The adaptive immune response is a critical component of host defense against infection and is essential for normal health. Unfortunately, adaptive immune responses are also sometimes elicited by antigens not associated with infectious agents, and this can cause serious disease. One circumstance in which this occurs is when harmful immune reactions known generally as hypersensitivity reactions are made in response to inherently harmless ‘environmental’ antigens such as pollen, food, and drugs.

Hypersensitivity reactions were classified into four types by Coombs and Gell (Fig. 13.1). Allergy, the commonest type of hypersensitivity, is often equated with type I hypersensitivity reactions, which are immediate-type hypersensitivity reactions mediated by IgE antibodies, but many of the allergic diseases discussed below also have features characteristic of other types of hypersensitivity, particularly of T cell-mediated type IV hypersensitivity reactions. In the majority of allergies, such as those to food, pollen, and house dust, reactions occur because of the individual has become sensitized to an innocuous antigen—the allergen—by producing IgE antibodies against it. Subsequent exposure to the allergen triggers the activation of IgE-binding cells, including mast cells and basophils, in the exposed tissue, leading to a series of responses that are characteristic of allergy and are known as allergic reactions. Allergic reactions can, however, be independent of IgE; T lymphocytes have the predominant role in allergic contact dermatitis.
The biological role of IgE is in protective immunity, especially in response to parasitic worms, which are prevalent in less developed countries. In the industrialized countries, allergic IgE responses to innocuous antigens predominate and are an important cause of disease (Fig. 13.2). Almost half the population of North America and Europe have allergies to one or more common environmental antigens and, although rarely life-threatening, these cause much distress and lost time from school and work. Much more is known about the pathophysiology of IgE-mediated responses than about the normal physiological role of IgE, probably because the prevalence of allergy in industrialized societies has doubled in the past 10–15 years.

In this chapter we first consider the mechanisms that favor the sensitization of an individual to an allergen through the production of IgE. We then describe the allergic reaction itself—the pathological consequences of the interaction between allergen and the IgE bound to the high-affinity Fcε receptor on mast cells and basophils. Finally, we consider the causes and consequences of other types of immunological hypersensitivity reactions.
IgE is produced both by plasma cells in lymph nodes draining the site of antigen entry and by plasma cells at the site of the allergic reaction, where germinal centers develop within the inflamed tissue. IgE differs from other antibody isotypes in being predominantly localized in tissues, where it is tightly bound to mast-cell surfaces through the high-affinity IgE receptor FcεRI (see Section 9-22). Binding of antigen to IgE cross-links these receptors, causing the release of chemical mediators from the mast cells that can lead to a type I hypersensitivity reaction. Basophils also express FcεRI and so can display surface-bound IgE and take part in type I hypersensitivity reactions. How an initial antibody response comes to be dominated by IgE is still being worked out. In this part of the chapter we describe the current understanding of the factors that contribute to this process.

13-1 Allergens are often delivered transmucosally at low dose, a route that favors IgE production.

Certain antigens and routes of antigen presentation to the immune system favor the production of IgE, which is driven by CD4 Th2 cells (see Section 9-9). Much human allergy is caused by a limited number of small inhaled proteins that reproducibly elicit IgE production in susceptible individuals. We inhale many different proteins that do not induce IgE production; this raises the question of what is unusual about those proteins that are common allergens. Although we do not yet have a complete answer, some general properties have emerged (Fig. 13.3). Most allergens are relatively small,
highly soluble proteins that are carried on dry particles such as pollen grains or mite feces. On contact with the mucosa of the airways, for example, the soluble allergen elutes from the particle and diffuses into the mucosa. Allergens are typically presented to the immune system at very low doses. It has been estimated that the maximum exposure of a person to the common pollen allergens in ragweed (*Ambrosia* species) does not exceed 1 μg per year. Yet many people develop irritating and even life-threatening Th2-driven IgE antibody responses to these minute doses of allergen. It should be emphasized, however, that only some people who are exposed to these substances make IgE antibodies against them.

It seems likely that presenting an antigen across a mucosal epithelium and at very low doses is a particularly efficient way of inducing Th2-driven IgE responses. IgE antibody production requires help from Th2 cells that produce interleukin-4 (IL-4) and IL-13, and it can be inhibited by Th1 cells that produce interferon-γ (IFN-γ) (see Fig. 9.13). Low doses of antigen can favor the activation of Th2 cells over Th1 cells (see Section 10-5), and many common allergens are delivered to the respiratory mucosa by the inhalation of a low dose. In the respiratory mucosa these allergens encounter dendritic cells that take up and process protein antigens very efficiently and thus become activated. In some circumstances, mast cells and eosinophils can also present antigen to T cells and promote the differentiation of Th2 cells.

13-2 Enzymes are frequent triggers of allergy.

Several lines of evidence suggest that the natural role of IgE is in the defense against parasitic worms (see Section 11-16). Many of these invade their hosts by secreting proteolytic enzymes that break down connective tissue and allow the parasite access to internal tissues, and it has been proposed that these enzymes are particularly active at promoting Th2 responses. This idea receives some support from the many examples of allergens that are enzymes. The major allergen in the feces of the house dust mite (*Dermatophagoides pteronyssimus*), which is responsible for allergy in about 20% of the North American population, is a cysteine protease known as Der p 1. This enzyme has been found to cleave occludin, a protein component of intercellular tight junctions. This reveals one possible reason for the allergenicity of certain enzymes. By destroying the integrity of the tight junctions between epithelial cells, Der p 1 may gain abnormal access to subepithelial antigen-presenting cells, resident mast cells, and eosinophils (Fig. 13.4).
The tendency of proteases to induce IgE production is highlighted by individuals with Netherton’s disease (Fig. 13.5), which is characterized by high levels of IgE and multiple allergies. The defect in this disease is the lack of a protease inhibitor called SPINK5, which is thought to inhibit the proteases released by bacteria such as Staphylococcus aureus, thus raising the possibility that protease inhibitors might be novel therapeutic targets in some allergic disorders. The cysteine protease papain, derived from the papaya fruit, is used as a meat tenderizer and causes allergy in workers preparing the enzyme; such allergies are called occupational allergies. Not all allergens are enzymes, however; two allergens identified from filarial worms are enzyme inhibitors, for example. Many protein allergens derived from plants have been identified and sequenced, but their biochemical functions are currently obscure. Thus, there seems to be no systematic association between enzymatic activity and allergenicity.

Knowledge of the identity of allergenic proteins can be important to public health and can have economic significance, as illustrated by the following cautionary tale. Some years ago, the gene for a protein from brazil nuts that encodes a protein rich in methionine and cysteine was transferred by genetic engineering into soy beans intended for animal feed. This was done to improve the nutritional value of soy beans, which are intrinsically poor in these sulfur-containing amino acids. This experiment led to the discovery that the protein, 2S albumin, was the major brazil nut allergen. Injection of extracts of the genetically modified soy beans into the epidermis triggered an allergic skin response in people with an allergy to brazil nuts. As there could be no guarantee that the modified soy beans could be kept out of the human food chain if they were produced on a large scale, development of this genetically modified food was abandoned.

13-3 Class switching to IgE in B lymphocytes is favored by specific signals.

The immune response leading to IgE production is driven by two main groups of signals. The first consists of the signals that favor the differentiation of naive T cells to a T_{H2} phenotype. The second comprises the action of cytokines and co-stimulatory signals from T_{H2} cells that stimulate B cells to switch to the production of IgE antibodies.

The fate of a naive CD4 T cell responding to a peptide presented by a dendritic cell is determined by the cytokines it is exposed to before and during this response, and by the intrinsic properties of the antigen, the antigen dose, and the route of presentation. Exposure to IL-4, IL-5, IL-9, and IL-13 favors the development of T_{H2} cells, whereas IFN-γ and IL-12 (and its relatives IL-23 and IL-27) favor T_{H1}-cell development (see Section 8-19). Immune defenses against multicellular parasites are found mainly at the sites of parasite entry—under the skin and in the mucosal-associated lymphoid tissues of the airways and the gut. Cells of the innate and adaptive immune systems at these sites are specialized to secrete cytokines that promote a T_{H2}-cell response. Dendritic cells taking up antigen in these tissues migrate to regional lymph nodes, where they tend to drive antigen-specific naive CD4 T cells to become effector T_{H2} cells; T_{H2} cells themselves secrete IL-4, IL-5, IL-9, and IL-13, thus maintaining an environment in which further differentiation of T_{H2} cells is favored.

There is evidence that the mix of cytokines and chemokines in the environment polarizes both dendritic cells and T cells in respect of T_{H2} differentiation. The chemokines CCL2, CCL7, and CCL13, for example, act on activated monocytes to suppress their production of IL-12, and thereby promote T_{H2} responses. In general, however, it seems that an interaction between antigen-presenting...
dendritic cells and naive T cells in the absence of inflammatory stimuli induced by bacterial or viral infection tends to polarize T-cell differentiation toward TH2 cells. In contrast, if antigen is encountered by dendritic cells in the context of pro-inflammatory signals, then the dendritic cells are stimulated to produce TH1-polarizing cytokines such as IL-12, IL-23, and IL-27.

The cytokines and chemokines produced by TH2 cells both amplify the TH2 response and stimulate the class switching of B cells to IgE production. As we saw in Chapter 9, IL-4 or IL-13 provide the first signal that switches B cells to IgE production. Cytokines IL-4 and IL-13 activate the Janus-family tyrosine kinases Jak1 and Jak3 (see Section 6-23), which ultimately leads to phosphorylation of the transcriptional regulator STAT6 in T and B lymphocytes. Mice lacking functional IL-4, IL-13, or STAT6 have impaired TH2 responses and impaired IgE switching, demonstrating the key importance of these cytokines and their signaling pathways. The second signal is a co-stimulatory interaction between CD40 ligand on the T-cell surface and CD40 on the B-cell surface. This interaction is essential for all antibody class switching; patients with the X-linked hyper IgM syndrome have a deficiency of CD40 ligand and produce no IgG, IgA, or IgE (see Section 12-10).

The IgE response, once initiated, can be amplified by mast cells and basophils, which also drive IgE production (Fig. 13.6). These cells express FceRI, and when they are activated by antigen cross-linking their FceRI-bound IgE, they express cell-surface CD40 ligand and secrete IL-4. Like TH2 cells, therefore, they can drive class switching and IgE production by B cells. The interaction between these specialized granulocytes and B cells can occur at the site of the allergic reaction, because B cells are observed to form germinai centers at inflammatory foci. One goal of therapy for allergies is to block this amplification process and thus prevent allergic reactions from becoming self-sustaining.

13-4 Both genetic and environmental factors contribute to the development of IgE-mediated allergy.

Studies have found that as many as 40% of people in the populations of Western industrialized countries show an exaggerated tendency to mount IgE responses to a wide variety of common environmental allergens. This state is called atopy, has a strong familial basis, and is influenced by several genetic loci. Atopic individuals have higher total levels of IgE in the circulation and higher levels of eosinophils than their normal counterparts and are more susceptible to allergic diseases such as hay fever and asthma. Environment and genetic variation each account for about 50% of the risk of allergic diseases such as asthma. Genome-wide linkage scans have uncovered a number of distinct susceptibility genes for the allergic diseases atopic dermatitis and...
asthma, although there is little overlap between the two, suggesting that the genetic predisposition differs somewhat (Fig. 13.7). In addition, there are many ethnic differences in the susceptibility genes for the same disease. Several of the chromosome regions associated with allergy or asthma are also associated with the inflammatory disease psoriasis and autoimmune diseases, suggesting the presence of genes that are involved in exacerbating inflammation (see Fig. 13.7).

One candidate susceptibility gene for asthma and atopic dermatitis, at chromosome 11q12–13, encodes the β subunit of the high-affinity IgE receptor (FcεRI). Another region of the genome associated with disease, 5q31–33, contains at least four types of candidate gene that might be responsible for increased susceptibility. First, there is a cluster of tightly linked genes for cytokines that promote TH2 responses by enhancing IgE class switching, eosinophil survival, and mast-cell proliferation. This cluster includes the genes for IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte–macrophage colony-stimulating factor (GM-CSF). In particular, genetic variation in the promoter region of the IL-4 gene has been associated with raised IgE levels in atopic individuals. The variant promoter directs increased expression of a reporter gene in experimental systems and thus might produce increased IL-4 \textit{in vivo}. Atopy has also been associated with a gain-of-function mutation of the α subunit of the IL-4 receptor that causes increased signaling after ligation of the receptor.

