IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

THIRD EDITION

Charles A. Janeway, Jr.
Yale University Medical School

■

Paul Travers
Birkbeck College, London University

with the assistance of

Simon Hunt
Oxford University

■

Mark Walport
Royal Postgraduate Medical School, London

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Allergy and Hypersensitivity

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Allergic reactions occur when an individual who has produced IgE antibody in response to an innocuous antigen, or **allergen**, subsequently encounters the same allergen. This triggers the activation of IgE-binding mast cells in the exposed tissue, leading to a series of responses that are characteristic of **allergy**. As we learned in Chapter 8, there are circumstances in which IgE mediates protective immunity, especially in response to parasitic worms, which are prevalent in underdeveloped countries. In more advanced countries, however, IgE responses to innocuous antigens predominate, and allergy is one of the most prevalent diseases (Fig. 11.1). Allergic reactions to common environmental antigens affect up to half the population in North America and Europe and, although rarely life-threatening, cause much distress and lost time from school and work. Owing to their medical importance in industrialized societies, much more is known about the pathophysiology of IgE-mediated immune responses than about their physiology.

Fig. 11.1 IgE-mediated reactions to extrinsic antigens. All IgE-mediated responses involve mast-cell degranulation, but the symptoms experienced by the patient can be very different depending on whether the allergen is injected, inhaled, or eaten, and depending also on the dose of the allergen (see also Fig. 11.12).

IgE-mediated allergic reactions

Syndrome	Common allergens	Route of entry	Response
Systemic anaphylaxis	Drugs Serum Venoms Peanuts	Intravenous (either directly or following rapid absorption)	Edema, Increased vascular permeability Tracheal occlusion Circulatory collapse Death
Wheal-and-flare	Insect bites Allergy testing	Subcutaneous	Local increase in blood flow and vascular permeability
Allergic rhinitis (hay fever)	Pollens (ragweed, timothy, birch) Dust-mite feces	Inhaled	Edema of nasal mucosa Irritation of nasal mucosa
Bronchial asthma	Pollens Dust-mite feces	Inhaled	Bronchial constriction Increased mucus production Airway inflammation
Food allergy	Shellfish Milk Eggs Fish Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

The term allergy was originally defined by Clemens Von Pirquet as 'an altered capacity of the body to react to a foreign substance', which was an extremely broad definition that included all immunological reactions. Allergy is now defined in a much more restricted manner as 'disease following an immune response to an otherwise innocuous antigen'. Allergy is a member of a class of immune responses that have been termed **hypersensitivity reactions**; these are harmful immune responses that produce tissue injury and may cause serious disease. Hypersensitivity reactions were classified into four types by Gell and Coombs (Fig. 11.2). Allergy is usually equated with type I, or immediate-type hypersensitivity reactions mediated by IgE, and will be used in this sense here.

In this chapter, we will first consider the mechanisms that favor the switching of the humoral immune response to the production of IgE. We will then describe the pathophysiological consequences of ligation by antigen of IgE bound by the high-affinity Fcε receptor (FcεRI) on mast cells. Finally, we will consider the causes and consequences of other types of immunological hypersensitivity reactions.

The production of IgE.

A **type I hypersensitivity reaction** is triggered by antigens cross-linking preformed IgE antibody that is bound to FcεRI on mast-cell surfaces. Basophils and activated eosinophils also express FcεRI. The factors that lead to an antibody response that is dominated by IgE are still being worked out. Here, we shall describe our current understanding of these processes, before turning to the question of how IgE mediates allergic reactions.

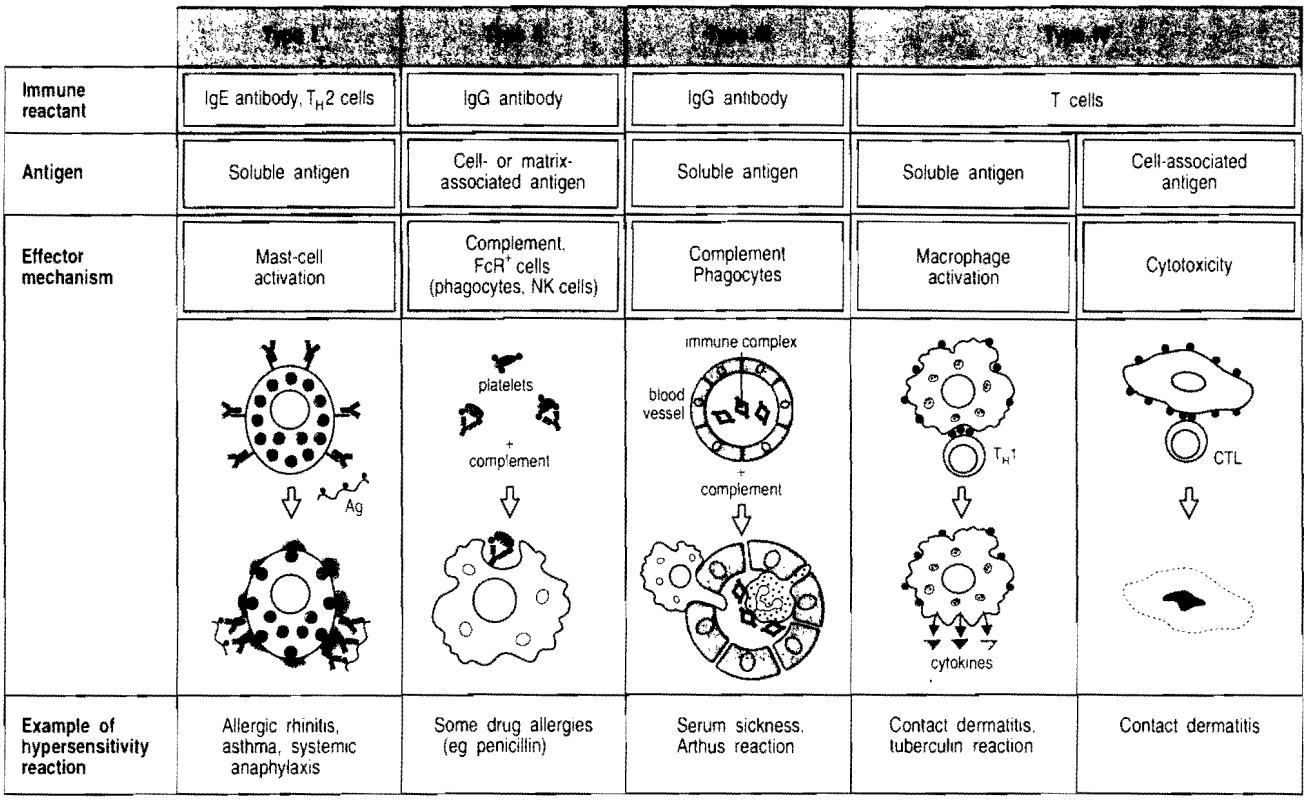

Fig. 11.2 There are four types of immune-mediated hypersensitivity reactions causing tissue damage. Types I–III are antibody-mediated and are distinguished by the different types of antigens recognized and the different classes of antibody involved. Type I responses are mediated by IgE, which induces mast-cell activation, while types II and III are mediated by IgG, which can engage complement-mediated and phagocytic effector mechanisms to varying degrees, depending on the subtype of IgG and the nature of the antigen involved. Type II responses are directed against cell-surface antigens and lead to cell-specific tissue damage, whereas type III responses are directed against soluble or matrix antigens, and the tissue damage involved is caused by responses triggered by immune complexes. Type IV hypersensitivity reactions are T-cell mediated, and can be subdivided into two classes: in the first class, tissue damage is caused by activation of inflammatory responses by T_H1 cells, mediated mainly by macrophages; and in the second, damage is caused directly by cytotoxic T cells (CTL).

11-1 Allergens are a class of antigen that evoke an IgE response and are often delivered transmucosally at low dose.

There are certain antigens and routes of antigen presentation to the immune system that favor the production of IgE. As we learned in Chapter 8, T_H2 cells can switch the antibody isotype from IgM to IgE as well as to IgG2 and IgG4 (human) or IgG1 and IgG3 (mouse). Antigens that selectively evoke T_H2 cells that drive an IgE response are known as allergens.

Much human allergy is caused by a limited number of inhaled protein allergens that reproducibly elicit IgE production in some individuals. Since we inhale many different proteins that do not induce IgE production, this has led researchers to ask what is unusual about the proteins that are common allergens. Although we still do not understand this completely, some general principles have emerged (Fig. 11.3).

It seems likely that transmucosal presentation of very low doses of allergen is particularly efficient at inducing T_H2-driven IgE responses. IgE antibody production requires IL-4-producing T_H2 cells and can be inhibited by T_H1 cells that produce interferon-γ (IFN-γ) (see Fig. 8.7). We have also learned (see Section 9-19) that the low doses at which

Features of inhaled allergens that may promote the priming of T_H2 cells that drive IgE responses	
Protein	Only proteins induce T-cell responses
Function	Protease
Low dose	Favors activation of IL-4-producing CD4 T cells
Low molecular weight	Diffuses out of particle into mucus
High solubility	Readily eluted from particle
Stable	Allows survival in desiccated particle
Contains peptides that bind host MHC class II	Required for T-cell priming

Fig. 11.3 Properties of inhaled allergens.

allergens enter the body across mucosal surfaces can favor activation of T_H2 cells over T_H1 cells. The dominant antigen-presenting cell type in the respiratory mucosa is a cell with characteristics similar to Langerhans' cells (see Chapters 7 and 9). These cells very efficiently take up and process protein antigens, a step that is accompanied by cellular activation. This in turn induces their migration to regional lymph nodes and differentiation into cells that are highly co-stimulatory in a manner that favors T_H2 differentiation.

