on subsequent visits to his grandparents. Beginning at age 4, he had attacks of coughing and wheezing every spring (April and May) and towards the end of the summer (second half of August and September). A sweat test at age 5 to rule out cystic fibrosis, a possible cause of chronic respiratory problems, was within the normal range.

As Frank got older, gym classes, basketball, and soccer games, and just going out of doors during the cold winter months could bring on coughing and sometimes wheezing. He had been able to avoid wheezing induced by exercise by inhaling albuterol 15–30 minutes before taking exercise. Frank had frequently suffered from a night cough and his colds had often been complicated by wheezing.

Frank’s chest symptoms have been treated as needed with bronchodilators such as oral theophylline and/or oral or inhaled albuterol. During the past 10 years Frank has been admitted three times to hospital for treatment of his asthma with inhaled bronchodilators and intravenous steroids. He has also made many emergency
visits with severe asthma attacks. He has had maxillary sinusitis at least three times, ascertained by the presence of fluid in the cavity of his maxillary sinuses, which shows up on the radiographs, each episode associated with exacerbation of his asthma and a green nasal discharge.

Since he was 4 years old Frank has also suffered from intermittent sneezing, nasal itching, and nasal congestion (rhinitis), which always worsens upon exposure to cats and dogs and in the spring and late summer. His face also swells up on exposure to a cat or a dog. The nasal symptoms have been treated as needed with oral antihistamines with moderate success. Frank had eczema as a baby but this cleared up by age 5.

Family history revealed that Frank’s only sibling (a 10-year-old sister), his mother and his maternal grandfather all have asthma. Frank’s mother, father, and paternal grandfather suffer from allergic rhinitis.

When he arrived at the allergy clinic, Frank was thin and unable to breathe easily. He had no fever. The nasal mucosa was severely congested, and wheezing could be heard over all the lung fields. Lung function tests were consistent with obstructive lung disease with a reduced peak flow rate (PFR) of 180 liter min⁻¹ (normal >350–400 liter min⁻¹) and expiratory volume in the first second of expiration (FEV₁) was reduced to 50% of that predicted for his sex, age, and height. A chest radiograph showed hyperinflation of the lungs and increased markings around the airways (Fig. 19.6).

A complete blood count was normal except for a high number of circulating eosinophils (1200 μl⁻¹; normal range <400 μl⁻¹). Serum IgE was high at 1750 international units ml⁻¹ (normal less than 200 units ml⁻¹). Radioallergosorbent assays (RAST) for antigen-specific IgE revealed IgE antibodies to dog and cat dander, dust mites, tree grass, and ragweed pollens in Frank’s serum. Levels of immunoglobulins IgG, IgA, and IgM were normal. Histological examination of Frank’s nasal fluid showed the presence of eosinophils.

Frank was given immediate inhalation treatment of 0.25 ml of the bronchodilator Ventolin (albuterol sulfate) at the clinic, after which he felt better, his PFR rose to 400 liter min⁻¹ and his FEV₁ rose to 65% of predicted. He was sent home on a 1-week course of the corticosteroid prednisone, taken orally in two doses daily, totalling 1 mg kg⁻¹ body weight per day. He was told to inhale albuterol three times a day with extra doses if needed but not more than every 4 hours. He was also put on inhaled Intal (disodium cromoglycate), a drug that decreases mast cell granule release and inhibits allergen-induced airway reactivity. To relieve his nasal congestion, Frank was given disodium cromoglycate and the steroid beclomethasone (Beconase, Vancenase) to inhale through the nose, and was advised to use an oral antihistamine as needed. He was asked to return to the clinic 2 weeks later for follow-up, and for immediate hypersensitivity skin tests to try to detect to which antigens he was allergic (Fig. 19.7).

On the next visit Frank had no symptoms except for a continually stuffy nose. His PFR and FEV₁ were normal. He was maintained on inhaled disodium cromoglycate and beclomethasone, and advised to inhale albuterol as needed. Skin tests for type I hypersensitivity were positive for multiple tree and grass pollens, dust mites, and dog and cat dander. He was advised to avoid contact with cats and dogs. To reduce his exposure to dust mites the pillows and mattresses in his room were covered with zippered plastic covers. Rugs, stuffed toys, and books were removed from his bedroom. He was also started on immunotherapy with injections of grass, tree, and ragweed pollens, and house dust mite antigens, to try to reduce his sensitivity to these antigens.