A second set of genes in this region of chromosome 5 is the TIM family (for T cell, immunoglobulin domain and mucin domain), which encode T-cell

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Fig. 13.7 Susceptibility loci identified by genome screens for asthma, atopic dermatitis, and other immune disorders. Only loci with significant linkages are indicated. Clustering of disease-susceptibility genes is found for the MHC on chromosome 6p21, and also in several other genomic regions. There is in fact little overlap between susceptibility genes for asthma and atopic dermatitis, suggesting that specific genetic factors are involved in both. There is also some overlap between susceptibility genes for asthma and those for autoimmune diseases, and between those for the inflammatory skin disease psoriasis and atopic dermatitis. Adapted from Cookson, W.: Nat. Rev. Immunol. 2004, 4:978–988.
surface proteins. In mice, Tim-3 protein is specifically expressed on T\textsubscript{H}1 cells and negatively regulates T\textsubscript{H}1 responses, whereas Tim-2 (and to a lesser extent Tim-1) is preferentially expressed in, and negatively regulates, T\textsubscript{H}2 cells. Mouse strains that carry different variants of the TIM genes differ both in their susceptibility to allergic inflammation of the airways and in the production of IL-4 and IL-13 by their T cells. Inherited variation in the TIM genes in humans has been correlated with levels of airway hyperreactivity, the condition in which a nonspecific irritant causes contraction of bronchial smooth muscle similar to that seen in asthma. The third candidate susceptibility gene in this part of the genome encodes p40, one of the two subunits of IL-12. This cytokine promotes T\textsubscript{H}1 responses, and genetic variation in p40 expression that could cause reduced production of IL-12 was found to be associated with more severe asthma. A fourth candidate susceptibility gene, that encoding the \( \beta \)-adrenergic receptor, is encoded in this region. Variation in this receptor might be associated with alteration in smooth muscle responsiveness to endogenous and pharmacological ligands.

This complexity illustrates a common challenge in identifying the genetic basis of complex disease traits. Relatively small regions of the genome, identified as containing genes for altered disease susceptibility, may contain many good candidates, judging by their known physiological activities. Identifying the correct gene, or genes, may require studies of several very large populations of patients and controls. For chromosome 5q31–33, for example, it is still too early to know how important each of the different polymorphisms is in the complex genetics of atopy.

A second type of inherited variation in IgE responses is linked to the HLA class II region (the human MHC class II region) and affects responses to specific allergens, rather than a general susceptibility to atopy. IgE production in response to particular allergens is associated with certain HLA class II alleles, implying that particular peptide:MHC combinations might favor a strong T\textsubscript{H}2 response; for example, IgE responses to several ragweed pollen allergens are associated with haplotypes containing the HLA class II allele \( DRB1^*1501 \). Many people are therefore generally predisposed to make T\textsubscript{H}2 responses and are specifically predisposed to respond to some allergens more than others. However, allergies to drugs such as penicillin show no association with HLA class II or the presence or absence of atopy.

There are also likely to be genes that affect only particular aspects of allergic disease. In asthma, for example, there is evidence that different genes affect at least three aspects of the disease—IgE production, the inflammatory response, and clinical responses to particular treatments. Polymorphism of the gene on chromosome 20 encoding ADAM33, a metalloproteinase expressed by bronchial smooth muscle cells and lung fibroblasts, has been associated with asthma and bronchial hyperreactivity. This is likely to be an example of genetic variation in the pulmonary inflammatory response and in the pathological anatomical changes that occur in the airways (airway remodeling), leading to increased susceptibility to asthma. Some of the best-characterized genetic polymorphisms of candidate genes associated with asthma are shown in Fig. 13.8, together with possible ways in which the genetic variation might affect the type of disease that develops and its response to drugs.

The prevalence of atopic allergy, and of asthma in particular, is increasing in economically advanced regions of the world, an observation that is best explained by environmental factors. The four main candidate environmental factors are changes in exposure to infectious diseases in early childhood, environmental pollution, allergen levels, and dietary changes. Pollution has been blamed for an increase in the incidence of non-allergic cardiopulmonary diseases such as chronic bronchitis, but an association with allergy...
has been less easy to demonstrate. There is, however, increasing evidence for
an interaction between allergens and pollution, particularly in genetically
sensitive individuals. Diesel exhaust particles are the best-studied pollutant
in this context; they increase IgE production 20–50-fold when combined with
allergen, with an accompanying shift to TH2 cytokine production. Reactive
oxidant chemicals seem to be generated and individuals less able to deal with
this onslaught may be at increased risk of allergic disease. Genes that might
be governing this susceptibility are \textit{GSTP1} and \textit{GSTM}, the members of the
glutathione-S-transferase superfamily, as people with variant alleles of these
genes showed airway hyperreactivity when exposed to allergen. Indeed,
genetic factors may explain why the epidemiological evidence for an associ-
ation between pollution and allergy remains moderate at best, as it may only
apply to genetically sensitive individuals.

A decrease in exposure to microbial pathogens as a possible cause of the
increase in allergy has also received much attention since the idea was first
mooted in 1989. This is known as the ‘hygiene hypothesis’ (Fig. 13.9). The
proposition is that less hygienic environments, specifically environments
that predispose to infections early in childhood, help to protect against atopy
and asthma. This implies that TH2 responses predominate over TH1
responses by default in early childhood, and that the immune system is
reprogrammed toward more TH1-dominated responses by the cytokine
response to early infections.

There is much evidence in support of this hypothesis, but also some obser-
vations that are difficult to reconcile with it. In favor, there is evidence for a
bias toward TH2 responses in newborn infants, in whom dendritic cells pro-
duce less IL-12 and T cells produce less IFN-\(\gamma\) than in older children and
adults. There is also evidence that exposure to childhood infections, with the
important exception of some respiratory infections that we consider below,
helps to protect against the development of atopic allergic disease. Younger

\begin{table}[h]
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\begin{tabular}{|l|l|l|}
\hline
Gene & Nature of polymorphism & Possible mechanism of association \\
\hline
IL-4 & Promoter variant & Variation in expression of IL-4 \\
\hline
IL-4 receptor \(\alpha\) chain & Structural variant & Increased signaling in response to IL-4 \\
\hline
High-affinity IgE receptor \(\beta\) chain & Structural variant & Variation in consequences of IgE ligation by antigen \\
\hline
MHC class II genes & Structural variants & Enhanced presentation of particular allergen-derived peptides \\
\hline
T-cell receptor \(\alpha\) locus & Microsatellite markers & Enhanced T-cell recognition of certain allergen-derived peptides \\
\hline
ADAM33 & Structural variants & Variation in airway remodeling \\
\hline
\(\beta_2\)-Adrenergic receptor & Structural variants & Increased bronchial hyperreactivity* \\
\hline
5-Lipoxigenase & Promoter variant & Variation in leukotriene production† \\
\hline
TIM gene family & Promoter and structural variants & Regulation of the TH1/TH2 balance \\
\hline
\end{tabular}
\caption{Candidate susceptibility genes for asthma. *May also affect response to bronchodilator therapy with \(\beta_2\)-adrenergic agonists. †Patients with alleles associated with reduced enzyme production failed to show a beneficial response to a drug inhibitor of 5-lipoxygenase. This is an example of a pharmacogenetic effect, in which genetic variation affects the response to medication.}
\end{table}
children from families with three or more older siblings, and children aged less than 6 months who are exposed to other children in daycare facilities—situations linked to a greater exposure to infections—are somewhat protected against atopy and asthma. Furthermore, early colonization of the gut by commensal bacteria such as lactobacilli and bifidobacteria, or infection by gut pathogens such as *Toxoplasma gondii* (which stimulates a TH1 response) or *Helicobacter pylori* are associated with a reduced prevalence of allergic disease.

A history of infection with measles or hepatitis A virus, or a positive tuberculosis skin test (suggesting previous exposure and an immune response to *Mycobacterium tuberculosis*), also seem to have a negative association with atopy. The human counterpart of the murine Tim-1 protein, which might be important in determining airway hyperreactivity and the production of IL-4 and IL-13 by T cells, is the cellular receptor for hepatitis A virus. The infection of T cells by hepatitis A virus could thus directly influence their differentiation and cytokine production, limiting the development of TH2 responses.

In contrast to these negative associations between childhood infection and the development of atopy and asthma, there is evidence that children who have had attacks of bronchiolitis associated with respiratory syncytial virus (RSV) infection are more prone to developing asthma later on. This effect of RSV may depend on the age at first infection. Infection of neonatal mice with RSV was followed by a decreased IFN-γ response compared with mice challenged at 4 or 8 weeks of age. When these mice were rechallenged at 12 weeks of age with RSV infection, animals that had been primarily infected as neonates suffered from more severe lung inflammation than animals infected at 4 or 8 weeks of age (Fig. 13.10). Similarly, children hospitalized with RSV infection have a skewed ratio of cytokine production away from IFN-γ toward IL-4, the cytokine that induces TH2 responses. All these findings suggest that an infection that evokes a TH1 immune response early in life might reduce the likelihood of TH2 responses later in life, and vice versa.

The biggest ‘fly in the ointment’ for the hygiene theory, however, is the strong negative correlation between infection by helminths (such as hookworm and schistosomes) and the development of allergy. A study in Venezuela showed that children treated for a prolonged period with antihelminthic agents had a higher prevalence of atopy compared with untreated and heavily parasitized children. As we have seen, however, helminths are strong drivers of TH2 responses, and it is difficult to reconcile this with the idea that the polarization of T-cell responses toward TH1 is a general mechanism by which infection protects against atopy.

These observations have led to a modification of the hygiene hypothesis known as the **counter-regulation hypothesis**. This proposes that all types of infection might protect against the development of atopy by driving the production of cytokines such as IL-10 and transforming growth factor (TGF)-β, which downregulate both TH1 and TH2 responses (see Section 8-19). In hygienic environments, children suffer fewer infections, resulting in a reduced production of these cytokines. Neither the molecular pathways induced by microbial exposure nor the tolerance-inducing responses in the host have yet been identified, but there are a variety of microbial products with immunoregulatory potential. For instance, exposure of dendritic cells to various Toll-like receptor (TLR) ligands, such as bacterial lipopolysaccharide (the ligand for TLR-4), CpG DNA (the ligand for TLR-9), or pro-inflammatory mediators such as IFN-γ can stimulate the production of indoleamine 2,3-dioxygenase (IDO), an enzyme that degrades the essential amino acid tryptophan. Dendritic cells expressing IDO can suppress TH2-driven inflammation and promote the differentiation of regulatory T cells, providing both immediate and long-term protective effects against allergy. Genetic factors
may also have a bearing on this type of regulation because newborn infants with a genetic predisposition to allergy have been found to have impaired regulatory T-cell function.

13-5 Regulatory T cells can control allergic responses.

Peripheral blood mononuclear cells (PBMCs) from atopic individuals have a tendency to secrete \( T_{H2} \) cytokines after nonspecific stimulation via the T-cell receptor, whereas those from non-atopic individuals do not. This has led to the suggestion that regulatory mechanisms have an important role in preventing IgE responses to allergens. Regulatory T cells, in particular, are receiving considerable attention with regard to all types of immunologically mediated disease. The different types of regulatory T cells (see Section 8-17) may all have a role in modulating allergy. Natural regulatory T cells (CD4 CD25 \( T_{reg} \) cells) from atopic individuals are defective in suppressing \( T_{H2} \) cytokine production compared with those from non-atopic individuals, and this defect is even more pronounced during the pollen season. More evidence comes from mice deficient in the transcription factor FoxP3, the master switch for producing CD4 CD25 \( T_{reg} \) cells, which develop manifestations of allergy including eosinophilia, hyper IgE, and allergic airway inflammation, suggesting that these result from the absence of regulatory T cells. This syndrome could be partially reversed by a concomitant deficiency in STAT6, which independently prevents the development of the \( T_{H2} \) response (see Section 13-3).

Regulatory T cells might also be induced by IDO secreted by a variety of cell types (see Section 13-4). Dendritic cells secrete IDO on activation through stimulation of the receptor TLR-9 by ligands containing unmethylated CpG DNA. IDO secretion from resident lung cells stimulated in this way has been shown to ameliorate experimental asthma in mice.

Summary.