11-2 Enzymes are frequent triggers of allergy.

Many parasites invade their hosts by secretion of proteolytic enzymes that break down connective tissue and allow the parasite access to host tissues. It has been proposed that these enzymes are particularly active at promoting T_H2 responses. This idea receives some support from the many examples of allergens that are enzymes. The major allergen of the house dust mite, *Dermatophagoides pteronyssimus*, responsible for allergy in up to 20% of the North American population, is a cysteine protease homologous to papain. Papain itself, derived from the papaya fruit, is used as a meat tenderizer and causes allergy in workers preparing the enzyme. Such allergies are called industrial allergies, and an analogous industrial allergy is the asthma caused by inhalation of the bacterial enzyme subtilisin, the 'biological' component of certain laundry detergents. Injection of enzymatically active papain (but not inactivated papain) into mice stimulates an IgE response. A closely related enzyme, chymopapain, is used in medicine to chemically destroy intervertebral disks in patients with sciatica; the major although rare complication of this procedure is anaphylaxis, an acute systemic response to allergens (see Section 11-10). However, it is not universally the case that allergens are enzymes; by complete contrast, two allergens identified from filarial worms are enzyme inhibitors. Although the amino acid sequences of many protein allergens derived from plants have been identified, their functions are presently obscure.

Most allergens are relatively small, highly soluble proteins that are inhaled in desiccated particles such as pollen grains or mite feces. The allergen elutes from the particle because it is readily soluble 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 common pollen allergens in ragweed (*Artemisia artemisiifolia*) cannot exceed 1 μg per year! Yet many people develop irritating and even life-threatening T_H2-driven IgE antibody responses to these minute doses of allergen. It is important to note that only a fraction of people who are exposed to these substances make IgE antibody to them. The host factors that influence which individuals will respond to allergens are considered in Section 11-4.

11-3 Class switching to IgE in B lymphocytes is favored by specific accessory signals.

IgE production requires cytokines that are released by T_H2 cells, in particular IL-4. T_H2 cells, in turn, arise when naive T cells first encounter antigen in the presence of IL-4. The importance of IL-4 in driving IgE production is seen in mice lacking a functional IL-4 gene: the major abnormality associated with this defect appears to be a reduced synthesis of IgE. In mice, the early production of IL-4 has been shown to be the result of activation of a small subset of CD4 T cells with unusual properties (Fig. 11.4). These cells, the $NK1.1^+$ subset, express T-cell receptors made

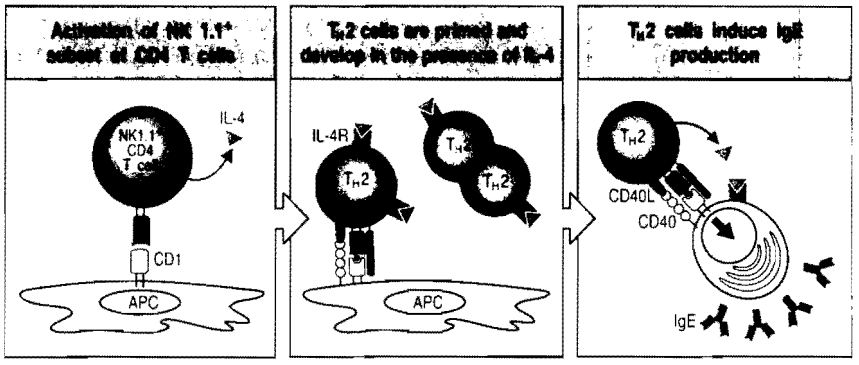

Fig. 11.4 IgE class switching in B cells is initiated by T_H2 cells, which develop in the presence of an early burst of IL-4. IL-4 is secreted early in some immune responses by a small subset of CD4 T cells ($NK1.1^+$ CD4 T cells), which interact with antigen-presenting cells bearing the non-classical MHC class I-like molecule, CD1. Naive T cells being primed by their first encounter with antigen are driven to differentiate into T_H2 cells in the presence of this early burst of IL-4. These effector T_H2 cells interact with antigen-specific B lymphocytes and stimulate switching of the antibody isotype to IgE, by secreting IL-4 and expressing CD40L. These same signals drive B-cell proliferation and thereby IgE production.

up of a restricted set of β chains and an invariant α chain, and develop in response to CD1, an MHC class I-like molecule found in humans as well as mice. Evidence for the development of these cells in response to CD1 derives from their absence in mice that cannot express CD1 molecules because of engineered defects in their β_2-microglobulin genes. The invariant T-cell receptor α chain expressed by these cells is encoded in a single V_α gene segment and a single J_α gene segment; similar cells in humans are also specific for the homolog of mouse CD1, called CD1d, and use the homologous V_α and J_α gene segments. These T cells produce IL-4 almost immediately upon encountering their CD1 ligand, which is expressed on cortical thymocytes and on Langerhans' cells and other antigen-presenting cells. In mice, CD1-specific T cells are the only known source of early IL-4: mice lacking β_2-microglobulin fail to make early IL-4 and are deficient in IgE production.

The early exposure of naive CD4 T cells to IL-4 produced in this way drives them to differentiate into T_H2 cells and inhibits T_H1 development. Once T_H2 cells are primed, they can deliver several molecular signals that favor class switching in B lymphocytes to the production of IgE antibody (see Fig. 11.4). Ligation of the T-cell receptor stimulates expression of CD40 ligand (CD40L) on the T_H2 cell surface, which interacts with CD40 on B cells. A second accessory signal is the production of IL-4 by the activated T_H2 cell, which in turn ligates the IL-4 receptor on B lymphocytes; recent studies show that IL-13 can also have this effect on B cells by interaction with a receptor that shares some properties with the IL-4 receptor. The combination of these signals drives productive class switching to IgE and B-cell proliferation.

The IgE response, once initiated, may be further amplified by basophils, mast cells, and eosinophils, which are also capable of driving IgE production (Fig. 11.5). All three cell types express the FcεRI, although eosinophils

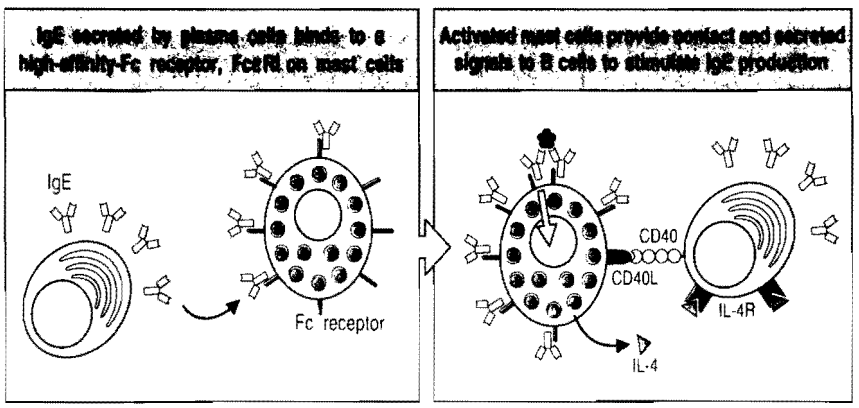

Fig. 11.5 IgE production is amplified following ligation by antigen of IgE bound to mast cells. IgE secreted by B lymphocytes binds to the high-affinity IgE receptor on mast cells, basophils, and activated eosinophils. Isotype switching and production of IgE by B cells can be amplified by these cells, which express CD40L and secrete IL-4 in response to ligation of surface-bound IgE by antigen. This may occur *in vivo* at the site of allergen-triggered inflammation, for example in bronchial-associated lymphoid aggregates.

only express it when activated. When these specialized granulocytes are activated by antigen crosslinking of their FcεRI-bound IgE, they can express cell-surface CD40L and secrete IL-4, driving class switching and IgE production by B cells in a manner similar to T_H2 cells. The interaction between these specialized granulocytes and B cells may occur at the site of the allergic reaction, as B cells are observed to form germinal centers at inflammatory foci.

11-4 Genetic factors contribute to the preferential priming of T_H2 cells and IgE-mediated allergy.

Up to 40% of people in western populations show an exaggerated tendency to mount IgE responses to a wide variety of common environmental antigens. This state is called **atopy** and appears to be influenced by several genetic loci. Atopic individuals have higher total levels of IgE measured in the circulation and higher eosinophil levels than their normal counterparts. They are more susceptible to allergic diseases such as hay fever and asthma. On the basis of family linkage studies, loci on chromosomes 11q and 5q have been implicated as containing genes that may be important in determining the presence of atopy, and candidate genes that might affect IgE responses are found in these areas. The candidate gene on chromosome 11 encodes the β subunit of the high-affinity IgE receptor, while on chromosome 5 there is a cluster of tightly linked genes that includes those encoding IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF. These cytokines play important roles in IgE isotype switching, eosinophil survival, and mast-cell proliferation. Of particular note, a polymorphism in the IL-4 promoter region is associated with raised IgE levels in atopic subjects and directs elevated expression of a reporter gene in experimental systems. It is too early to know whether this polymorphism plays an important role in the complex genetics of atopy.