A year and a half later Frank’s asthma continues to be stable with occasional use of albuterol during upper respiratory tract infections and in the spring. His rhinitis and nasal congestion now require much less medication.
Allergic asthma.

Millions of adults and children like Frank suffer from allergic asthma. About 70% of patients with asthma have a family history of allergy. This genetic predisposition to develop allergic diseases is called atopy. Wheezing and coughing are the main symptoms of asthma, and both are due to the forced expiration of air through airways that have become temporarily narrowed by constriction of smooth muscle as a result of the allergic reaction. As a consequence of the narrowed airways, air gets trapped in the lung and the lung volume is increased during an attack of asthma.

Once asthma is established, an asthma attack can be triggered not only by the allergen but by viral infection, cold air, exercise, or pollutants such as sulfur dioxide. This is due to a general hyperirritability of the airway, which leads it to constrict in response to nonspecific shocks and irritants, reducing the airflow. The degree of hyperirritability can be measured by determining the threshold dose of inhaled metacholine (a cholinergic agent) or histamine that results in a 20% reduction in airway flow. Airway irritability correlates positively with serum IgE levels.

Although asthma is a reversible disease, a severe attack can be fatal. The mortality from asthma has been rising alarmingly in recent years. Three classes of drugs are commonly used to treat it. Disodium cromoglycate reduces airway irritability by inhibiting the release of chemical mediators (e.g., histamine) from mast cells and therefore inhibits both the immediate and late phases of the allergic reaction. The precise mechanism of action of this drug is unknown. β2 agonists (e.g., albuterol) bind to the β2-adrenergic receptor, which is expressed on the surface of bronchial smooth muscle cells. β2 agonists relax smooth muscle and thus rapidly relieve airway constriction, and are helpful in treating the immediate phase of the allergic reaction in the lungs. Anti-inflammatory corticosteroids (e.g., oral prednisone and inhaled beclomethasone) inhibit the cells involved in airway inflammation and are most useful in the late phase of the allergic reaction. The treatment of allergic asthma also includes minimizing exposure to allergens, and trying to desensitize the patient by immunotherapy.

Discussion and questions.

1. Explain the basis of Frank’s chest tightness and radiograph findings.

During inspiration, the negative pressure on the airways causes their diameter to increase, allowing inflow of air. During expiration, the positive expiratory pressure tends to narrow the airways. This narrowing is exaggerated when the airway is inflamed and bronchial smooth muscle is constricted, as in asthma. This causes air to be trapped in the lungs with an increase in residual lung volume at the end of expiration. Breathing at high residual lung volume means more work for the muscles and increased expenditure of energy; this results in the sensation of tightness in the chest. The high residual lung volume is also the cause of the hyperinflated chest observed on the chest radiograph. The peribronchial inflammation in asthma causes bronchial marking around the airways.
2. Explain the failure of Frank’s asthma to improve despite the frequent use of bronchodilators, and his response to steroid therapy.

Chronic allergic asthma is not simply due to constriction of the smooth muscles that surround the airway. It is largely due to the inflammatory reaction in the airway, which consists of cellular infiltration, increased secretion of mucus, and swelling of the bronchial tissues. This explains the failure of bronchodilators, which dilate smooth muscles, to maintain an open airway and their failure to reverse completely the decreased air flow during Frank’s acute attacks. Steroids are therefore given to combat the inflammatory reaction of the late-phase response.

3. Many members of Frank’s family are predisposed to develop IgE-mediated allergic responses, a condition known as atopy. What is the basis for this familial predisposition?

Analysis of the genetic linkage of atopy to various polymorphic DNA markers suggests that this trait maps to chromosome 5q11 in the area containing the genes for IL-4, IL-5, and IL-9, cytokines that are involved in regulating the IgE response. Because IL-4 is required to induce B cells to undergo isotype switching to IgE, it is possible that the underlying cause of the high IgE levels in atopic individuals is the excessive production of IL-4.