Allergic reactions are the result of the production of specific IgE antibody against common, innocuous antigens. Allergens are small antigens that commonly provoke an IgE antibody response. Such antigens normally enter the body at very low doses by diffusion across mucosal surfaces and therefore trigger a \( T_{H2} \) response. The differentiation of naive allergen-specific T cells
into T_{h}2 cells is also favored by cytokines such as IL-4 and IL-13. Allergen-specific T_{h}2 cells producing IL-4 and IL-13 drive allergen-specific B cells to produce IgE. The specific IgE produced in response to the allergen binds to the high-affinity receptor for IgE on mast cells, basophils, and activated eosinophils. IgE production can be amplified by these cells because, upon activation, they produce IL-4 and CD40 ligand. The tendency to IgE overproduction is influenced by genetic and environmental factors. Once IgE is produced in response to an allergen, reexposure to the allergen triggers an allergic response. Immunoregulation is critical in the control of allergic disease through a variety of mechanisms, including regulatory T cells. We describe the mechanism and pathology of the allergic responses themselves in the next part of the chapter.

**Effector mechanisms in allergic reactions.**

Allergic reactions are triggered when allergens cross-link preformed IgE bound to the high-affinity receptor FcεRI on mast cells. Mast cells line the body surfaces and serve to alert the immune system to local infection. Once activated, they induce inflammatory reactions by secreting chemical mediators stored in preformed granules and by synthesizing prostaglandins, leukotrienes, and cytokines after activation occurs. In allergy, they provoke very unpleasant reactions to innocuous antigens that are not associated with invading pathogens that need to be expelled. The consequences of IgE-mediated mast-cell activation depend on the dose of antigen and its route of entry; symptoms range from the irritating sniffles of hay fever when pollen is inhaled, to the life-threatening circulatory collapse that occurs in systemic anaphylaxis (Fig. 13.11). The immediate allergic reaction caused by mast-cell degranulation is followed by a more sustained inflammation, known as the late-phase response. This late response involves the recruitment of other...
effector cells, notably T\(_{H2}\) lymphocytes, eosinophils, and basophils, which contribute significantly to the immunopathology of an allergic response.

**13-6 Most IgE is cell-bound and engages effector mechanisms of the immune system by different pathways from other antibody isotypes.**

Antibodies engage effector cells such as mast cells by binding to receptors specific for the Fc constant regions. Most antibodies engage Fc receptors only after the antibody variable region has bound specific antigen, forming an immune complex of antigen and antibody. IgE is an exception, because it is captured by the high-affinity Fc\(_e\) receptor in the absence of bound antigen. This means that, unlike other antibodies, which are found mainly in body fluids, IgE is mostly found fixed in the tissues on mast cells that bear this receptor as well as on circulating basophils and activated eosinophils. The ligation of the cell-bound IgE antibody by specific antigen triggers the activation of these cells at the sites of antigen entry into the tissues. The release of inflammatory lipid mediators, cytokines, and chemokines at sites of IgE-triggered reactions recruits eosinophils and basophils to augment the type I hypersensitivity response. It also recruits other effector cells, including T lymphocytes, that can mediate a local type IV hypersensitivity response.

There are two types of IgE-binding Fc receptor. The first, Fc\(_eRI\), is a high-affinity receptor of the immunoglobulin superfamily that binds IgE on mast cells, basophils, and activated eosinophils (see Section 9-24). When the cell-bound IgE is cross-linked by specific antigen, Fc\(_eRI\) transduces an activating signal. High levels of IgE, such as those that exist in people with allergic diseases or parasite infections, can result in a marked increase in Fc\(_eRI\) on the surface of mast cells, an enhanced sensitivity of such cells to activation by low concentrations of specific antigen, and a markedly increased IgE-dependent release of chemical mediators and cytokines.

The second IgE receptor, Fc\(_eRII\), usually known as CD23, is a C-type lectin and is structurally unrelated to Fc\(_eRI\); it binds IgE with low affinity. CD23 is present on many cell types, including B cells, activated T cells, monocytes, eosinophils, platelets, follicular dendritic cells, and some thymic epithelial cells. This receptor was thought to be crucial for the regulation of IgE levels, but mouse strains in which the CD23 gene has been inactivated still develop relatively normal polyclonal IgE responses. Nevertheless, CD23 does seem to be involved in enhancing IgE antibody levels in some situations. Responses against a specific antigen are known to be increased in the presence of the same antigen complexed with IgE, but such enhancement fails to occur in mice that lack the CD23 gene. This has been interpreted to indicate that CD23 on antigen-presenting cells has a role in the capture of antigen complexed with IgG.

**13-7 Mast cells reside in tissues and orchestrate allergic reactions.**

Mast cells were described by Ehrlich in the mesentery of rabbits and named *Mastzellen* (‘fattened cells’). Like basophils, mast cells contain granules rich in acidic proteoglycans that take up basic dyes. Mast cells are derived from hematopoietic stem cells but mature locally, often residing near surfaces exposed to pathogens and allergens. The major factors for mast-cell growth and development include stem-cell factor (the ligand for the receptor tyrosine kinase Kit), IL-3, and T\(_{H2}\)-associated cytokines such as IL-4 and IL-9. Mice with defective Kit lack differentiated mast cells, and although they produce IgE they cannot make IgE-mediated inflammatory responses. This shows that such responses depend almost exclusively on mast cells. Mast-cell activation depends on the activation of phosphatidylinositol 3-kinase (PI 3-kinase) in
mast cells by Kit, and pharmacological inactivation of the p110δ isoform of PI
3-kinase protects mice against allergic responses. p110δ is thus a potential
target for therapy in allergy and other mast-cell related pathologies.

Mast cells express FcεRI constitutively on their surface and are activated
when antigens cross-link IgE bound to these receptors (see Fig. 9.35). Different
levels of stimulation result in varied responses; for instance, low
levels of allergen resulting in low receptor occupancy provide a strong
signal leading to allergic inflammation. Conversely, higher levels of antigen
occupancy can induce the production of immunoregulatory cytokines such
as IL-10. Thus, mast cells display various responses depending upon the
signals they receive.

Mast cell degranulation begins within seconds, releasing an array of pre-
formed and newly generated inflammatory mediators (Fig. 13.12). Among
these are histamine—a short-lived vasoactive amine that causes an immedi-
ate increase in local blood flow and vessel permeability—and enzymes such
as mast-cell chymase, tryptase, and serine esterases. These enzymes can
in turn activate matrix metalloproteinases, which break down tissue matrix
proteins, causing tissue destruction. Large amounts of the cytokine tumor
necrosis factor (TNF)-α are also released by mast cells after activation. Some
comes from stores in mast-cell granules; some is newly synthesized by the
activated mast cells. TNF-α activates endothelial cells, causing an increased
expression of adhesion molecules, which promotes the influx of inflamma-
tory leukocytes and lymphocytes into tissues (see Chapter 2).

On activation, mast cells also synthesize and release chemokines, lipid medi-
ators such as prostaglandins, leukotrienes, and platelet-activating factor (PAF),
and cytokines such as IL-4 and IL-13, which perpetuate the T_{H2}
response. These mediators contribute to both the acute and the chronic
inflammatory responses. The lipid mediators, in particular, act rapidly to
cause smooth muscle contraction, increased vascular permeability, and the

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
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<tbody>
<tr>
<td>Enzyme</td>
<td>Trypsin, chymase, cathepsin G, carboxypeptidase</td>
<td>Remodel connective tissue matrix</td>
</tr>
<tr>
<td>Toxic mediator</td>
<td>Histamine, heparin</td>
<td>Toxic to parasites Increase vascular permeability Cause smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-4, IL-13</td>
<td>Stimulate and amplify T_{H2}-cell response</td>
</tr>
<tr>
<td></td>
<td>IL-3, IL-5, GM-CSF</td>
<td>Promote eosinophil production and activation</td>
</tr>
<tr>
<td></td>
<td>TNF-α (some stored preformed in granules)</td>
<td>Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium</td>
</tr>
<tr>
<td>Chemokine</td>
<td>CCL3</td>
<td>Attracts monocytes, macrophages, and neutrophils</td>
</tr>
<tr>
<td>Lipid mediator</td>
<td>Prostaglandins {D_1, E_2} Leukotrienes B_4, C_4</td>
<td>Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Attracts leukocytes Amplifies production of lipid mediators Activates neutrophils, eosinophils, and platelets</td>
</tr>
</tbody>
</table>
secretion of mucus, and also induce the influx and activation of leukocytes, which contribute to the late phase of the allergic response. The lipid mediators derive from membrane phospholipids, which are cleaved to release the precursor molecule arachidonic acid. This molecule can be modified via two pathways to give rise to prostaglandins, thromboxanes, and leukotrienes. Prostaglandin D₂ is the major prostaglandin produced by mast cells and recruits T_{H}2 cells, eosinophils, and basophils, all of which express its receptor protein (PTGDR). Prostaglandin D₂ is critical to the development of allergic diseases such as asthma, and polymorphisms in PTGDR have been linked to an increased risk of developing asthma. The leukotrienes, especially B₄ and C₄, are also important in sustaining inflammatory responses in tissues. Many anti-inflammatory drugs are inhibitors of arachidonic acid metabolism. Aspirin, for example, is an inhibitor of the enzyme cyclooxygenase and blocks the production of prostaglandins.

IgE-mediated activation of mast cells thus orchestrates an important inflammatory cascade that is amplified by the recruitment of several cell types including eosinophils, basophils, T_{H}₂ lymphocytes, B cells, and dendritic cells. The physiological importance of this reaction is as a defense against parasite infection (see Section 9-25). In allergy, however, the acute and chronic inflammatory reactions triggered by mast-cell activation have important pathophysiological consequences, as seen in the diseases associated with allergic responses to environmental antigens. Increasingly, mast cells are also considered to have a role in immunoregulation as well as being drivers of pro-inflammatory reactions. High concentrations of allergen, leading to high occupancy of the receptor IgE, produce immunoregulatory rather than inflammatory consequences. Mast cells can also participate in autoimmune reactions.

13-8 Eosinophils are normally under tight control to prevent inappropriate toxic responses.

Eosinophils are granulocytic leukocytes that originate in bone marrow. They are so called because their granules, which contain arginine-rich basic proteins, are colored bright orange by the acidic stain eosin. Only very small numbers of these cells are normally present in the circulation; most eosinophils are found in tissues, especially in the connective tissue immediately underneath respiratory, gut, and urogenital epithelium, implying a likely role for these cells in defense against invading organisms. Eosinophils have two kinds of effector functions. First, on activation they release highly toxic granule proteins and free radicals, which can kill microorganisms and parasites but also cause significant tissue damage in allergic reactions. Second, activation induces the synthesis of chemical mediators such as prostaglandins, leukotrienes, and cytokines. These amplify the inflammatory response by activating epithelial cells and recruiting and activating more eosinophils and leukocytes (Fig. 13.13). Eosinophils also secrete a number of proteins involved in airway tissue remodeling.

The activation and degranulation of eosinophils is strictly regulated, as their inappropriate activation would be harmful to the host. The first level of control acts on the production of eosinophils by the bone marrow. Few eosinophils are produced in the absence of infection or other immune stimulation. But when T_{H}₂ cells are activated, cytokines such as IL-5 are released that increase the production of eosinophils in the bone marrow and their release into the circulation. However, transgenic animals overexpressing IL-5 have increased numbers of eosinophils (eosinophilia) in the circulation but not in their tissues, indicating that the migration of eosinophils from the circulation into tissues is regulated separately, by a second set of controls. The key molecules in this case are CC chemokines. Most of these cause chemotaxis...
of several types of leukocytes, but three are particularly important in attracting and activating eosinophils, and have been named the eotaxins: CCL11 (eotaxin 1), CCL24 (eotaxin 2), and CCL26 (eotaxin 3).

The eotaxin receptor on eosinophils, CCR3, is quite promiscuous and binds other CC chemokines, including CCL7, CCL13, and CCL5, which also induce eosinophil chemotaxis and activation. Identical or similar chemokines stimulate mast cells and basophils. For example, eotaxins attract basophils and cause their degranulation, and CCL2, which binds to CCR2, similarly activates mast cells in both the presence and the absence of antigen. CCL2 can also promote the differentiation of naive T cells to TH2 cells; TH2 cells also carry the receptor CCR3 and migrate toward eotaxins. It is striking that these interactions between different chemokines and their receptors show a high degree of overlap and redundancy; we do not understand the significance of this complexity. However, these findings show that families of chemokines, as well as cytokines, can coordinate certain kinds of immune response.