A second type of inherited variation in IgE responses is linked to the MHC class II region and affects responses to specific allergens. Many studies have shown that specific IgE production to individual allergens is associated with particular HLA class II alleles, implying that particular MHC:peptide combinations may favor a strong T_H2 response. As an example, IgE responses to several ragweed pollen allergens are particularly associated with haplotypes containing the MHC class II allele, DRB1 1501. Many individuals are therefore generally predisposed to make T_H2 responses and specifically predisposed to respond to some allergens more than others. However, allergies to common drugs such as penicillin show no association with MHC class II and the presence or absence of atopy.

Summary.

Allergic reactions are the result of the production of specific IgE antibody to common, innocuous antigens. Allergens are antigens that commonly provoke an IgE antibody response. Such antigens normally enter the body at very low doses by diffusion across mucosal surfaces, and trigger a T_H2 response. Naive allergen-specific T cells are induced to develop into T_H2 cells in the presence of an early burst of IL-4, which appears to be derived from a specialized subset of T cells. The allergen-specific T_H2 cells drive allergen-specific B cells to produce IgE. The IgE 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 CD40L. The production of IgE is influenced by host genetic factors. Once IgE is produced in response to an allergen, re-exposure to the allergen triggers an allergic response by mechanisms to which we now turn.

Effector mechanisms in allergic reactions.

Allergic reactions are triggered when allergens crosslink preformed IgE bound to the high-affinity FcεRI on mast cells. Mast cells line the body surfaces and serve to alert the immune system to local infection. In allergy, they have the unfortunate ability to provoke very unpleasant allergic reactions to innocuous antigens which are not associated with invading pathogens that need to be expelled. Mast cells act by releasing stored mediators by granule exocytosis, and also by synthesizing leukotrienes and cytokines (Fig. 11.6). The consequences of IgE-mediated mast-cell activation depend on the dose of antigen and its route of entry, ranging from the irritating sniffles of hay fever when pollen is inhaled, to the life-threatening circulatory collapse that occurs in systemic anaphylaxis. The immediate allergic reaction caused by mast-cell degranulation is followed by a more sustained inflammation, known as the late-phase response. This involves the recruitment of other effector cells, notably T_H2 lymphocytes, eosinophils, and basophils, which contribute significantly to the immunopathology of an allergic response.

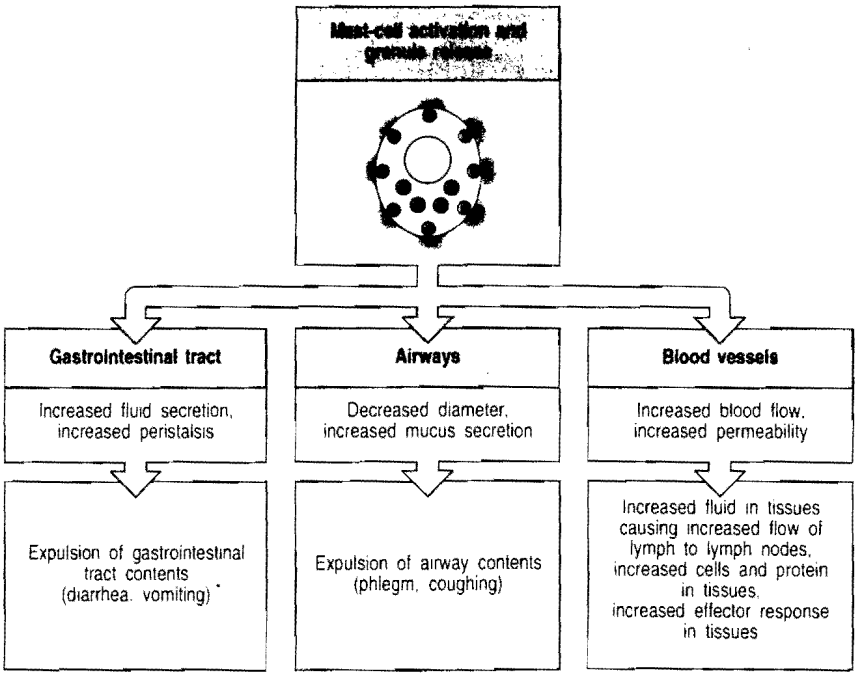

Fig. 11.6 Mast cells secrete an extensive range of cytokines and mediators of inflammation. Mast-cell products can be divided into two categories: first, those molecules, both preformed and rapidly synthesized, that mediate acute inflammatory events following mast-cell activation; and second, cytokines and lipid mediators, which induce a late-phase chronic inflammatory response with influx and activation of T_H2 lymphocytes, monocytes, eosinophils, and neutrophils. There is some overlap between mediators that induce acute and chronic inflammatory responses, particularly among the lipid mediators, which have rapid effects causing smooth muscle contraction, increased vascular permeability, and mucus secretion, and also induce influx and activation of leukocytes, which contribute to the late-phase response.

11-5 Most IgE is cell-bound and engages effector mechanisms of immunity by different pathways from other antibody isotypes.

Most antibodies are found in body fluids and engage effector cells through receptors specific for their Fc constant regions only after binding specific antigen through their variable domains. IgE is an exception, however, as it is captured by high-affinity receptors specific for the IgE Fc region in the absence of bound antigen. This means that 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 mast cells are highly specialized leukocytes, located prominently as resident cells in mucosal and epithelial tissues, where they are well-placed to guard against invading pathogens (see Sections 8-20 and 8-21), as well as

in subendothelial regions in connective tissue. The ligation of cell-bound IgE by antigen triggers activation of these cells at the site of antigen entry into the tissues. The release of inflammatory lipid mediators, cytokines, and chemokines at sites of IgE-triggered reactions results in the recruitment of eosinophils and basophils to augment the type I response.

There are two types of IgE-binding Fc receptor. The first, **FcεRI**, is a high-affinity receptor of the immunoglobulin superfamily, which mediates the binding of IgE to mast cells, basophils, and activated eosinophils (see Chapter 8). This molecule transduces the signal that activates these cells following crosslinking of cell-bound IgE. The second IgE receptor, **CD23**, is a structurally unrelated molecule that binds IgE with low affinity. CD23 is widely distributed on cells, including B cells, activated T cells, monocytes, eosinophils, platelets, follicular dendritic cells, and some thymic epithelial cells. This receptor was thought to play a crucial role in regulation of IgE antibody levels; however, a mouse strain in which the CD23 gene was deleted by homologous recombination (see Section 2-37) shows no major abnormality in the development of polyclonal IgE responses. However, CD23 deficient mice did not show antigen-specific Ig-mediated enhancement of antibody responses. This demonstrates a role for CD23 on antigen presenting cells in the capture of antigen by specific IgE.

11-6 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 have granules rich in acidic molecules that take up basic dyes. However, in spite of this resemblance, and the similar range of mediators stored in these basophilic granules, the mast cells are derived from a different myeloid lineage from basophils and eosinophils. Mast cells are located in tissues, mainly in the vicinity of small blood vessels and postcapillary venules. They home to tissues as agranular cells and their final differentiation with granule formation occurs after they have arrived in the tissues. The major mast-cell growth factor is stem-cell factor (SCF), which acts on its receptor, c-Kit (CD117), which is encoded by a proto-oncogene. Mice with defective c-Kit lack differentiated mast cells and studies of these mice have shown that IgE-mediated inflammatory responses are almost exclusively mast-cell dependent.

Mast cells express FcεRI constitutively on their surface and they are activated when antigens crosslink FcεRI-bound IgE. Degranulation occurs within seconds, releasing a variety of preformed mediators (see Figs. 8.29 and 11.11). Among these are histamine, a short-lived vasoactive amine which causes an immediate increase in local blood flow and permeability, mast-cell chymase, tryptase, and serine esterases that may in turn activate matrix metalloproteinases, which collectively break down tissue matrix proteins. TNF-α is also stored in mast-cell granules and is released in large amounts on mast-cell activation. This causes endothelial activation with upregulation of the expression of adhesion molecules, which promotes the influx of inflammatory leukocytes and lymphocytes.

Chemokines, lipid mediators known as leukotrienes, and further cytokines such as IL-4, are synthesized upon activation and act to sustain the inflammatory response. Thus, the IgE-mediated activation of mast cells orchestrates an important inflammatory cascade which is amplified by the recruitment of eosinophils, basophils, and T_H2 lymphocytes. The physiological importance of this is as a host defense mechanism, as we learned in Chapter 8. However, the acute and chronic inflammatory reactions triggered by mast-cell activation can also have important pathophysiological consequences, as seen in the diseases associated with allergic responses to environmental antigens.

11-7 Eosinophils and basophils are specialized granulocytes that release toxic mediators in IgE-mediated responses.

Eosinophils are bone marrow-derived granulocytic leukocytes, so named because their granules, which contain arginine-rich basic proteins, are colored bright orange by the acidic stain eosin (Fig. 11.7). Only very small numbers of these cells are normally present in the circulation; the majority of eosinophils reside in tissues, especially in the respiratory, gut, and urogenital subepithelium, implying a likely role for these cells in defense against invading organisms. The effector functions of eosinophils are of two types. First, they release highly toxic granule proteins and free radicals, which can kill microorganisms and parasites but which can also cause significant tissue damage in allergic reactions. Second, they produce molecules including prostaglandins, leukotrienes, and cytokines, which amplify the inflammatory response by recruiting and activating further eosinophils, leukocytes, and epithelial cells (Fig. 11.8).