4. Eosinophilia (Fig. 19.8) is often detected in the blood and in the nasal and bronchial secretions of patients with allergic rhinitis and asthma. What is the basis for this finding?

Allergic individuals have a tendency to respond to allergens with an immune response skewed to producing Th2 cells rather than Th1. The cells produce the interleukins IL-4 and IL-13, cytokines that induce IgE production in humans. Th2 cells also make IL-5, which is essential for eosinophil maturation. Furthermore, activated T cells and bronchial epithelial cells secrete eotaxin, which attracts eosinophils in the airways. Production of IL-4 and IL-5 by Th2 cells responding to allergens in atopic individuals explains the frequent association of IgE antibody response and eosinophilia in these patients.

5. What is the basis of the wheal-and-flare reaction that appeared 20 minutes after Frank had had a skin test for hypersensitivity to ragweed pollen?

IgE-mediated hypersensitivity to an allergen is tested for by injecting a small amount of the allergen intradermally. In allergic individuals, this is followed within 10-20 minutes by a wheal-and-flare reaction at the site of injection (see Fig. 19.7), which subsides within an hour. The wheal-and-flare reaction is due mainly to the release of histamine by mast cells in the skin. This increases the permeability of blood vessels and leakage of their contents into the tissues, resulting in the swollen wheal; dilation of the fine blood vessels around the area produces the diffuse red ‘flare’ seen around the wheel. This reaction is almost completely inhibited by antagonists to the histamine type 1 receptor, the major histamine receptor expressed in the skin.

6. Frank called 24 hours after his skin test to report that redness and swelling had recurred at several of the skin test sites. Explain this observation.
The recurrence of the redness and swelling at the site of previous immediate allergic reactions represents the late-phase response characterized by a cellular infiltrate.

7. Frank asks to be skin tested for sensitivity to rabbits because he wishes to have a rabbit as a pet. What do you do?

Because Frank has made IgE antibodies to numerous allergens, it is very likely that should he become exposed to a rabbit, he would mount an IgE antibody response to rabbit allergens, which would probably cause allergic symptoms. A negative skin test would probably simply reflect the fact that Frank has not yet been exposed to rabbit allergens. Therefore Frank should be advised not to get a rabbit regardless of the result of the skin test.

8. How would the immunotherapy that Frank received help to alleviate his allergies?

Repeated administration of relatively high doses of antigen by subcutaneous injection is thought to favor antigen presentation by antigen-presenting cells that produce IL-12. This results in the induction of inflammatory CD4 T cells (Th1 cells) rather than Th2 cells. The presence of Th1 cells tends to lead to an IgG antibody response rather than an IgE response, as the Th1 cells produce interferon-γ, which prevents further isotype switching to IgE. The IgG antibody competes for antigen with IgE. Furthermore, IgG bound to allergen inhibits mast-cell activation (via FceRI) and B-cell activation (via surface Ig) by allergen because of inhibitory signals delivered subsequent to binding of Fcγ receptors on these cells. This is thought to be one mechanism damping down the allergic response. Another is no further boosting of IgE production as IL-4 and IL-13 are not secreted. Existing IgE levels themselves may not fall by much, as IFN-γ does not affect B cells that have already switched to IgE production.

9. Although atopic children are repeatedly immunized with protein antigens such as tetanus toxoid, they almost never develop allergic reactions to these antigens. Explain.

Most human allergy is caused by a limited number of inhaled protein allergens that elicit a Th2 response in genetically predisposed individuals. These allergens are relatively small, highly soluble protein molecules that are presented to the immune system by the mucosal route at very low doses. It has been estimated that the maximum exposure to ragweed pollen allergens is less than 1 μg per year. It seems that transmucosal presentation of very low doses of allergens favors activation of IL-4-producing Th2 cells and is particularly efficient at inducing IgE responses. The dominant antigen-presenting cell type in the respiratory mucosa expresses high levels of costimulatory B7.2 molecules. Expression of B7.2 on antigen-presenting cells is thought to favor the development of Th2 cells. In contrast, injection of antigen subcutaneously in large doses, as occurs on vaccination, results in antigen uptake in the local lymph nodes by a variety of antigen-presenting cells and favors the development of Th1 cells, which inhibit antibody switching to IgE.