A third set of controls regulates the state of eosinophil activation. In their nonactivated state, eosinophils do not express high-affinity IgE receptors and have a high threshold for release of their granule contents. After activation by cytokines and chemokines this threshold drops, FcεRI is expressed, and the number of Fcγ receptors and complement receptors on the cell surface also increases. The eosinophil is now primed to carry out its effector activity—degranulation in response to antigen that cross-links specific IgE bound to FcεRI on the eosinophil surface.
Eosinophils and basophils cause inflammation and tissue damage in allergic reactions.

What were later to be defined as eosinophils were observed in the 19th century in the first pathological description of fatal status asthmaticus, but the precise role of these cells in allergic disease is still unclear. In a local allergic reaction, mast-cell degranulation and T\textsubscript{H}2 activation cause eosinophils to accumulate in large numbers and to become activated. Eosinophils can also present antigens to T cells and secrete T\textsubscript{H}2 cytokines. Eosinophils seem to promote the apoptosis of T\textsubscript{H}1 cells, and their promotion of T\textsubscript{H}2-cell expansion may be partly due to a relative reduction in T\textsubscript{H}1-cell numbers. Their continued presence is characteristic of chronic allergic inflammation and they are thought to be major contributors to tissue damage.

Basophils are also present at the site of an inflammatory reaction and growth factors for basophils are very similar to those for eosinophils; they include IL-3, IL-5, and GM-CSF. There is evidence for reciprocal control of the maturation of the stem-cell population into basophils or eosinophils. For example, TGF-\textbeta in the presence of IL-3 suppresses eosinophil differentiation and enhances that of basophils. Basophils are normally present in very low numbers in the circulation and seem to have a similar role to that of eosinophils in defense against pathogens. Like eosinophils, they are recruited to the sites of allergic reactions. Basophils express Fc\textepsilon RI on the cell surface and, on activation by cytokines or antigen, they release histamine from the basophilic granules after which they are named; they also produce IL-4 and IL-13.

Eosinophils, mast cells, and basophils can interact with each other. Eosinophil degranulation releases major basic protein, which in turn causes degranulation of mast cells and basophils. This effect is augmented by any of the cytokines that affect eosinophil and basophil growth, differentiation, and activation, such as IL-3, IL-5, and GM-CSF.

Allergic reactions can be divided into immediate and late-phase responses.

The inflammatory response after IgE-mediated mast-cell activation occurs as an immediate reaction, starting within seconds, and a late reaction, which takes up to 8–12 hours to develop. These reactions can be distinguished clinically (Fig. 13.14). The immediate reaction is due to the activity of histamine,
prostaglandins, and other preformed or rapidly synthesized mediators that cause a rapid increase in vascular permeability and the contraction of smooth muscle. The late-phase reaction, which occurs in about 50% of patients with an early-phase response, is caused by the induced synthesis and release of mediators including prostaglandins, leukotrienes, chemokines, and cytokines such as IL-5 and IL-13 from the activated mast cells and basophils (see Fig. 13.12). These recruit other leukocytes, including eosinophils and T_{H}2 lymphocytes, to the site of inflammation. Late-phase reactions are associated with a second phase of smooth muscle contraction mediated by T cells, with sustained edema, and with tissue remodeling such as smooth muscle hypertrophy (an increase in size due to cell growth) and hyperplasia (an increase in the number of cells).

The late-phase reaction and its long-term sequel, chronic allergic inflammation, which is in essence a type IV hypersensitivity reaction (see Fig. 13.1), contribute to much serious long-term illness, such as chronic asthma. The chronic phase of asthma is characterized by the presence of both T_{H}1 cytokines (such as IFN-γ) and T_{H}2 cytokines, though the latter seem to predominate.

13-11 The clinical effects of allergic reactions vary according to the site of mast-cell activation.

When reexposure to allergen triggers an allergic reaction, the effects are focused on the site at which mast-cell degranulation occurs. In the immediate response, the preformed mediators released are short-lived, and their potent effects on blood vessels and smooth muscles are therefore confined to the vicinity of the activated mast cell. The more sustained effects of the late-phase response are also focused on the site of initial allergen-triggered activation, and the particular anatomy of this site may determine how readily the inflammation can be resolved. Thus, the clinical syndrome produced by an allergic reaction depends critically on three variables: the amount of allergen-specific IgE present; the route by which the allergen is introduced; and the dose of allergen (Fig. 13.15).

If an allergen is introduced directly into the bloodstream or is rapidly absorbed from the gut, the connective tissue mast cells associated with all blood vessels can become activated. This activation causes a very dangerous syndrome called systemic anaphylaxis. Disseminated mast-cell activation has a variety of potentially fatal effects: the widespread increase in vascular permeability leads to a catastrophic loss of blood pressure; airways constrict, causing difficulty in breathing; and swelling of the epiglottis can cause suffocation. This potentially fatal syndrome is called anaphylactic shock. It can occur if drugs are administered to people who have IgE specific for that drug, or after an insect bite in individuals allergic to insect venom. Some foods, for example peanuts or brazil nuts, can cause systemic anaphylaxis in susceptible individuals. This syndrome can be rapidly fatal but can usually be controlled by the immediate injection of epinephrine, which relaxes the smooth muscle and inhibits the cardiovascular effects of anaphylaxis.

The most frequent allergic reactions to drugs occur with penicillin and its relatives. In people with IgE antibodies against penicillin, administration of the drug by injection can cause anaphylaxis and even death. Great care should be taken to avoid giving a drug to patients with a past history of allergy to that drug or one that is closely related structurally. Penicillin acts as a hapten (see Appendix I, Section A-1); it is a small molecule with a highly reactive β-lactam ring that is crucial for its antibacterial activity. This ring reacts with amino groups on host proteins to form covalent conjugates. When penicillin is ingested or injected, it forms conjugates with self proteins,
and the penicillin-modified self peptides provoke a T<sub>H2</sub> response in some individuals. These T<sub>H2</sub> cells then activate penicillin-binding B cells to produce IgE antibody against the penicillin hapten. Thus, penicillin acts both as the B-cell antigen and, by modifying self peptides, as the T-cell antigen. When penicillin is injected intravenously into an allergic individual, the penicillin-modified proteins can cross-link IgE molecules on tissue mast cells and circulating basophils and thus cause anaphylaxis.

Fig. 13.15 The dose and route of allergen administration determine the type of IgE-mediated allergic reaction that results. There are two main anatomical distributions of mast cells: those associated with vascularized connective tissues, called connective tissue mast cells, and those found in submucosal layers of the gut and respiratory tract, called mucosal mast cells. In an allergic individual, all of these are loaded with IgE directed against specific allergens. The overall response to an allergen then depends on which mast cells are activated. Allergen in the bloodstream activates connective tissue mast cells throughout the body, resulting in the systemic release of histamine and other mediators. Subcutaneous administration of allergen activates only local connective tissue mast cells, leading to a local inflammatory reaction. Inhaled allergen, penetrating across epithelia, activates mainly mucosal mast cells, causing smooth muscle contraction in the lower airways; this leads to bronchoconstriction and difficulty in expelling inhaled air. Mucosal mast-cell activation also increases the local secretion of mucus by epithelial cells and causes irritation. Similarly, ingested allergen penetrates across gut epithelia, causing vomiting due to intestinal smooth muscle contraction and diarrhea due to outflow of fluid across the gut epithelium. Food allergens can also be disseminated in the bloodstream, causing urticaria (hives) when the allergen reaches the skin.
Allergen inhalation is associated with the development of rhinitis and asthma.

Inhalation is the most common route of allergen entry. Many people have mild allergies to inhaled antigens, manifesting as sneezing and a runny nose. This is called **allergic rhinitis** and results from the activation of mucosal mast cells beneath the nasal epithelium by allergens such as pollens that release their protein contents, which can then diffuse across the mucous membranes of the nasal passages. Allergic rhinitis is characterized by intense itching and sneezing, local edema leading to blocked nasal passages, a nasal discharge, which is typically rich in eosinophils, and irritation of the nose as a result of histamine release. A similar reaction to airborne allergens deposited on the conjunctiva of the eye is called **allergic conjunctivitis**. Allergic rhinitis and conjunctivitis are commonly caused by environmental allergens that are present only during certain seasons of the year. For example, hay fever (known clinically as seasonal rhinoconjunctivitis) is caused by a variety of allergens, including certain grass and tree pollens. Summer and autumnal symptoms may be caused by weed pollen, such as that of ragweed or the spores of fungi such as *Alternaria*. Perennial allergens such as cat dander and house dust mites can be a cause of year-round misery.

A more serious syndrome is **allergic asthma**, which is triggered by allergen-induced activation of submucosal mast cells in the lower airways (Fig. 13.16). This leads within seconds to bronchial constriction and an increased secretion of fluid and mucus, making breathing more difficult by trapping inhaled air in the lungs. Patients with allergic asthma usually need treatment, and asthmatic attacks can be life threatening. The same allergens that cause allergic rhinitis and conjunctivitis commonly cause asthma attacks. For example, respiratory arrest caused by severe attacks of asthma in the summer or autumn has been associated with the inhalation of spores of *Alternaria*. An important feature of asthma is chronic inflammation of the airways, which is characterized by the continued presence of increased numbers of TH2 lymphocytes, eosinophils, neutrophils, and other leukocytes (Fig. 13.17). These cells conspire to cause **airway remodeling**—a thickening of the airway walls due to hyperplasia and hypertrophy of the smooth muscle layer and mucous glands, with the eventual development of fibrosis. This remodeling leads to a permanent narrowing of the airways accompanied by increased secretion of mucus, and is responsible for many of the clinical manifestations of asthma. In chronic asthmatics, a general hyperresponsiveness or **hyperreactivity** of the airways to non-immunological stimuli also often develops.
The direct action of TH2 cytokines such as IL-9 and IL-13 on airway epithelial cells may have a dominant role in one of the major features of the disease, the induction of goblet-cell metaplasia, which is the increased differentiation of epithelial cells as goblet cells, and the consequent increase in secretion of mucus. Lung epithelial cells can also produce the chemokine receptor CCR3 and at least two of the ligands for this receptor—CCL5 and CCL11. These chemokines enhance the TH2 response by attracting more TH2 cells and eosinophils to the damaged lungs. The direct effects of TH2 cytokines and chemokines on airway smooth muscle cells and lung fibroblasts cause the apoptosis of epithelial cells and airway remodeling, induced in part by the production of TGF-β, which has numerous effects on the epithelium, ranging from inducing apoptosis to stimulating cell proliferation.

A disease resembling human asthma develops in mice that lack the transcription factor T-bet, which is required for TH1 differentiation (see Section 8-19), and in which T-cell responses are thought to be skewed to TH2. These mice have increased levels of the TH2 cytokines IL-4, IL-5, and IL-13 and develop airway inflammation involving lymphocytes and eosinophils (Fig. 13.18). They also develop nonspecific airway hyperreactivity to non-immunological stimuli, similar to that seen in human asthma. These changes occur in the absence of any exogenous inflammatory stimulus and show that, in extreme circumstances, a genetic imbalance toward TH2 responses can cause allergic disease. The involvement of eosinophils in asthma seems somewhat different in humans and in mice. In human asthma patients, the number of eosinophils is directly associated with the severity of asthma. In mice deficient in eosinophils, however, the only consistent finding relevant to asthma pathophysiology is a reduction in airway remodeling without a reduction in airway hyperreactivity.

**Fig. 13.17** Morphological evidence of chronic inflammation in the airways of an asthmatic patient. Panel a shows a section through a bronchus of a patient who died of asthma; there is almost total occlusion of the airway by a mucous plug. In panel b, a close-up view of the bronchial wall shows injury to the epithelium lining the bronchus, accompanied by a dense inflammatory infiltrate that includes eosinophils, neutrophils, and lymphocytes. Photographs courtesy of T. Krausz.