Important regulatory mechanisms inhibit the inappropriate activation and degranulation of eosinophils, which could otherwise be very harmful to the host. The first level of control regulates the production of eosinophils by the bone marrow, which remain low in the absence of infection or other immune stimulation. When T_H2 cells are activated, cytokines such as IL-5 are released, which increase the production of eosinophils in the bone marrow and promote their release into the circulation. However, transgenic animals over-expressing IL-5 show eosinophilia in the circulation but not in tissues. This demonstrates that a second level of control on eosinophil activity regulates the migration of eosinophils from the circulation into tissues. The key molecules for this response are products of the chemokine family of genes (see Chapter 9). The majority

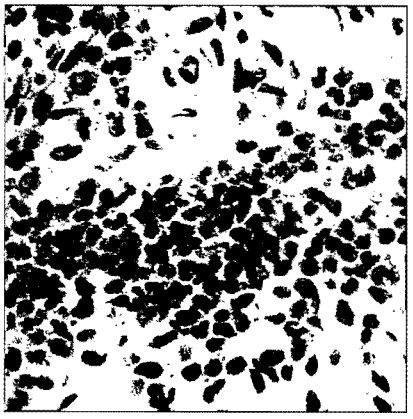

Fig. 11.7 Eosinophils can be detected readily in tissue sections by their bright orange coloration. A dense infiltrate of eosinophils is seen infiltrating a Langerhans' cell histiocytosis. Photograph courtesy of T Krausz.

Class of product	Examples	Biological effects
Enzyme	Eosinophil peroxidase	Toxic to targets by catalyzing halogenation Triggers histamine release from mast cells
	Eosinophil collagenase	Remodeling of connective tissue matrix
Toxic protein	Major basic protein	Toxic to parasites and mammalian cells Triggers histamine release from mast cells
	Eosinophil cationic protein	Toxic to parasites Neurotoxin
	Eosinophil-derived neurotoxin	Neurotoxin
Cytokine	IL-3, IL-5, GM-CSF	Amplify eosinophil production by bone marrow Cause eosinophil activation
Chemokine	IL-8	Promote influx of leukocytes
Lipid mediators	Leukotrienes C4 and D4	Smooth muscle contraction Increased vascular permeability Mucus secretion
	Platelet-activating factor	Chemotactic to leukocytes Amplifies production of lipid mediators Neutrophil, eosinophil, and platelet activation

Fig. 11.8 Eosinophils secrete a range of highly toxic granule proteins and other mediators of inflammation.

of chemokines cause chemotaxis of several types of leukocytes; one of the newest members of this family of molecules shows specific activity for eosinophils and has been named **eotaxin**.

The third level of eosinophil regulation is control of their state of activation. In the basal state, eosinophils do not express high-affinity IgE receptors and have a high threshold for release of their granule contents. Following cytokine and chemokine activation, these thresholds drop, FcεRI is expressed, and the numbers of surface complement and Fcγ receptors increase. The consequence of these changes is that the eosinophil is primed to express effector activity.

The potential for eosinophils to cause tissue injury to the host is illustrated by rare hypereosinophilic syndromes. These are sometimes seen in association with T-cell lymphomas in which unregulated IL-5 secretion drives a dramatic blood eosinophilia. The clinical manifestations of hypereosinophilia are damage to the endocardium (Fig. 11.9) and nerves, leading to heart failure and neuropathy, both thought to be caused by the toxic effects of eosinophil granule proteins.

In a local allergic reaction, mast-cell degranulation and T_H2 activation cause activated eosinophils to accumulate in large numbers. Their continued presence is characteristic of chronic allergic inflammation and they are thought to be the chief contributors to the tissue damage that occurs.

Basophils are bone marrow-derived granulocytes, which share a common stem-cell precursor with eosinophils. Basophil growth factors are very similar to those for eosinophils and 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-β in the presence of IL-3 suppresses eosinophil and enhances basophil differentiation. Basophils are normally present in very low numbers in the circulation and appear to play a similar role to eosinophils in host defense against parasitic disease. Like eosinophils, they are recruited to the sites of allergic reactions. Basophils express FcεRI on the cell surface and, on activation, they release toxic mediators from their basophilic granules which give them their name.

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

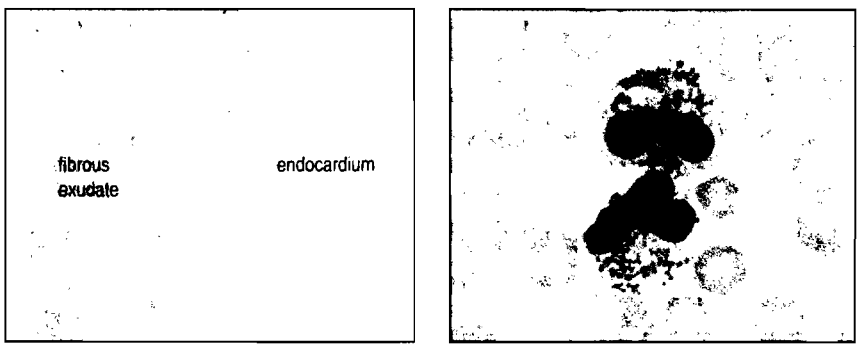

Fig. 11.9 Hypereosinophilia can cause injury to the endocardium. The left hand panel shows a section of the endocardium from a patient with hypereosinophilic syndrome. There is an organized fibrous exudate and the underlying endocardium is thickened by fibrous tissue. Although there are large numbers of circulating eosinophils, these cells are not seen in the injured endocardium, which is thought to be damaged by granules released from circulating eosinophils. The panel on the right shows two partially degranulated eosinophils (center) surrounded by erythrocytes in a peripheral blood film. Photographs courtesy of D Swirsky and T Krausz.

11-8 Allergic reactions following ligation of IgE on mast cells may be divided into an immediate and a late response.

The inflammatory response following 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. 11.10). The immediate reaction follows from the activity of histamine, prostaglandins, and other preformed or rapidly synthesized toxic molecules, which cause a rapid increase in vascular permeability and the contraction of smooth muscle. The second, **late-phase reaction** is caused by the induced synthesis and release of mediators including leukotrienes, chemokines, and cytokines from the activated mast cells (Fig. 11.11). Although this reaction is clinically less dramatic than the immediate response, it is associated with a second phase of smooth muscle contraction and sustained edema.

The late-phase reaction is an important cause of much more serious long-term morbidity, as for example in chronic asthma. This is because the late reaction induces the recruitment of inflammatory leukocytes, including especially eosinophils and T_H2 lymphocytes, to the site of the allergen-triggered mast-cell response. This can easily convert into a chronic inflammatory response if antigen persists, allowing allergen-specific T_H2 cells to promote eosinophilia and IgE production.

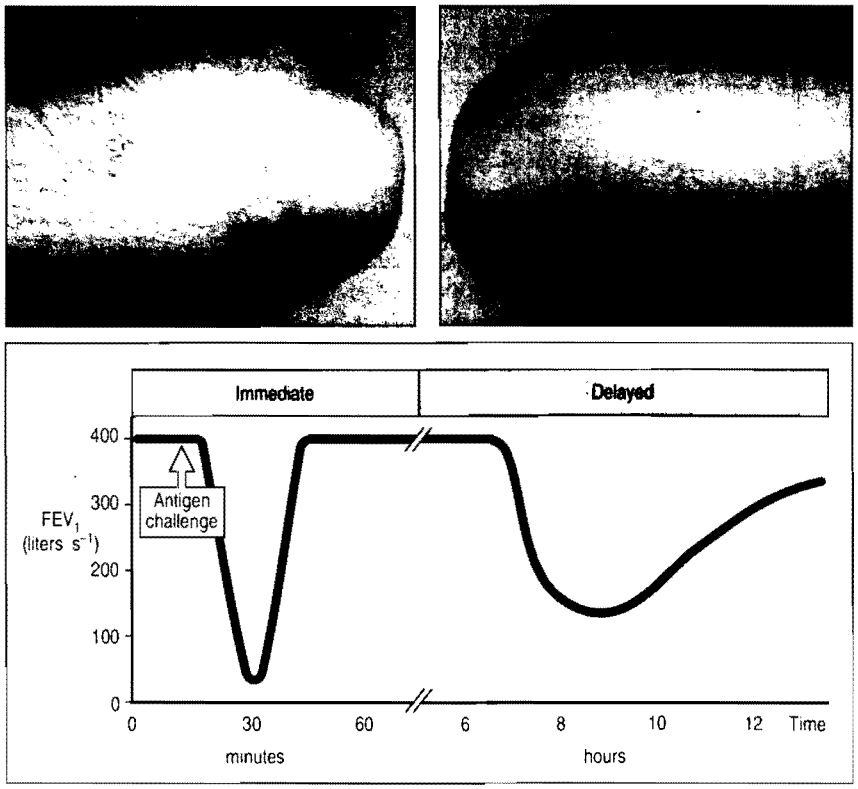

Fig. 11.10 Allergic reactions can be divided into an immediate- and a late-phase response. A wheal-and-flare allergic reaction develops within a minute or two of superficial injection of antigen into the epidermis and lasts for up to 30 minutes. The reaction to an intracutaneous injection of house dust mite antigen is shown in the upper left panel and is labeled HDM; the area labeled saline shows the absence of any response to a control injection of saline solution. A more widespread edematous response, as shown in the upper right panel develops approximately 8 hours later and may persist for some hours. An asthmatic response in the lungs with narrowing of the airways caused by constriction of bronchial smooth muscle can be measured as a fall in the forced expired volume of air in one second (FEV_1). This immediate response (see bottom panel), following inhalation of antigen, peaks within minutes and then subsides, but 8 hours after antigen challenge, there is a late-phase response that also results in a fall in the FEV_1. The immediate response is caused by the direct effects on blood vessels and smooth muscle of rapidly metabolized mediators such as histamine released by mast cells. The late-phase response is caused by the effects of an influx of inflammatory leukocytes attracted by chemokines and other mediators released by mast cells during and following the immediate response. Photographs courtesy of A B Kay.

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodeling of connective tissue matrix
Toxic mediators	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF-α (stored pre-formed in granules)	Promote inflammation, stimulate cytokine production by many cell types, activate endothelium
Lipid mediators	Leukotrienes C4 and D4	Smooth muscle contraction Increased vascular permeability Mucus secretion
	Platelet-activating factor	Chemotactic to leukocytes Amplifies production of lipid mediators Neutrophil, eosinophil, and platelet activation

Fig. 11.11 Molecules synthesized and released by mast cells upon stimulation by antigen binding to IgE. Mast cells release a wide variety of biologically active proteins and other chemical mediators. The lipid mediators derive from membrane phospholipids, which are cleaved to release the precursor molecule arachidonic acid. This molecule can be modified by two pathways, to give rise to prostaglandins, thromboxanes, and leukotrienes. Important products of mast cells are the leukotrienes, which sustain inflammatory responses in the tissues. This is especially true of the leukotriene molecules C4, D4, and E4. Many anti-inflammatory drugs are inhibitors of arachidonic acid metabolism. Aspirin, for example, is an inhibitor of cyclo-oxygenase and blocks the production of prostaglandins.

11-9 The clinical effects of allergic reactions vary according to the site of mast-cell activation.

When re-exposure 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 immediate 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 produced can be resolved. Thus the clinical syndrome produced by an allergic reaction depends critically on three variables: the amount of allergen-specific IgE antibody present; the route by which the allergen is introduced; and its dose (Fig. 11.12).

11-10 The degranulation of mast cells in the walls of blood vessels following systemic absorption of allergen may cause generalized cardiovascular collapse.

If an allergen is given systemically or is rapidly absorbed from the gut, the connective tissue mast cells associated with all blood vessels may be activated. This causes a very dangerous syndrome called **systemic anaphylaxis**. Disseminated mast-cell activation causes a widespread increase in vascular permeability, leading to a catastrophic loss of blood pressure, constriction of the airways, and epiglottal swelling that may cause suffocation, a syndrome called **anaphylactic shock**. This can occur if drugs are administered to allergic people, or after an insect bite in individuals allergic to insect venom. Some foods, for example peanuts or brazil nuts, may be associated with systemic anaphylaxis. This syndrome may be rapidly fatal but can usually be controlled by immediate injection of epinephrine (see Section 11-14).

The most frequent allergic reactions to drugs occur with penicillin and its relatives. In people with IgE antibodies to penicillin, intravenous

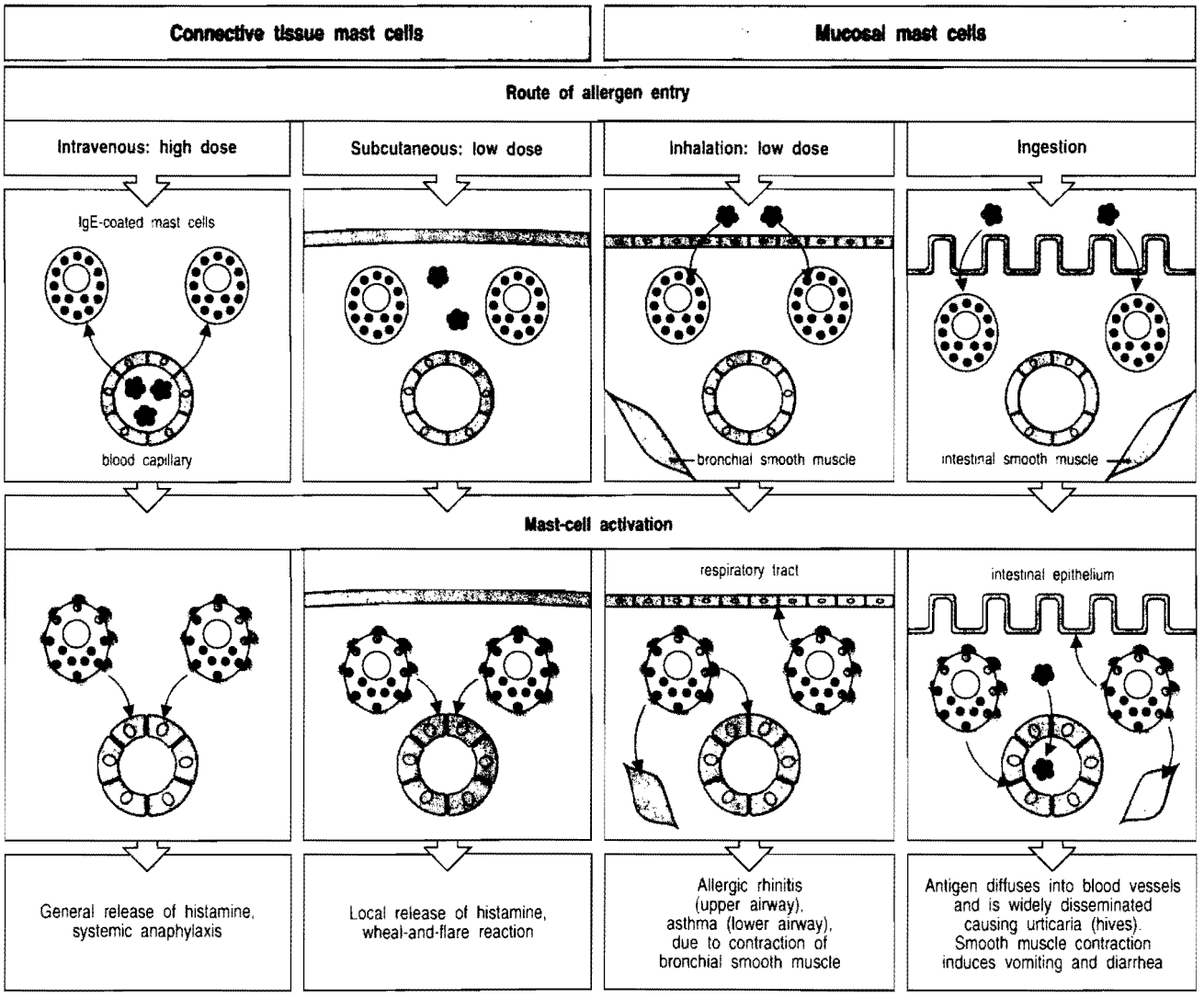

Fig. 11.12 The dose and route of allergen administration determines the type of IgE-mediated allergic reaction that results. There are two main classes of mast cells: those associated with blood vessels, called connective tissue mast cells; and those found in submucosal layers, called mucosal mast cells. 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 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, which 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 smooth muscle contraction; the food allergen is also disseminated in the bloodstream, causing urticaria (hives).

administration can cause anaphylaxis and even death. Great care should taken to avoid giving drugs to patients with a past history of allergy to the same drug, or one that is closely related structurally. Penicillin acts as a hapten (see Section 8-2); it is a small molecule with a highly reactive β-lactam ring, crucial for its antibiotic 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 these penicillin-modified self peptides may provoke a T_H2 response in some individuals. These T_H2 cells then activate penicillin-binding B cells to produce IgE antibody to 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 allergic individuals, the penicillin-modified proteins crosslink IgE molecules on the mast cells to cause anaphylaxis.

11-11 Exposure of the airways to allergens is associated with the development of rhinitis and asthma.

Inhalation is the most common route for allergen entry. Many people have mild allergies to inhaled antigens, manifesting as sneezing and a runny nose. This is called **allergic rhinitis** or hay fever, and results from activation of mucosal mast cells beneath the nasal epithelium by allergens that diffuse across the mucous membrane of the nasal passages. Allergic rhinitis is characterized by local edema leading to nasal obstruction, a nasal discharge, which is typically rich in eosinophils, and irritation of the nose from histamine release. A similar reaction to airborne allergens deposited on the conjunctiva of the eye is called allergic conjunctivitis. These reactions are annoying but cause little lasting damage.

A more serious syndrome is **allergic asthma**, which is triggered by allergen-induced activation of submucosal mast cells in the lower airways. This leads, within seconds, to bronchial constriction and increased fluid and mucus secretion, making breathing more difficult by trapping inhaled air in the lungs. Patients with allergic asthma often need treatment and asthmatic attacks can be life-threatening. An important feature of asthma is chronic inflammation of the airways (Fig. 11.13), characterized morphologically by the continued presence of increased T_H2 lymphocytes, eosinophils, neutrophils, and other leukocytes (Fig. 11.14).