**Fig. 13.18** Mice lacking the transcription factor T-bet develop asthma and T-cell responses polarized toward TH2. T-bet binds to the promoter of the gene encoding IL-2 and is present in TH1 but not TH2 cells. Mice with a gene-targeted deletion of T-bet (T-bet−/−) developed a spontaneous asthma-like phenotype in the lungs. Left-hand panels: lung and airways in normal mice. Right-hand panels: T-bet-deficient mice showed lung inflammation, with lymphocytes and eosinophils around the airway and blood vessels (top) and airway remodeling with increased collagen around the airway (bottom). Photographs courtesy of L. Glimcher.
Although allergic asthma is initially driven by a response to a specific allergen, the subsequent chronic inflammation seems to be perpetuated even in the apparent absence of exposure to allergen. The airways become characteristically hyperreactive, and factors other than antigen can trigger asthma attacks. Asthmatics characteristically show hyperresponsiveness to environmental chemical irritants such as cigarette smoke and sulfur dioxide. Viral or, to a smaller extent, bacterial respiratory tract infections can also exacerbate the disease by inducing a TH2-dominated local response.

13-13 Skin allergy is manifested as urticaria or chronic eczema.

The same dichotomy between immediate and delayed responses is seen in cutaneous allergic responses. The skin forms an effective barrier to the entry of most allergens but it can be breached by the local injection of small amounts of allergen, for example by a stinging insect. The entry of allergen into the epidermis or dermis causes a localized allergic reaction. Local mast-cell activation in the skin leads immediately to a local increase in vascular permeability, which causes extravasation of fluid and swelling. Mast-cell activation also stimulates the release of chemicals from local nerve endings by a nerve axon reflex, causing the vasodilation of surrounding cutaneous blood vessels, which causes redness of the surrounding skin. The resulting skin lesion is called a wheal-and-flare reaction. About 8 hours later, a more widespread and sustained edematous response appears in some individuals as a consequence of the late-phase response (see Fig. 13.14). A disseminated form of the wheal-and-flare reaction, known as urticaria or hives, sometimes appears when ingested allergens enter the bloodstream and reach the skin. Histamine released by mast cells activated by allergen in the skin causes large, itchy, red swellings of the skin.

Allergists take advantage of the immediate response to test for allergy by injecting minute amounts of potential allergens into the epidermal layer of the skin. Although the reaction after the administration of antigen by intraepidermal injection is usually very localized, there is a small risk of inducing systemic anaphylaxis. Another standard test for allergy is to measure levels of IgE antibody specific for a particular allergen in a sandwich ELISA (see Appendix I, Section A-6).

Although acute urticaria is commonly caused by allergens, the causes of chronic urticaria, in which the urticarial rash can recur over long periods, are less well understood. It seems likely that up to one-third of cases of chronic urticaria are caused by autoantibodies against the \( \alpha \) chain of FcεRI, and are thus due to autoimmunity. This is an example of a type II hypersensitivity reaction (see Fig. 13.1) in which an autoantibody against a cellular receptor triggers cellular activation, in this case causing mast-cell degranulation with resulting urticaria.

A more prolonged inflammatory response is sometimes seen in the skin, most often in atopic children. They develop a persistent skin rash called eczema or atopic dermatitis, due to a chronic inflammatory response with features of tissue remodeling and fibrosis similar to those seen in the bronchial walls of patients with asthma. Although allergy is often considered solely in the context of a TH2 phenotype, in human disease (as opposed to murine models) both TH1 and TH2 cytokines can contribute to the immunopathogenesis. Atopic dermatitis is an excellent example of this. About one-third of patients show minimal, if any, elevation of IgE in their sera, and TH1-cell development is preferentially observed in the lesions of atopic dermatitis patients with a persistent history of the disease.

Innate immune responses due to activation of TLRs by microbial products can exacerbate atopic dermatitis. Activation of these receptors usually initiates a TH1-cell response by stimulating the production of IL-12 and IL-18.
An experimental situation in which these cytokines are overproduced is in mutant mice that overexpress the enzyme caspase-1 specifically in their keratinocytes (KCASP1Tg mice). These mice are born healthy but develop cutaneous changes similar to human atopic dermatitis and start frequent scratching at around 8–10 weeks after birth. Serum IgE and IgG levels also begin to rise at that time. The overexpression of caspase-1 leads to increased apoptosis of keratinocytes, but also to increased levels of IL-1 and IL-18, because caspase-1 is required to activate these cytokines. As the mice grow, the skin lesions expand and the disease becomes more severe. The mice are, however, completely protected from developing the condition when they are made deficient in IL-18, and thus do not develop a strong TH1 response. They are not protected when made deficient in STAT6, which leads to a lack of a TH2-cell response (Fig. 13.19). This type of allergy has been classified as innate-type allergy, in contrast to TH2-dependent classical allergy.

T\(_2\) responses are, however, important in natural atopic dermatitis and may lead indirectly to exacerbation of the disease by making the individual more susceptible to certain infections. For example, individuals with atopic dermatitis are more susceptible to cutaneous inflammation after vaccination with vaccinia virus. The increased susceptibility results from the spread of the vaccinia virus due to the actions of the T\(_2\) cytokines IL-4 and IL-13. The T\(_2\) response also inhibits the production of the antimicrobial peptide cathelicidin, which is normally induced as a result of stimulation of TLR-3. Thus, one could envisage a vicious circle of infection triggering atopic dermatitis resulting in increased susceptibility to further infection.

**13-14 Allergy to foods causes systemic reactions as well as symptoms limited to the gut.**

Genuine food allergy affects about 1–4% of American and European populations, although food intolerances and dislikes are ubiquitous and often misnamed ‘allergy’ by the sufferer. About one-quarter of true food allergy in the United States and Europe is accounted for by allergy to peanuts, which is increasing in incidence—tripling in the past 5 years. Food allergy causes approximately 30,000 anaphylactic reactions each year in the United States, including 200 deaths. This is a significant public-health problem, especially in school, where children may be unwittingly exposed to peanuts, which are present in many different foods. Fig. 13.20 illustrates the risk factors for the development of food allergy.

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**Fig. 13.19 A deficiency of IL-18 prevents the development of atopic dermatitis in susceptible mice.** KCASP1Tg mice overexpress the enzyme caspase-1 in their keratinocytes and develop a condition similar to human atopic dermatitis. Left panel: in skin sections stained by hematoxylin and eosin (HE) (top row), the lesions are characterized by hyperkeratosis and dense infiltration with leukocytes and lymphocytes. When stained by toluidine blue (bottom row), a dense accumulation of mast cells can be seen. The dark-purple stained cells are mast cells. Far greater numbers of mast cells (indicated by arrows) are present in the lesion at 16 weeks compared with 4 weeks. Right panel: KCASP1Tg mice deficient in STAT6 have serum IgE concentrations below detectable levels, but still suffer from similar changes in the skin, whereas KCASP1Tg mice deficient in IL-18 are free from dermatitis. This suggests that T\(_2\) cytokines are not important in this model. KIL-18Tg mice, which overexpress mature IL-18 in their keratinocytes, show the same symptoms as KCASP1Tg mice except for the delay in disease onset. KCASP1Tg, keratinocyte-specific caspase-1-transgenic mice; KIL-18Tg, keratinocyte-specific mature IL-18-transgenic mice; ND, not detectable. Photographs courtesy of Tsutsui, H., et al.: Immunol. Rev. 2004, 202: 115–138.
One of the characteristic features of food allergens is a high degree of resistance to digestion by pepsin in the stomach. This allows them to reach the mucosal surface of the small intestine as intact allergens. When an allergen is eaten, two types of allergic responses are seen. Activation of mucosal mast cells associated with the gastrointestinal tract leads to transepithelial fluid loss and smooth muscle contraction, causing diarrhea and vomiting. For reasons that are not fully understood, connective tissue mast cells in the dermis and subcutaneous tissues can also be activated after ingestion of allergen, presumably by allergen that has been absorbed into the bloodstream, and this results in urticaria. Urticaria is a common reaction when penicillin is given orally to a patient who already has penicillin-specific IgE antibodies. Ingestion of food allergens can also lead to the development of asthma and of generalized anaphylaxis, accompanied by cardiovascular collapse. Certain foods, most importantly peanuts, tree nuts, and shellfish, are particularly associated with this type of life-threatening response. Food allergy can be either IgE mediated, as in asthma or systemic anaphylaxis, or non-IgE mediated. An important example of the latter is celiac disease.

13-15 Celiac disease is a model of antigen-specific immunopathology.

Celiac disease is a chronic condition of the upper small intestine caused by an immune response directed at gluten, a complex of proteins present in wheat, oats, and barley. Elimination of gluten from the diet restores normal gut function, but must be continued throughout life. The pathology of celiac disease is characterized by the loss of the slender, finger-like villi formed by the intestinal epithelium (a condition termed villous atrophy), together with an increase in the size of the sites in which epithelial cells are renewed (crypt hyperplasia) (Fig. 13.21). These pathological changes result in the loss of the mature epithelial cells that cover the villi and which normally absorb and digest food, and is accompanied by severe inflammation of the intestinal wall, with increased numbers of T cells, macrophages, and plasma cells in the lamina propria, as well as increased numbers of lymphocytes in the epithelial layer. Gluten seems to be the only food protein that provokes intestinal inflammation in this way, a property that reflects gluten’s ability to stimulate both specific and innate immunity in genetically susceptible individuals.

Celiac disease shows an extremely strong genetic predisposition, with more than 95% of patients expressing the HLA-DQ2 class II MHC allele, and there is an 80% concordance in monozygotic twins (that is, if one twin develops it, there is an 80% probability that the other will), but only a 10% concordance in dizygotic twins. Nevertheless, most individuals expressing HLA-DQ2 do not develop celiac disease despite the almost universal presence of gluten in the Western diet. Thus, other genetic factors must make important contributions to susceptibility.

Most evidence indicates that celiac disease requires the aberrant priming of IFN-γ-producing CD4 T cells by antigenic peptides present in α-gliadin, one of the major proteins in gluten. It is generally accepted that only a limited number of peptides can provoke an immune response leading to celiac disease. This is likely to be due to the unusual structure of the peptide-binding groove of the HLA-DQ2 molecule. The key step in the immune recognition of α-gliadin is the deamidation of its peptides by the enzyme tissue transglutaminase (tTG), which converts selected glutenine residues to negatively charged glutamic acid. Only peptides containing negatively charged residues in certain positions bind strongly to HLA-DQ2, and thus the transamination reaction promotes the formation of peptide:HLA-DQ2 complexes, which can activate antigen-specific CD4 T cells (Fig. 13.22). Multiple peptide epitopes can be generated from gliadin. Activated gliadin-specific
CD4 T cells accumulate in the lamina propria, producing IFN-γ, a cytokine that leads to intestinal inflammation.

Celiac disease is entirely dependent on the presence of a foreign antigen (gluten) and is not associated with a specific immune response against antigens in the tissue—the intestinal epithelium—that is damaged during the

Figure 13.21 The pathological features of celiac disease. Left: the surface of the normal small intestine is folded into finger-like villi, which provide an extensive surface for nutrient absorption. Right: The local immune response against the food protein α-gliadin provokes destruction of the villi. In parallel, there is lengthening and increased mitotic activity in the underlying crypts where new epithelial cells are produced. There is also a marked inflammatory infiltrate in the intestinal mucosa, with increased numbers of lymphocytes in the epithelial layer and accumulation of CD4 T cells, plasma cells, and macrophages in the deeper layer, the lamina propria. Because the villi contain all the mature epithelial cells that digest and absorb foodstuffs, their loss results in life-threatening malabsorption and diarrhea. Photographs courtesy of Allan Mowat.

Fig. 13.22 Molecular basis of immune recognition of gluten in celiac disease. After the digestion of gluten by gut digestive enzymes, deamidation of epitopes by tissue transglutaminase leads to their binding to HLA-DQ molecules and priming of the immune system.
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Fig. 13.23 A hypothesis to explain antibody production against tissue transglutaminase (tTG) in the absence of T cells specific for tTG in celiac patients. tTG-reactive B cells endocytose gluten–tTG complexes and present gluten peptides to the gluten-specific T cells. The stimulated T cells can now provide help to these B cells, which produce autoantibodies against tTG.

Gluten peptides activate mucosal epithelial cells to express MIC molecules

Intraepithelial lymphocytes (IELs) express NKG2D, which binds to MIC molecules and activates the IELs to kill the epithelial cell

### 13-16 Allergy can be treated by inhibiting either IgE production or the effector pathways activated by the cross-linking of cell-surface IgE.