Although allergic asthma is initially driven by a response to a specific allergen, the subsequent chronic inflammation appears to be perpetuated even in the apparent absence of further exposure to allergen, and factors other than re-exposure to antigen may then trigger subsequent

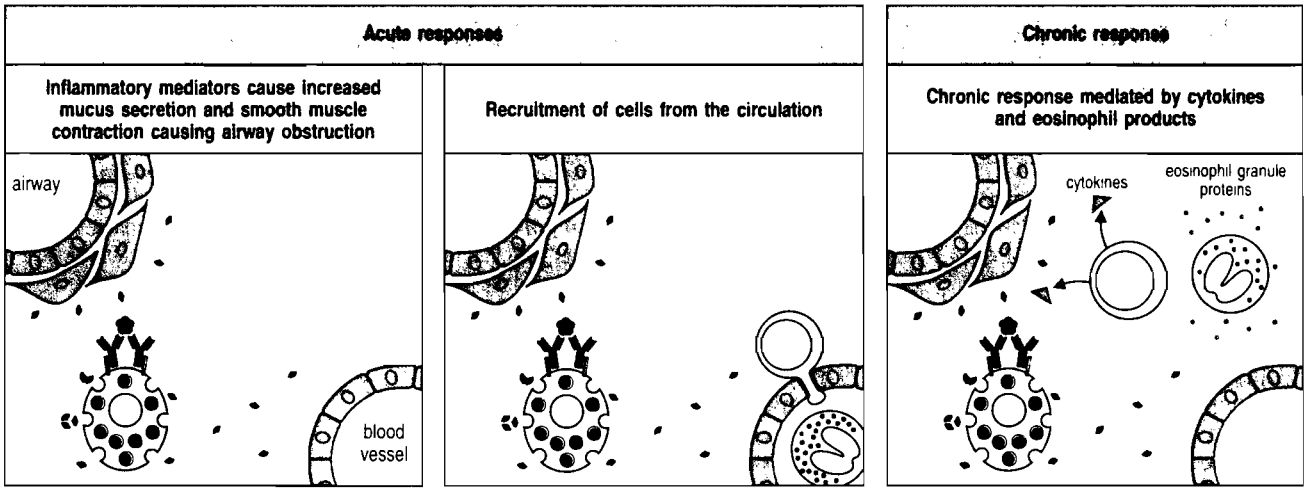

Fig. 11.13 Allergic asthma is characterized by T_H2-mediated chronic inflammation of the airways. T_H2 lymphocytes specific for peptides derived from allergens secrete cytokines that cause B cells to switch to IgE production and also activate eosinophils. Crosslinking of specific IgE on the surface of mast cells by inhaled allergen triggers them to secrete inflammatory mediators, causing bronchial smooth muscle contraction and an influx of inflammatory cells. Activated mast cells also augment eosinophil activation and degranulation, which causes further tissue injury and influx of inflammatory cells. The end result is chronic inflammation, which may then cause irreversible damage to the airways.

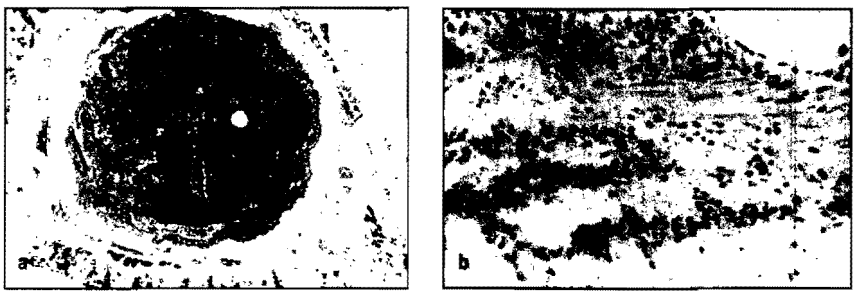

Fig. 11.14 Morphological evidence of chronic inflammation in the airways of an asthmatic patient. Panel a shows a section through a bronchus of a patient who died of asthma; there is almost total occlusion of the airway by a mucus plug. In panel b, a close-up view of the bronchial wall shows injury to the epithelium lining the bronchus, accompanied by a dense inflammatory infiltrate that includes eosinophils, neutrophils, and lymphocytes. Photographs courtesy of T Krausz.

asthmatic attacks. For example, the airways of asthmatics characteristically show hyper-responsiveness to environmental chemical irritants such as cigarette smoke and sulfur dioxide. Disease may be exacerbated further by a T_H2-dominated local immune response to bacterial or viral respiratory tract infections.

11-12 Skin allergy is manifest 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. However, this barrier can be breached by local injection of small amounts of allergen into the skin, for example by a stinging insect. This 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. The mast-cell activation also stimulates a nerve axon reflex, causing vasodilation of surrounding cutaneous blood vessels. 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. 11.10).

Allergists take advantage of the immediate response to test for allergy by injecting minute amounts of potential allergens intracutaneously. Although the reaction following administration of antigen by injection is usually very localized, there is a small risk of induction of systemic anaphylaxis following intracutaneous injection of allergen. Another standard test for allergy is to measure specific IgE antibody levels to a particular allergen in a sandwich ELISA (see Section 2-7).

A more prolonged allergic response is seen mainly in atopic children. They develop a chronic skin rash called **eczema**, due to a chronic inflammatory response similar to that seen in the bronchial walls of patients with asthma. The etiology of eczema is not well understood and it usually clears in adolescence, unlike rhinitis and asthma, which may persist throughout life.

11-13 Allergy to foods can cause symptoms limited to the gut but also commonly causes systemic reactions.

When an allergen is eaten, two types of allergic response are seen. Activation of mucosal mast cells associated with the gastrointestinal tract can lead to transepithelial fluid loss and smooth muscle contraction, generating vomiting and diarrhea. For reasons that are not understood, connective tissue mast cells in the deeper layers of the skin are also activated, presumably by IgE binding to the ingested and absorbed allergen borne by the blood. Histamine released by activated mast cells in these

sites produces **urticaria** or hives—large, itchy red swellings beneath the skin. This is a common reaction when penicillin is ingested by an allergic patient.

11-14 Allergy may be treated by inhibition of the effector pathways activated by antigen crosslinking of cell-surface IgE or by inhibiting IgE production.

The approaches to the treatment and prevention of allergy are set out in Fig. 11.15. The most desirable approach is to shift the antibody response away from an IgE-dominated response towards one dominated by IgG, which can prevent the allergen from activating IgE-mediated effector pathways. A technique to achieve this, known as **desensitization**, has been used in clinical practice for many years. Patients are injected with escalating doses of allergen, starting with tiny amounts. This immunization schedule appears gradually to divert an IgE-dominated response, driven by T_H2 cells, to one driven by T_H1 cells, with the consequent downregulation of IgE production. Recent evidence shows that desensitization is also associated with a reduction in the numbers of mast cells at the site of the allergic reaction.

An alternative and still experimental approach is to vaccinate with peptides derived from common allergens. This procedure induces T-cell anergy *in vivo* by downregulation of expression of the TCR:CD3 complex without triggering IgE-mediated responses, because IgE can only recognize the intact antigen. A major difficulty with this approach is that individual peptide responses are restricted by specific MHC class II alleles and therefore different allergen-derived peptides may be recognized by allergen-specific T cells in individuals expressing different MHC class II alleles. This may present a problem in the outbred human population which expresses a wide variety of polymorphic MHC class II products.

The signaling pathways that enhance the IgE response are potential targets for therapy in allergic disease. Inhibitors of IL-4, IL-5, and IL-13 might reduce IgE responses, although redundancy between some of the activities of these cytokines might make this approach difficult in practice. An alternative approach is to use the cytokines that promote T_H1-type responses. IFN-γ, IFN-α, IL-10, IL-12, and TGF-β have each been shown to reduce IL-4-stimulated IgE synthesis *in vitro* and IFN-γ and IFN-α reduce IgE synthesis *in vivo*.

Step affected	Mechanism	Specific approach
T_H2 activation	Reverse T_H2/T_H1 balance	Injection of specific antigen or peptides
Activation of B cell to produce IgE	Block co-stimulation Inhibit T_H2 cytokines	Inhibit CD40L Inhibit IL-4 or IL-13
Mast-cell activation	Inhibit effects of IgE binding to mast cell	Blockade of IgE receptor
Mediator action	Inhibit effects of mediators on specific receptors Inhibit synthesis of specific mediators	Antihistamine drugs Cyclo-oxygenase inhibitors eg aspirin

Fig. 11.15 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 are believed to divert the immune response to the allergen from a T_H2 to a T_H1 type. The second approach is the use of specific inhibitors to block the effects or synthesis of mast cell inflammatory mediators.

A third approach to the treatment of IgE-mediated disease is to target the high-affinity IgE receptor. An effective competitor for IgE binding to this receptor would block access of IgE with harmful specificities to the surfaces of mast cells, basophils, and eosinophils. Candidate molecules as inhibitors include modified IgE Fc constructs lacking variable regions.