Current drug treatments for allergic disease either treat the symptoms only, as do the antihistamines, or are general immunosuppressants such as the corticosteroids used for the long-term treatment of asthma and other chronic allergic diseases. They are largely palliative, rather than curative, often need to be taken for life, and consequently incur a wide range of side effects, which we discuss in Chapter 15. Anaphylactic reactions are treated with epinephrine, which stimulates the re-formation of endothelial tight junctions, promotes the relaxation of constricted bronchial smooth muscle, and also stimulates the heart. Inhaled bronchodilators that act on β-adrenergic receptors to relax constricted muscle are used to relieve acute asthma attacks. Antihistamines that block the histamine H₁ receptor reduce the urticaria that follows the release of histamine from mast cells and basophils. Relevant H₁ receptors include those on blood vessels that cause increased permeability of the vessel wall, and those on unmyelinated nerve fibers that are thought to mediate the itching sensation. In chronic allergic disease it is extremely important to treat and prevent the chronic inflammatory injury to tissues. Topical or systemic corticosteroids (see Section 15-1) are used to suppress the immune response. It is therefore not considered an autoimmune disease. Nevertheless, autoantibodies against tissue transglutaminase are found in all patients with celiac disease; indeed, the presence of serum IgA antibodies against this enzyme is used as a sensitive and specific test for the disease. Interestingly, no tTG-specific T cells have been found and it has been proposed that gluten-reactive T cells provide help to B cells reactive to tissue transglutaminase. In support of this hypothesis, gluten can complex with the enzyme and therefore could be taken up by tTG-reactive B cells (Fig. 13.23). There is no evidence that these autoantibodies contribute to tissue damage.

Chronic T-cell responses against food proteins are normally prevented by the development of oral tolerance (see Section 11-13). Why this breaks down in patients with celiac disease is unknown. The properties of the HLA-DQ2 molecule provide a partial explanation, but there must be additional factors because most HLA-DQ2-positive individuals do not develop celiac disease and the high concordance rates in monozygotic twins indicate a role for additional genetic factors. Polymorphisms in the gene for CTLA-4 or in other immunoregulatory genes may be associated with susceptibility. There could also be differences in how individuals digest gliadin in the intestine, so that differing amounts survive for deamination and presentation to T cells.

The gluten protein also seems to have several properties that contribute to pathogenesis. As well as its relative resistance to digestion, there is mounting evidence that some gliadin-derived peptides stimulate the innate immune system by inducing the release of IL-15 by intestinal epithelial cells. This process is antigen-nonspecific and involves peptides that cannot be bound by HLA-DQ2 molecules or recognized by CD4 T cells. IL-15 release leads to the activation of dendritic cells in the lamina propria, as well as the upregulation of MIC-A expression by epithelial cells. CD8 T cells in the mucosal epithelium can be activated via their NKG2D receptors, which recognize MIC-A, and they can kill MIC-A-expressing epithelial cells via these same NKG2D receptors (Fig. 13.24). Triggering of these innate immune responses by α-gliadin may create some intestinal damage on its own and also induce some of the co-stimulatory events necessary for initiating an antigen-specific CD4 T-cell response to other parts of the α-gliadin molecule. The ability of gluten to stimulate both innate and adaptive immune responses may thus explain its unique ability to induce celiac disease.
chronic inflammatory changes seen in asthma, rhinitis, and eczema. What is really needed, however, is a means of regulating the T-cell response to the allergenic peptide antigen in an antigen-specific manner.

Some of the newer approaches to the treatment and prevention of allergy that attempt to do this are set out in Fig. 13.25. Two treatments are commonly used in clinical practice—one is desensitization or specific allergen immunotherapy and the other is blockade of the effector pathways. There are also several approaches still in the experimental stage. In desensitization the aim is to restore tolerance to the allergen by reducing its tendency to induce IgE production. The key to this therapy seems to be the induction of regulatory T cells secreting IL-10 and/or TGF-β, which skew the response away from IgE (see Section 13-3). Beekeepers exposed to multiple stings are often naturally protected from severe allergic reactions such as anaphylaxis through a mechanism involving IL-10-secreting T cells. Similarly, specific allergen immunotherapy for sensitivity to insect venom and airborne allergens induces the increased production of IL-10 and in some cases TGF-β, as well as the induction of IgG isotypes, particularly IgG4, an isotype selectively promoted by IL-10. Patients are desensitized by injection with escalating doses of allergen, starting with tiny amounts, an injection schedule that gradually decreases the IgE-dominated response. Allergen injection immunotherapy in fact seems to downregulate both T H1- and T H2-driven hypersensitivity disease, in line with its presumed induction of T reg cells. Recent evidence shows that desensitization is also associated with a reduction in the numbers of late-phase inflammatory cells at the site of the allergic reaction. A potential complication of the desensitization approach is the risk of inducing IgE-mediated allergic responses. This strategy is not always successful, for example in treating severe reactions against food allergens such as peanut allergy.

An alternative, and still experimental, approach to desensitization is vaccination with peptides derived from common allergens. This procedure induces

<table>
<thead>
<tr>
<th>Target step</th>
<th>Mechanism of treatment</th>
<th>Specific approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>T H2 activation</td>
<td>Induce regulatory T cells</td>
<td>Injection of specific antigen or peptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration of cytokines, e.g., IFN-γ, IL-10, IL-12, TGF-β</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of adjuvants such as CpG oligodeoxynucleotides to stimulate T H1 response</td>
</tr>
<tr>
<td>Activation of B cell to</td>
<td>Block co-stimulation</td>
<td>Inhibit CD40L</td>
</tr>
<tr>
<td>produce IgE</td>
<td>Inhibit T H2 cytokines</td>
<td>Inhibit IL-4 or IL-13</td>
</tr>
<tr>
<td>Mast-cell activation</td>
<td>Inhibit effects of IgE binding to mast cell</td>
<td>Blockade of IgE receptor</td>
</tr>
<tr>
<td>Mediator action</td>
<td>Inhibit effects of mediators on specific receptors</td>
<td>Antihistamine drugs</td>
</tr>
<tr>
<td>Eosinophil-dependent</td>
<td>Block cytokine and chemokine receptors that mediate</td>
<td>Lipoxygenase inhibitors</td>
</tr>
<tr>
<td>inflammation</td>
<td>eosinophil recruitment and activation</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 13.25 Approaches to the treatment of allergy. Possible methods of inhibiting allergic reactions are shown. Two approaches are in regular clinical use. The first is the injection of specific antigen in desensitization regimes, which is believed to restore tolerance to the allergen—perhaps through the production of regulatory T cells. The second clinically useful approach is the use of specific inhibitors to block the synthesis or effects of inflammatory mediators produced by mast cells.
T-cell anergy (see Section 8-15), which is associated with multiple changes in T-cell phenotype, including the production of IL-10 and upregulation of the cell-surface protein CD5. IgE-mediated responses are not induced by the peptides because IgE, in contrast to T cells, can recognize only the intact antigen. A difficulty with this approach is that an individual's responses to peptides are restricted by their MHC class II alleles; patients with different MHC class II molecules therefore respond to different allergen-derived peptides. One possible solution is the use of peptides that contain short sequences with multiple overlapping MHC-binding motifs that would provide coverage for the majority of the population.

Another vaccination strategy that shows promise in experimental models of allergy is the use of oligodeoxynucleotides rich in unmethylated CpG as adjuvants for desensitization regimes. These oligonucleotides mimic the CpG motifs in bacterial DNA and strongly promote TH1 responses, probably through the stimulation of TLR-9 in dendritic cells (see Section 8-7). The mechanism of action of adjuvants is discussed in Appendix I, Section A-4.

The signaling pathways that enhance the IgE response in allergic disease are also potential targets for therapy. Inhibitors of IL-4, IL-5, and IL-13 would be predicted to reduce IgE responses, but redundancy between some of the activities of these cytokines might make this approach difficult to implement in practice. A second approach to manipulating the response is to give cytokines that promote TH1-type responses. IFN-γ, IFN-α, and IL-12 have each been shown to reduce IL-4-stimulated IgE synthesis in vitro, and IFN-γ and IFN-α have been shown to reduce IgE synthesis in vivo. Administration of IL-12 to patients with mild allergic asthma caused a decrease in the number of eosinophils in blood and sputum but had no effect on immediate or late-phase responses to inhaled allergen. The treatment with IL-12 was accompanied by quite severe flu-like symptoms in most patients, which is likely to limit its possible therapeutic value.

Another target for therapeutic intervention might be the high-affinity IgE receptor. An effective competitor for IgE at this receptor could prevent the binding of IgE to the surfaces of mast cells, basophils, and eosinophils. Clinical trials have taken place of a humanized mouse anti-IgE monoclonal antibody named omalizumab, which binds to the portion of IgE that ligates the high-affinity IgE receptor. Because IgE is present in plasma at low levels it was possible to give a large molar excess of omalizumab that caused a decrease in IgE levels of more than 95%. This was accompanied by down-regulation of the numbers of high-affinity IgE receptors on basophils and mast cells. This antibody blocked both the immediate and late-phase responses to experimentally inhaled allergen. Patients with asthma and allergic rhinitis receiving omalizumab in clinical trials had fewer exacerbations than patients on the placebo, and were able to reduce their use of corticosteroids. The efficacy of this agent, which has led to its being licensed for use to treat patients with asthma, provides a clear-cut demonstration of the importance of IgE in the atopic allergic diseases. Targeting the inhibitory receptor FcγRIIb is a potential new therapy for allergy to cat's dander. A chimeric fusion protein consisting of human Fcγ and the cat allergen Fel d 1 blocked the skin reaction in a mouse model of cat allergy and inhibited the release of inflammatory mediators from basophils. This inhibition is specific to the allergen.

A further approach to treatment would be to block the recruitment of eosinophils to sites of allergic inflammation. The eotaxin receptor CCR3 is a potential target in this context. The production of eosinophils in bone marrow and their exit into the circulation might also be reduced by a blockade of IL-5 action. Studies using anti-IL-5 treatment have not been encouraging,
however: anti-IL-5 did reduce the numbers of eosinophils in blood and sputum but did not alter immediate and late-phase responses to inhaled allergen or airway hyperreactivity to histamine.

Summary.

The allergic response to innocuous antigens reflects the pathophysiological aspects of a defensive immune response whose physiological role is to protect against helminth parasites. It is triggered by the binding of antigen to IgE antibodies bound to the high-affinity IgE receptor FcεRI on mast cells. Mast cells are strategically distributed beneath the mucosal surfaces of the body and in connective tissue. Antigen cross-linking the IgE on their surface causes them to release large amounts of inflammatory mediators. The resulting inflammation can be divided into early events, characterized by short-lived mediators such as histamine, and later events that involve leukotrienes, cytokines, and chemokines, which recruit and activate eosinophils and basophils. The late phase of this response can evolve into chronic inflammation, characterized by the presence of effector T cells and eosinophils, which is most clearly seen in chronic allergic asthma.

Hypersensitivity diseases.

In this part of the chapter we focus on immunological responses involving IgG antibodies or specific T cells that cause adverse hypersensitivity reactions. Although these effector arms of the immune response normally participate in protective immunity to infection, they occasionally react with noninfectious antigens to produce acute or chronic hypersensitivity reactions. Although the mechanisms initiating the various forms of hypersensitivity are different, much of the pathology is due to the same immunological effector mechanisms. We also consider here a newly characterized category of hypersensitivity disease, in which certain variants of the genes regulating inflammatory responses cause the inappropriate triggering of inflammation, leading to severe disease.

13-17 Innocuous antigens can cause type II hypersensitivity reactions in susceptible individuals by binding to the surfaces of circulating blood cells.

Antibody-mediated destruction of red blood cells (hemolytic anemia) or platelets (thrombocytopenia) can be caused by some drugs, including the antibiotics penicillin and cephalosporin. These are examples of type II hypersensitivity reactions in which the drug binds to the cell surface and serves as a target for anti-drug IgG antibodies that cause destruction of the cell (see Fig. 13.1). The anti-drug antibodies are made in only a minority of people and it is not clear why these individuals make them. The cell-bound antibody triggers the clearance of the cell from the circulation, predominantly by tissue macrophages in the spleen, which bear Fcγ receptors.

13-18 Systemic disease caused by immune-complex formation can follow the administration of large quantities of poorly catabolized antigens.

Type III hypersensitivity reactions can arise with soluble antigens (see Fig. 13.1). The pathology is caused by the deposition of antigen:antibody
aggregates, or **immune complexes**, in particular tissues and sites. Immune complexes are generated in all antibody responses, but their pathogenic potential is determined, in part, by their size and by the amount, affinity, and isotype of the responding antibody. Larger aggregates fix complement and are readily cleared from the circulation by the mononuclear phagocyte system. However, the small complexes that form when antigen is in excess tend to be deposited in blood vessel walls. There they can ligate Fc receptors on leukocytes, leading to leukocyte activation and tissue injury.