The fourth approach is to block the effector pathways of the allergic response, with the aim of limiting the inflammatory response that follows the activation of cells induced by crosslinking of surface IgE by antigen. This is the mainstay of therapy at present. Epinephrine is an effective inhibitor of anaphylactic reactions by stimulating the reformation of endothelial tight junctions, promoting the relaxation of constricted bronchial smooth muscle, and stimulating the heart. Antihistamines that block the H1 receptor reduce the urticaria following histamine release from cutaneous mast cells and eosinophils. Systemic or local corticosteroids (see Chapter 13) may be needed to suppress the chronic inflammatory changes seen in asthma, rhinitis, or eczema.

Summary.

The allergic response to innocuous antigens reflects the pathophysiological aspect of a response that may have been selected over evolutionary time for its physiological role in protecting hosts against helminthic parasites. It is triggered by IgE antibody bound to the high-affinity mast cell IgE receptor FcεRI. Mast cells are strategically distributed beneath the mucosal surfaces of the body and in connective tissue. The resulting inflammation can be divided into early events, characterized by rapidly dispersed mediators like histamine, and later events that involve leukotrienes, cytokines, and chemokines, which recruit and activate particularly eosinophils, but also basophils. The late phase of this response can evolve into chronic inflammation, which is most clearly seen in allergic asthma.

Hypersensitivity diseases.

In the first part of this chapter we have seen how IgE mediates allergic reactions, also known as type I hypersensitivity. Immunological responses mediated by IgG antibodies or specific T cells can also cause adverse hypersensitivity reactions. Although these effector arms of the immune response normally participate in protective immunity to infection, they occasionally react with non-infectious antigens to produce acute or chronic hypersensitivity reactions. We shall describe common examples of such reactions in this last part of this chapter.

11-15 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) is an uncommon side-effect associated with the intake of some drugs, such as the antibiotic penicillin, the anti-cardiac arrhythmia drug, quinidine, or the anti-hypertensive agent, methyldopa. This is an example of a **type II hypersensitivity reaction** in which the drug binds to the cell surface and serves as a target for anti-drug antibodies, which initiate complement activation on the cell surface (see Fig. 11.2). The anti-drug antibodies are only made in a minority of

individuals whose susceptibility to develop such antibodies is not understood. The combination of cell-bound antibody and complement trigger clearance of the cell from the circulation, predominantly by tissue macrophages in the spleen, which bear Fcγ and complement receptors.

11-16 Systemic immune complex-mediated disease may follow the administration of large quantities of poorly catabolized antigens.

Type III hypersensitivity reactions arise when the antigen is soluble. The pathology is caused by the deposition of antigen:antibody aggregates or **immune complexes** in certain tissue sites. Immune complexes are generated in every antibody response. The pathogenic potential of immune complexes is determined, in part, by their size. Larger aggregates fix complement and are readily cleared from the circulation by the mononuclear phagocytic system, while the small complexes that form at antigen excess (see Fig. 2.13) tend to deposit in blood vessel walls, and it is here that they cause tissue damage by ligation of Fc and complement receptors on leukocytes, which in turn cause tissue injury.

A local **type III hypersensitivity reaction** can be triggered in the skin of sensitized individuals possessing IgG antibodies directed against the sensitizing antigen. When antigen is injected into the skin, IgG antibody that has diffused into the tissues forms immune complexes locally. The immune complexes bind Fc receptors on leukocytes and also activate complement, releasing C5a, which creates a local inflammatory response with increased vascular permeability. The enhanced vascular permeability allows fluid and cells, especially polymorphonuclear leukocytes, to enter the site from the local vessels. This reaction, called an **Arthus reaction** (Fig. 11.16), is absent in mice lacking expression of

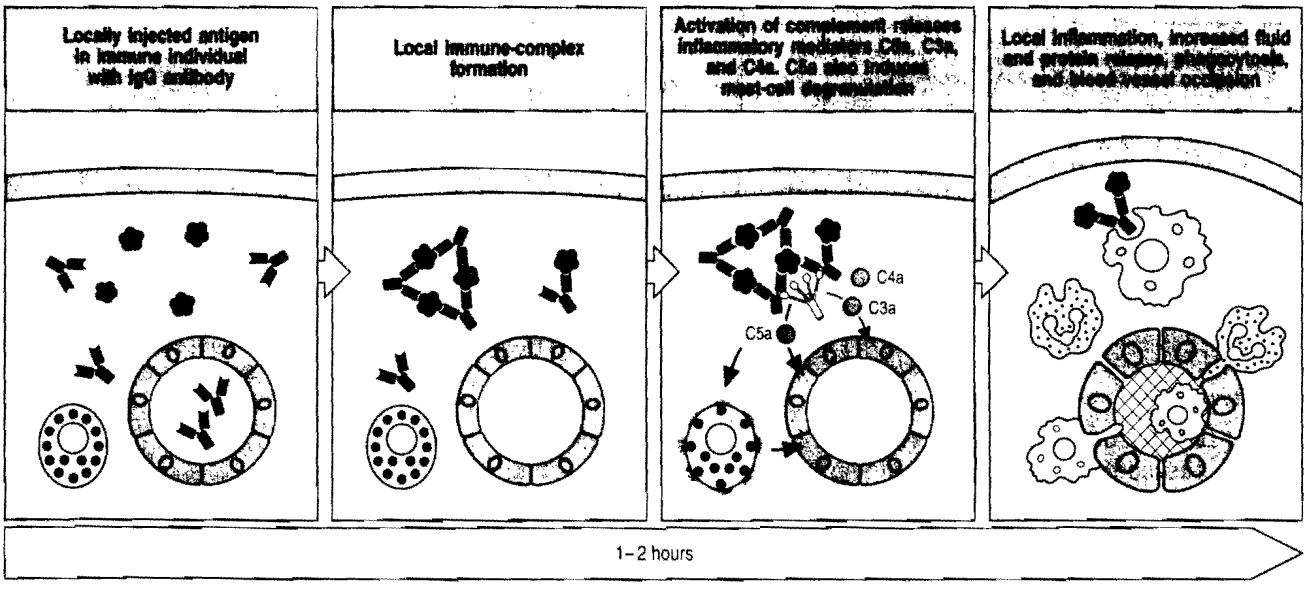

Fig. 11.16 The deposition of immune complexes in local tissues causes a local inflammatory response known as an Arthus reaction (type III hypersensitivity reaction). In individuals who have already made IgG antibody to allergen, allergen injected into the skin forms immune complexes with IgG antibody that has diffused out of the capillaries. Since the dose of antigen is low, the immune complexes are only formed close to the site of injection, where they activate Fcγ receptor-bearing cells and complement. As a result, inflammatory cells invade the site, and blood vessel permeability and blood flow are increased. Platelets also accumulate at the site, ultimately leading to vessel occlusion.

the γ chain common to all Fc receptors, showing the primary importance of Fc receptors on leukocytes in triggering inflammatory responses.

Systemic injection of large quantities of a poorly catabolized foreign antigen may cause a type III hypersensitivity reaction which is known as **serum sickness**. This term described the illness that followed the administration of therapeutic horse antiserum. In the pre-antibiotic era, immune horse serum was often used to treat pneumococcal pneumonia. Specific antibodies in the horse serum would help the patient to clear the infection. In much the same way, anti-venin (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.

Serum sickness follows 7–10 days after the injection of the horse serum, a time interval which corresponds with the time for a primary immune response against the foreign antigen. The clinical features of serum sickness are chills, fevers, rash, arthritis, and sometimes glomerulonephritis. Urticaria is a prominent feature of the rash, implying a role for histamine derived from mast-cell degranulation.

The immunopathological basis of serum sickness is illustrated in Fig. 11.17. The onset of disease coincides with the development of antibodies, which form immune complexes with the antigen throughout the body. These immune complexes fix complement and bind and activate all leukocyte types bearing Fc and complement receptors, which in turn cause widespread tissue injury. The formation of immune complexes causes clearance of the foreign antigen and for this reason, serum sickness is a self-limiting disease. Serum sickness following a second dose of horse antiserum follows the kinetics of a secondary antibody response and the onset of disease occurs typically within a day or two. Serum sickness is nowadays seen following the use of anti-lymphocyte globulin, used as an immunosuppressive agent in transplant recipients (see Chapter 13), and also rarely after the administration of streptokinase, a bacterial enzyme that is used as a thrombolytic agent to treat patients with a myocardial infarction or heart attack.

A similar type of immunopathological response is seen in response to soluble antigens in two other situations in which antigen persists. The first is when an adaptive antibody response fails to clear an infectious agent, for example in subacute bacterial endocarditis or in chronic viral hepatitis. In this situation, the multiplying bacteria or viruses are continuously generating new antigen in the presence of a persistent antibody response, which fails to eliminate the organism. Immune complex disease ensues, with injury to small blood vessels in many organs including the skin, kidneys, and nerves. Immune complexes also form in autoimmune diseases such as systemic lupus erythematosus where, because the antigen persists, the deposition of immune complexes continues, and serious disease can result (see Section 12-6).

Some inhaled allergens provoke IgG rather than IgE antibody responses, perhaps because they are present at much higher levels in inhaled air. When a person is re-exposed to high doses of such inhaled antigens, immune complexes form in the alveolar wall of 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 occurs in certain occupations such as farming, where exposure to hay dust or mold spores is repetitive. The disease that results is therefore called **farmer's lung**. It can lead to permanent damage to the alveolar membranes if exposure is sustained.