A local type III hypersensitivity reaction called an **Arthus reaction** (Fig. 13.26) can be triggered in the skin of sensitized individuals who possess IgG antibodies against the sensitizing antigen. When antigen is injected into the skin, circulating IgG antibody that has diffused into the skin forms immune complexes locally. The immune complexes bind Fc receptors such as FcγRIII on mast cells and other leukocytes, generating a local inflammatory response and increased vascular permeability. Fluid and cells, especially polymorphonuclear leukocytes, then enter the site of inflammation from local blood vessels. The immune complexes also activate complement, leading to the production of the complement fragment C5a. This is a key participant in the inflammatory reaction because it interacts with C5a receptors on leukocytes to activate these cells and attract them to the site of inflammation (see Section 2-5). Both C5a and FcγRIII have been shown to be required for the experimental induction of an Arthus reaction in the lung by macrophages in the walls of the alveoli, and they are probably required for the same reaction induced by mast cells in the skin and the linings of joints (synovia).

A systemic type III hypersensitivity reaction, known as **serum sickness**, can result from the injection of large quantities of a poorly catabolized foreign antigen. This illness was so named because it frequently followed the administration of therapeutic horse antiserum. In the pre-antibiotic era, antiserum made by immunizing horses was often used to treat pneumococcal pneumonia; the specific anti-pneumococcal antibodies in the horse serum would help the patient to clear the infection. In much the same way, **antivenin** (serum from horses immunized with snake venoms) is still used today as a source of neutralizing antibodies to treat people suffering from the bites of poisonous snakes. The increasing use of monoclonal antibodies in the treatment of disease (for example, anti-TNF-α in rheumatoid arthritis) has led to the development of serum sickness in a small minority of patients.
Serum sickness occurs 7–10 days after the injection of horse serum, an interval that corresponds to the time required to mount an IgG-switched primary immune response against the foreign antigens. The clinical features of serum sickness are chills, fever, rash, arthritis, and sometimes glomerulonephritis (inflammation of the glomeruli of the kidneys). Urticaria is a prominent feature of the rash, implying a role for histamine derived from mast-cell degranulation. In this case, the mast-cell degranulation is triggered by the ligation of cell-surface FcγRIII by IgG-containing immune complexes.

The course of serum sickness is illustrated in Fig. 13.27. The onset of disease coincides with the development of antibodies against the abundant soluble proteins in the foreign serum; these antibodies form immune complexes with their antigens throughout the body. These immune complexes fix complement and can bind to and activate leukocytes bearing Fc and complement receptors; these in turn cause widespread tissue damage. The formation of immune complexes causes clearance of the foreign antigen, so serum sickness is usually a self-limiting disease. Serum sickness after a second dose of antigen follows the kinetics of a secondary antibody response (see Section 10-14), with symptoms typically appearing within a day or two.

Pathological immune-complex deposition is seen in other situations in which antigen persists. One is when an adaptive antibody response fails to clear the infecting pathogen, as occurs in subacute bacterial endocarditis or chronic viral hepatitis. In these situations, the replicating pathogen is continuously generating new antigen in the presence of a persistent antibody response, with the consequent formation of abundant immune complexes. These are deposited within small blood vessels, with consequent injury in many tissues and organs, including the skin, kidneys, and nerves.

Immune-complex disease also occurs when inhaled allergens provoke IgG rather than IgE antibody responses, perhaps because they are present at relatively high levels in the air. When a person is reexposed to high doses of such allergens, immune complexes form in the walls of alveoli in the lung. This leads to the accumulation of fluid, protein, and cells in the alveolar wall, slowing blood–gas interchange and compromising lung function. This type of reaction is more likely to occur in occupations such as farming, where there is repeated exposure to hay dust or mold spores, and the resulting disease is known as farmer’s lung. If exposure to antigen is sustained, the lining of the lungs can be permanently damaged.

13-19 Delayed-type hypersensitivity reactions are mediated by T_{H1} cells and CD8 cytotoxic T cells.

Unlike the immediate hypersensitivity reactions described so far, which are mediated by antibodies, delayed-type hypersensitivity or type IV hypersensitivity reactions are mediated by antigen-specific effector T cells. These function in essentially the same way as they do in a response to a pathogen, as described in Chapter 8. The causes and consequences of some syndromes in which type IV hypersensitivity responses predominate are listed in Fig. 13.28. These responses can be transferred between experimental animals by purified T cells or cloned T-cell lines. Much of the inflammation seen in some of the allergic diseases described in the earlier parts of this chapter is in fact due to delayed-type hypersensitivity.

The prototypic delayed-type hypersensitivity reaction is an artifact of modern medicine—the tuberculin test (see Appendix I, Section A-38). This is used to determine whether an individual has previously been infected with *M. tuberculosis*. Small amounts of tuberculin—a complex mixture of peptides and carbohydrates derived from *M. tuberculosis*—are injected intradermally. In people who have been exposed to the bacterium, either by infection or by
immunization with the BCG vaccine (an attenuated form of \textit{M. tuberculosis}), a local T cell-mediated inflammatory reaction evolves over 24–72 hours. The response is caused by TH1 cells, which enter the site of antigen injection, recognize complexes of peptide:MHC class II molecules on antigen-presenting cells, and release inflammatory cytokines such as IFN-$\gamma$ and TNF-$\beta$. These stimulate the expression of adhesion molecules on endothelium and increase local blood vessel permeability, allowing plasma and accessory cells to enter the site, thus causing a visible swelling (Fig. 13.29). Each of these phases takes several hours and so the fully developed response only appears 24–48 hours after challenge. The cytokines produced by the activated TH1 cells and their actions are shown in Fig. 13.30.

Very similar reactions are observed in several cutaneous hypersensitivity responses. These can be elicited by either CD4 or CD8 T cells, depending on the pathway by which the antigen is processed. Typical antigens that cause cutaneous hypersensitivity responses are highly reactive small molecules that can easily penetrate intact skin, especially if they cause itching that leads to scratching. These chemicals then react with self proteins, creating

**Fig. 13.28** Type IV hypersensitivity responses. These reactions are mediated by T cells and all take some time to develop. They can be grouped into three syndromes, according to the route by which antigen passes into the body. In delayed-type hypersensitivity the antigen is injected into the skin; in contact hypersensitivity it is absorbed into the skin; and in gluten-sensitive enteropathy it is absorbed by the gut. DNFB, dinitrofluorobenzene.

**Fig. 13.29** The stages of a delayed-type hypersensitivity reaction. The first phase involves uptake, processing, and presentation of the antigen by local antigen-presenting cells. In the second phase, T$_{H1}$ cells that were primed by a previous exposure to the antigen migrate into the site of injection and become activated. Because these specific cells are rare, and because there is little inflammation to attract cells into the site, it can take several hours for a T cell of the correct specificity to arrive. These cells release mediators that activate local endothelial cells, recruiting an inflammatory cell infiltrate dominated by macrophages and causing the accumulation of fluid and protein. At this point the lesion becomes apparent.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antigen</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-type hypersensitivity</td>
<td>Proteins: Insect venom M. tuberculosis proteins (tuberculin, lepromin)</td>
<td>Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis</td>
</tr>
<tr>
<td>Contact hypersensitivity</td>
<td>Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate</td>
<td>Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy (celiac disease)</td>
<td>Gliadin</td>
<td>Villous atrophy in small bowel Malabsorption</td>
</tr>
</tbody>
</table>
hapten:protein complexes that can be processed to hapten:peptide complexes capable of being presented by MHC molecules and recognized by T cells as foreign antigens. There are two phases to a cutaneous hypersensitivity response: sensitization and elicitation. During the sensitization phase, cutaneous Langerhans cells take up and process antigen, and migrate to regional lymph nodes, where they activate T cells (see Fig. 8.13) with the consequent production of memory T cells, which end up in the dermis. In the elicitation phase, a subsequent exposure to the sensitizing chemical leads to antigen presentation to memory T cells in the dermis, with the release of T-cell cytokines such as IFN-γ and IL-17. This stimulates the keratinocytes of the epidermis to release IL-1, IL-6, TNF-α, GM-CSF, the chemokine CXCL8, and the interferon-inducible chemokines CXCL11 (IP-9), CXCL10 (IP-10), and CXCL9 (Mig; monokine induced by IFN-γ). The cytokines and chemokines enhance the inflammatory response by inducing the migration of monocytes into the lesion and their maturation into macrophages, and by attracting more T cells (Fig. 13.31).

The rash produced by contact with poison ivy (Fig. 13.32) is caused by a CD8 T-cell response to a chemical in the poison ivy leaf called pentadecacatechol. This compound is lipid-soluble and can therefore cross the cell membrane and modify intracellular proteins. The modified proteins generate modified peptides within the cytosol, and these are translocated into the endoplasmic reticulum and delivered to the cell surface bound to MHC class I molecules. CD8 T cells recognizing the peptides cause damage either by killing the eliciting cell or by secreting cytokines such as IFN-γ. The well-studied chemical picryl chloride produces a CD4 T-cell hypersensitivity reaction. It modifies extracellular self proteins, which are then processed by the exogenous pathway (see Section 5-5) into modified self peptides that bind to self-MHC class II molecules and are recognized by T_{H1} cells. When sensitized T_{H1} cells recognize these complexes, they produce extensive inflammation by activating macrophages (see Fig. 13.31). Because the chemicals in these examples
are delivered by contact with the skin, the rash that follows is called a contact hypersensitivity reaction.

Some insect proteins also elicit a delayed-type hypersensitivity response. However, the early phases of the host reaction to an insect bite are often IgE-mediated or result from the direct effects of insect venoms. Important delayed-type hypersensitivity responses to divalent cations such as nickel have also been observed. These divalent cations can alter the conformation or the peptide binding of MHC class II molecules, and thus provoke a T-cell response. Finally, although this section has focused on the role of T cells in inducing delayed-type hypersensitivity reactions, there is evidence that antibody and complement might also have a role. Mice deficient in B cells, antibody, or complement show impaired contact hypersensitivity reactions. In particular, IgM antibodies (produced in part by B1 cells), which activate the complement cascade, facilitate the initiation of these reactions.

13-20 Mutation in the molecular regulators of inflammation can cause hypersensitive inflammatory responses resulting in ‘autoinflammatory disease.’

We have seen throughout this book that host defense against infection depends on the engagement by the immune system of effector mechanisms that limit the spread of infection and kill the infectious agent. In this chapter we have seen how inappropriate responses to noninfectious immunological stimuli may cause diseases as diverse as asthma and hypersensitivity to nickel. There is a very fine balance between host underresponsiveness to infectious stimuli, allowing the uncontrolled spread of infection, and overresponsiveness, killing not only the infection but potentially also the host. There are a small number of diseases in which mutations in genes that control the life, death, and activities of inflammatory cells are associated with severe inflammatory disease. These conditions represent a failure to limit...
damage during inflammation and immune responses to infection and are known as **autoinflammatory diseases** (Fig. 13.33).

The name **familial Mediterranean fever** (FMF) describes the key features of one such severe inflammatory illness, inherited as an autosomal recessive disorder. The pathogenesis of FMF was a total mystery until its cause was discovered to be mutations in the gene encoding the protein pyrin, named to reflect its association with fever. This gene was also discovered by a second group of researchers at much the same time and named marenostrin, after the Latin name *mare nostrum* for the Mediterranean sea. The name pyrin has stuck and has been extended to describe a domain in this protein that is the prototype of ‘pyrin domains’ found in some proteins involved in apoptosis.

A disease with similar clinical manifestations is **familial Hibernian fever** (FHF) (also known as **TNF-receptor associated periodic syndrome** (TRAPS)). Although inherited as an autosomal dominant disease, it was romantically thought to have been a variant of FMF brought to Ireland by sailors of the Spanish Armada, until genetic analysis showed it to be caused by mutations in a completely different gene, that encoding the TNFR-I receptor (a receptor for TNF-α). Patients have reduced levels of TNFR-1, which leads to increased levels of TNF-α in the circulation because it is not mopped up by receptors. The disease responds to therapeutic blockade with anti-TNF agents such as etanercept, a soluble TNF receptor fortuitously developed to treat patients with rheumatoid arthritis (see Section 15-8). Both FMF and FHF are characterized by episodic attacks of severe inflammation associated with fever, an acute-phase response, severe malaise and, in FMF, attacks of pleural or peritoneal inflammation known as pleurisy and peritonitis, respectively. Mutations in the gene encoding CD2-binding protein 1 (CD2BP1), a pyrin-interacting protein, are associated with another dominantly inherited autoinflammatory syndrome—**pyogenic arthritis, pyoderma gangrenosum, and acne** (PAPA). These mutations accentuate the interaction between pyrin and CD2BP1.

<table>
<thead>
<tr>
<th>Disease (common abbreviation)</th>
<th>Clinical features</th>
<th>Inheritance</th>
<th>Mutated gene</th>
<th>Protein (alternative name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean fever (FMF)</td>
<td>Periodic fever, serositis (inflammation of the pleural and/or peritoneal cavity), arthritis, acute-phase response</td>
<td>Autosomal recessive</td>
<td>MEFV</td>
<td>Pyrin (marenostrin)</td>
</tr>
<tr>
<td>TNF-receptor associated periodic syndrome (TRAPS) (also known as familial Hibernian fever)</td>
<td>Periodic fever, myalgia, rash, acute-phase response</td>
<td>Autosomal dominant</td>
<td>TNFRSF1A</td>
<td>TNF-α 55 kDa receptor (TNFR-I)</td>
</tr>
<tr>
<td>Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)</td>
<td>Periodic fever, urticarial rash, joint pains, conjunctivitis</td>
<td>Autosomal dominant</td>
<td>PTSTPIP</td>
<td>CD2-binding protein 1</td>
</tr>
<tr>
<td>Muckle–Wells syndrome</td>
<td>Cold-induced periodic fever, urticarial rash, joint pains, conjunctivitis</td>
<td>Autosomal dominant</td>
<td>CIAS1</td>
<td>Cryopyrin</td>
</tr>
<tr>
<td>Familial cold autoinflammatory syndrome (FCAS) (familial cold urticaria)</td>
<td>Neonatal onset recurrent fever, urticarial rash, chronic arthropathsy, facial dysmorphism, neurologic involvement</td>
<td>Autosomal dominant</td>
<td>CIAS1</td>
<td>Cryopyrin</td>
</tr>
<tr>
<td>Chronic infantile neurologic, cutaneous articular syndrome (CINCA)</td>
<td>Periodic fever, elevated IgD levels, lymphadenopathy</td>
<td>Autosomal recessive</td>
<td>MVK</td>
<td>Mevalonate synthase</td>
</tr>
<tr>
<td>Hyper-IgD syndrome (HIDS)</td>
<td>Granulomatous inflammation of skin, eye, and joints</td>
<td>Autosomal dominant</td>
<td>NOD2 (CARD15)</td>
<td>NOD2 (CARD15)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Granulomatous inflammatory bowel disease, sometimes eye, skin, and joint granuloma</td>
<td>Complex trait</td>
<td></td>
<td></td>
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</tbody>
</table>

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How mutations in pyrin cause FMF is not known, but the pyrin domain is found in proteins that participate in pathways leading to the activation of caspases involved in the proteolytic processing and activation of the inflammatory cytokines pro-1β and pro-IL-18, and in apoptosis. It is not difficult to envisage how unregulated cytokine activity and defective apoptosis could result in a failure to control inflammation. In mice, an absence of pyrin causes an increased sensitivity to lipopolysaccharide and a defect in macrophage apoptosis. A related protein, named cryopyrin, encoded by the gene CIAS1, is mutated in the episodic inflammatory diseases Muckle–Wells syndrome and familial cold autoinflammatory syndrome (FCAS). These dominantly inherited syndromes present with episodes of fever—which is induced by exposure to cold in the case of FCAS—as well as urticarial rash, joint pains, and conjunctivitis. Mutations in CIAS1 are also associated with the autoinflammatory disorder chronic infantile neurologic cutaneous and articular syndrome (CINCA), in which short recurrent fever episodes are common, although severe arthropathic, neurologic, and dermatologic symptoms predominate. Both pyrin and cryopyrin are predominantly expressed in leukocytes and in cells that act as barriers to pathogens, such as intestinal epithelial cells. The stimuli that modulate pyrin and related molecules include inflammatory cytokines and lipopolysaccharide. The mechanism underlying these diseases is not fully understood but is thought to be a failure to regulate NFκB and IL-1 production. Indeed, Muckle–Wells syndrome responds dramatically to the drug anakinra, an antagonist of the receptor for IL-1.

Not all autoinflammatory diseases are caused by mutations in genes involved in the regulation of apoptosis. Hyper IgD syndrome (HIDS), which is associated with attacks of fever starting in infancy, high levels of IgD in serum, and lymphadenopathy, is caused by mutations that result in a partial deficiency of mevalonate kinase, an enzyme in the pathway for the synthesis of isoprenoids and cholesterol. It is not yet clear how this enzyme deficiency causes the autoinflammatory disease.

13-21 Crohn’s disease is a relatively common inflammatory disease with a complex etiology.

The heritable autoinflammatory diseases just described are fortunately rare, although they illustrate well the importance of the precise regulation of inflammatory responses. A much commoner inflammatory disease is Crohn’s disease, an intestinal disorder of the type known generally as inflammatory bowel disease. The other main inflammatory bowel disease is ulcerative colitis. Crohn’s disease is thought to result from an abnormal overresponsiveness to the normal commensal gut flora; unlike the autoinflammatory diseases discussed previously, it has multiple genetic risk factors. Patients have episodes of severe inflammation that commonly affect the terminal ileum—hence the alternative name of regional ileitis for this disease—but any part of the gastrointestinal tract can be involved. The disease is characterized by a chronic inflammation of the mucosa and submucosa of the intestine that includes the prominent development of granulomatous lesions (Fig. 13.34) similar to those seen in the type IV hypersensitivity responses discussed in Section 13-19. Genetic analysis of patients with Crohn’s disease and their families has identified a disease-susceptibility gene named NOD2 (also known as CARD15) that is expressed predominantly in monocytes, dendritic cells, and the Paneth cells of the small intestine. Mutations and uncommon polymorphic variants of the NOD2 protein are strongly associated with the presence of Crohn’s disease, with around 30% of patients carrying a loss-of-function mutation in NOD2. Mutations in the same gene are also the cause of a dominantly inherited granulomatous disease named Blau syndrome, in which granulomas typically develop in the skin, eyes, and joints. Whereas
Crohn's disease represents a loss of function of NOD2, it is thought that Blau syndrome represents a gain of function.

NOD2 serves as an intracellular receptor for the muramyl dipeptide derived from bacterial peptidoglycan, and its stimulation leads to activation of the transcription factor NFκB and the induction of genes encoding pro-inflammatory cytokines (see Section 2-10). This pro-inflammatory response is believed to be important for the clearance of gut bacteria whose presence would otherwise lead to sustained chronic inflammation (see Section 11-11). The mutant forms of NOD2 have lost this function, and it is thought that this allows the development of chronic inflammation.

A further complication to the story is the identification of a deficiency in innate immunity in patients with Crohn's disease, in which a failure to clear pathogenic bacteria was found to be due to defective CXCL8 production and defective neutrophil accumulation. This may not lead to abnormal bowel pathology unless there is also a defect in NOD2, thereby promoting abnormal inflammation. Thus, it has been proposed that defects in innate immunity and in the regulation of inflammation act synergistically to promote the pathology of Crohn's disease.

Analysis of the autoinflammatory diseases has opened a new field of study in the medical sciences; it is likely that many other diseases will turn out to be caused by or modified by polymorphic genetic variants or mutants in the genes that regulate innate immune responses and the control of inflammation. A minor infection or physiological stress with no adverse consequences in most people might turn out to have devastating effects in a minority of genetically predisposed people. A second important message from these illnesses is that a more robust classification of diseases will be possible when we understand their underlying molecular basis.

Summary.

Hypersensitivity diseases reflect normal immune mechanisms that are inappropriately directed against innocuous antigens or inflammatory stimuli. They can be mediated by IgG antibodies bound to modified cell surfaces, or by complexes of antibodies bound to poorly catabolized antigens, as occurs in serum sickness. Hypersensitivity reactions mediated by T cells can be activated by modified self proteins or by injected proteins such as those in the mycobacterial extract tuberculin. These T cell-mediated responses require the induced synthesis of effector molecules and develop more slowly, which is why they are termed delayed-type hypersensitivity. A genetic failure to regulate inflammation gives rise to rare autoinflammatory syndromes, whereas Crohn's disease is associated with a failure to control commensal gut bacteria and prevent them from causing chronic inflammation.

Summary to Chapter 13.

In some people, immune responses to otherwise innocuous antigens produce allergic or hypersensitivity reactions upon reexposure to the same antigen. Most allergies involve the production of IgE antibody against common environmental allergens. Some people are intrinsically prone to making IgE antibodies against many allergens, and such people are said to be atopic. IgE production is driven by antigen-specific TH2 cells; the response is polarized toward TH2 by an array of chemokines and cytokines that engage specific signaling pathways. The IgE produced binds to the high-affinity IgE receptor FceRI on mast cells and basophils. Specific effector T cells, mast cells, and eosinophils, in combination with TH1 and TH2 cytokines and chemokines,
orchestrate chronic allergic inflammation, which is the major cause of the chronic morbidity of asthma. Failure to regulate these responses can occur at many levels of the immune system, including defects in regulatory T cells. Antibodies of other isotypes and antigen-specific effector T cells contribute to hypersensitivity to other antigens. The autoinflammatory syndromes are due to uncontrolled inflammation in the absence of disease, whereas Crohn's disease is thought to represent a failure to control the numbers of commensal gut bacteria.

Questions.

13.1 List three hypersensitivities that involve IgE and three that involve other mechanisms.

13.2 Describe how a person becomes sensitized to an allergen.

13.3 Discuss the factors predisposing to the production of IgE.

13.4 What are the key features that differentiate acute and chronic allergic reactions?

13.5 How can the innate immune system contribute to allergy?

13.6 How do infectious agents modulate allergy?

13.7 Which types of white blood cells participate in allergic responses, and what do they do?

13.8 Describe how an ingested food allergen can give rise to the allergic skin reaction urticaria.

13.9 How does desensitization therapy work?

13.10 What are the main features of (a) type II hypersensitivity disease; (b) type III hypersensitivity disease; and (c) type IV hypersensitivity disease? Give an example of each type.

13.11 How does autoinflammatory disease differ from allergy?

13.12 How is the regulation of cell death and autoinflammatory disease linked?
General references.


Section references.

13-1 Allergens are often delivered transmucosally at low dose, a route that favors IgE production.


13-2 Enzymes are frequent triggers of allergies.


13-3 Class switching to IgE in B lymphocytes is favored by specific signals.


13-4 Both genetic and environmental factors contribute to the development of IgE-mediated allergy.


13-6 Most IgE is cell-bound and engages effector mechanisms of the immune system by different pathways from other antibody isotypes.


13-7 Mast cells reside in tissues and orchestrate allergic reactions.


13-8 Eosinophils are normally under tight control to prevent inappropriate toxic responses.


13-9 Eosinophils and basophils cause inflammation and tissue damage in allergic reactions.


13-10 Allergic reactions can be divided into immediate and late-phase responses.


13-11 The clinical effects of allergic reactions vary according to the site of mast-cell activation.


13-12 Allergic inhalation is associated with the development of rhinitis and asthma.


Chapter 13: Allergy and Hypersensitivity

13-15 Celiac disease is a model of antigen-specific immunopathology.


13-16 Allergy can be treated by inhibiting either IgE production or the effector pathways activated by the cross-linking of cell-surface IgE.


13-20 Mutation or genetic variation in the molecular regulators of inflammation can cause hypersensitive inflammatory responses resulting in ‘autoinflammatory disease.’


INF EVERS [http://fmf.igh.cnrs.fr/infevers].


13-17 Innocuous antigens can cause type II hypersensitivity reactions in susceptible individuals by binding to the surfaces of circulating blood cells.


13-18 Systemic disease caused by immune-complex formation can follow the administration of large quantities of poorly catabolized antigens.


13-19 Delayed-type hypersensitivity reactions are mediated by Tυ1 cells and CD6 cytokotic T cells.


13-21 Crohn’s disease is a common inflammatory bowel disease.