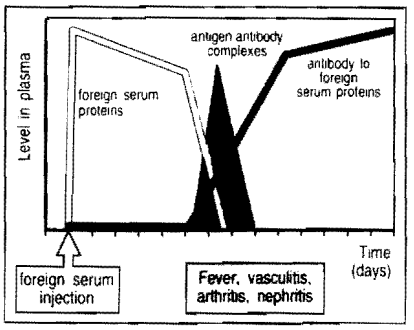

Fig. 11.17 Serum sickness is a classical example of a transient immune-complex-mediated syndrome. An injection of a foreign protein or proteins, in this case derived from horse serum, leads to an antibody response. These antibodies form immune complexes with the circulating foreign proteins. These complexes are deposited in small vessels and activate complement and phagocytes, inducing fever, and the symptoms of vasculitis, nephritis, and arthritis. All these effects are transient and resolve when the foreign protein is cleared.

11-17 Delayed-type hypersensitivity reactions are mediated by T_H1 cells and CD8 cytotoxic T cells.

Unlike the immediate hypersensitivity reactions, which are mediated by antibodies, **delayed-type hypersensitivity** or **type IV hypersensitivity reactions** are mediated by specific T cells. Such effector T cells function in essentially the same way as during a response to an infectious pathogen, as described in Chapter 7. Diseases in which type IV hypersensitivity responses predominate are shown in Fig. 11.18. These responses are clearly caused by T cells, since they can be seen in agammaglobulinemic individuals. Such responses can also be transferred between experimental animals using pure T cells or cloned T-cell lines.

The prototypic delayed-type hypersensitivity reaction is an artefact of modern medicine, the tuberculin test (see Section 2-30). This is a way of determining whether an individual has previously been infected with *Mycobacterium tuberculosis*. When small amounts of a protein from *M. tuberculosis* are injected into subcutaneous tissue, a T-cell mediated local inflammatory reaction evolves over 24–72 hours in individuals who have previously responded to this pathogen. The response is mediated by T_H1 cells, which enter the site of antigen injection, recognize complexes of peptide:MHC class II on antigen-presenting cells, and release inflammatory cytokines that increase local blood vessel permeability, bringing fluid and protein into the tissue and recruiting accessory cells to the site (Figs. 11.19 and 11.20). Each of these phases takes several hours and so the mature response appears only 24–48 hours after challenge.

Very similar reactions are observed in several cutaneous hypersensitivity responses. For instance, the rash produced by poison ivy is caused by a T-cell response to a chemical in the poison ivy leaf called pentadecacatechol. This compound binds covalently to host proteins. The modified self proteins are then cleaved into modified self peptides, which may bind to self MHC class II molecules where they can be recognized by T_H1 cells. When specifically sensitized T cells recognize these complexes, they can produce extensive inflammation. As the chemical is delivered by contact with the skin, this is called a **contact hypersensitivity reaction**. The compounds that cause such reactions must be chemically active so that they can form stable complexes with host proteins.

Fig. 11.18 Type IV responses in allergy. 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.

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells

Syndrome	Antigen	Consequence
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Contact dermatitis
Gluten-sensitive enteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

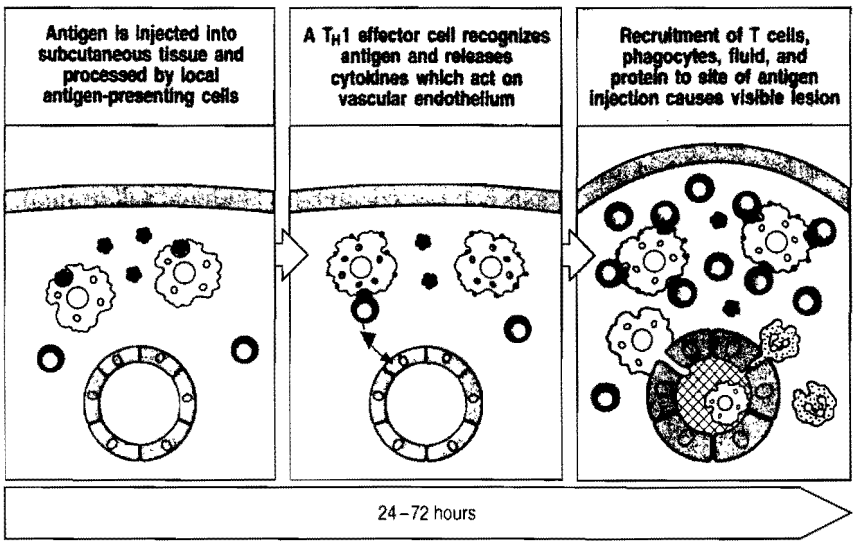

Fig. 11.19 The time course of a delayed-type hypersensitivity reaction. The first phase involves uptake, processing, and presentation of the antigen by local antigen-presenting cells. In the second phase, T_H1 cells that were primed by a previous exposure to the antigen migrate to the site of injection and become activated. Since these specific cells are rare, and since there is no inflammation to attract cells to the site, it may 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 accumulation of fluid and protein. At this point, the lesion becomes apparent.

Some insect proteins also elicit delayed-type hypersensitivity responses. However, the early phases of the host reaction to an insect bite are often IgE-mediated or the result of the direct effects of insect venoms. Finally, some unusual delayed-type hypersensitivity responses to divalent cations have been observed, for example to nickel, which may alter the conformation or peptide binding of MHC class II molecules.

Type IV hypersensitivity reactions can also involve CD8 T cells, which damage tissues mainly by cell-mediated cytotoxicity. Some chemicals, including pentadecacatechol, are soluble in lipid and can therefore cross the cell membrane and modify intracellular proteins. These modified proteins generate modified peptides within the cytosol, which are translocated into the endoplasmic reticulum and delivered to the cell surface by MHC class I molecules. These are recognized by CD8 T cells, which can cause damage either by killing the eliciting cell or by secreting cytokines such as IFN-γ.

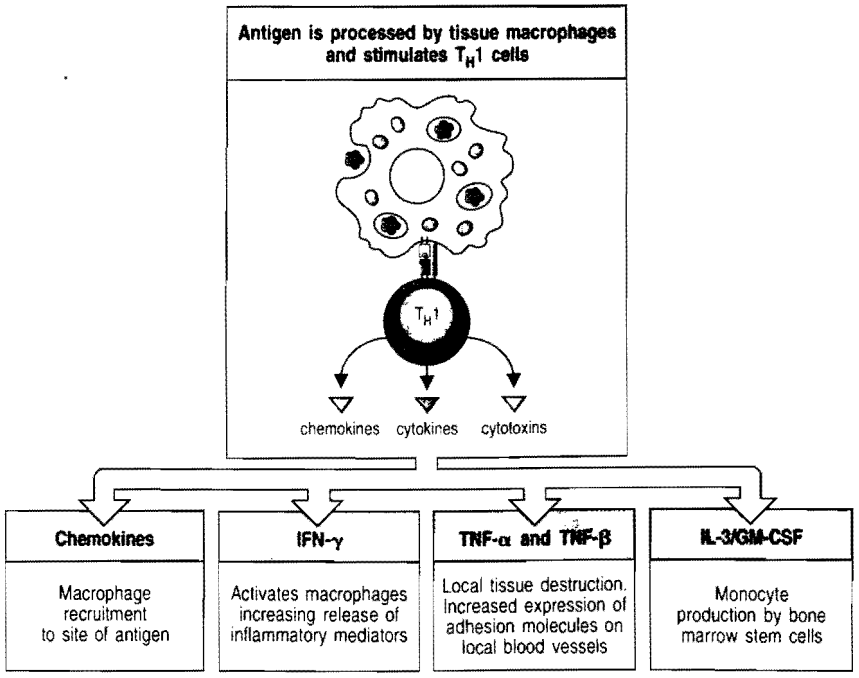

Fig. 11.20 The delayed-type (type IV) hypersensitivity response is directed by cytokines released by T_H1 cells stimulated by antigen. Antigen in the local tissues is processed by antigen-presenting cells and presented on MHC class II molecules. Antigen-specific T_H1 cells can recognize the antigen locally at the site of injection, and release chemokines and cytokines that recruit macrophages to the site of antigen deposition. Antigen presentation by the newly recruited macrophages then amplifies the response. T cells may also affect local blood vessels through release of TNF-β and TNF-α, and stimulate the production of macrophages through the release of IL-3 and GM-CSF. Finally, T_H1 cells activate macrophages through release of IFN-γ and TNF-α, and kill macrophages and other sensitive cells through release of TNF-β or by expression of the Fas ligand.

Summary.

Hypersensitivity diseases reflect normal immune mechanisms directed to innocuous antigens. 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 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.

Summary to Chapter 11.

Immune responses to otherwise innocuous antigens produce allergic or hypersensitive reactions upon re-exposure to the same antigen. Most allergies involve the production of IgE antibody to 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 T_H2 cells, which are initially primed in the presence of a burst of IL-4 released by specialized T cells early in the immune response. The IgE produced binds to the high-affinity IgE receptor FcεRI on mast cells, basophils, and activated eosinophils. Physiologically, this provides front-line defense against pathogens but, in advanced societies, the IgE bound to mast cells triggers allergic reactions. Antibodies of other isotypes and specific effector T cells contribute to hypersensitivity to other antigens.

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