Veterinary Immunology: An Introduction, 8th Edition

25 CHAPTER 25 Type I Hypersensitivity

25.1 KEY POINTS

- Type I hypersensitivities, also called immediate hypersensitivity, are mediated by immunoglobulin E (IgE) attached to mast cells.

- Disease is caused by the rapid release of inflammatory molecules from mast cells following the binding of antigens to IgE.

- The clinical signs of allergic disease depend in large part on the route by which antigens (allergens) enter the body.

- Massive systemic release of inflammatory molecules by mast cells may give rise to allergic anaphylaxis. In this syndrome animals may collapse and die rapidly as a result of the contraction of critical smooth muscles such as those lining the bronchi.

- Animals commonly suffer from allergies to foods, inhaled antigens, vaccines, or drugs.

- In many cases, especially in the dog, these allergies may be manifested by intense pruritus.

- Treatment may include epinephrine for allergic anaphylaxis, corticosteroids for local inflammation, and desensitizing injections of allergen for prolonged control. However, by far the most satisfactory solution is to prevent exposure to the offending allergens.

The role of mast cells in causing acute inflammation was discussed at the beginning of this book. Mast cells serve as sentinel cells. They are covered by an array of receptors that permit them to react in response to many different stimuli. For example, they release inflammatory molecules in response to microbial invasion or tissue damage (see Chapter 2). This release normally occurs in a controlled manner and ensures that the severity of the inflammation is appropriate to the body's immediate needs. Type I hypersensitivity reactions, in contrast, are a form of inflammation that result from the interaction of antigens with immunoglobulin E (IgE) bound to mast cell IgE receptors. This leads to the rapid release of mast cell secretory granule contents (Figure 25-1). The granule contents in turn cause acute inflammation.

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FIGURE 25-1 The mechanism of type I hypersensitivity reactions. Numerous biologically active molecules are released by mast cells and basophils when antigen cross-links two immunoglobulin E *(IgE)* molecules on the mast cell surface. Some are produced immediately. Others may be synthesized within minutes or hours.
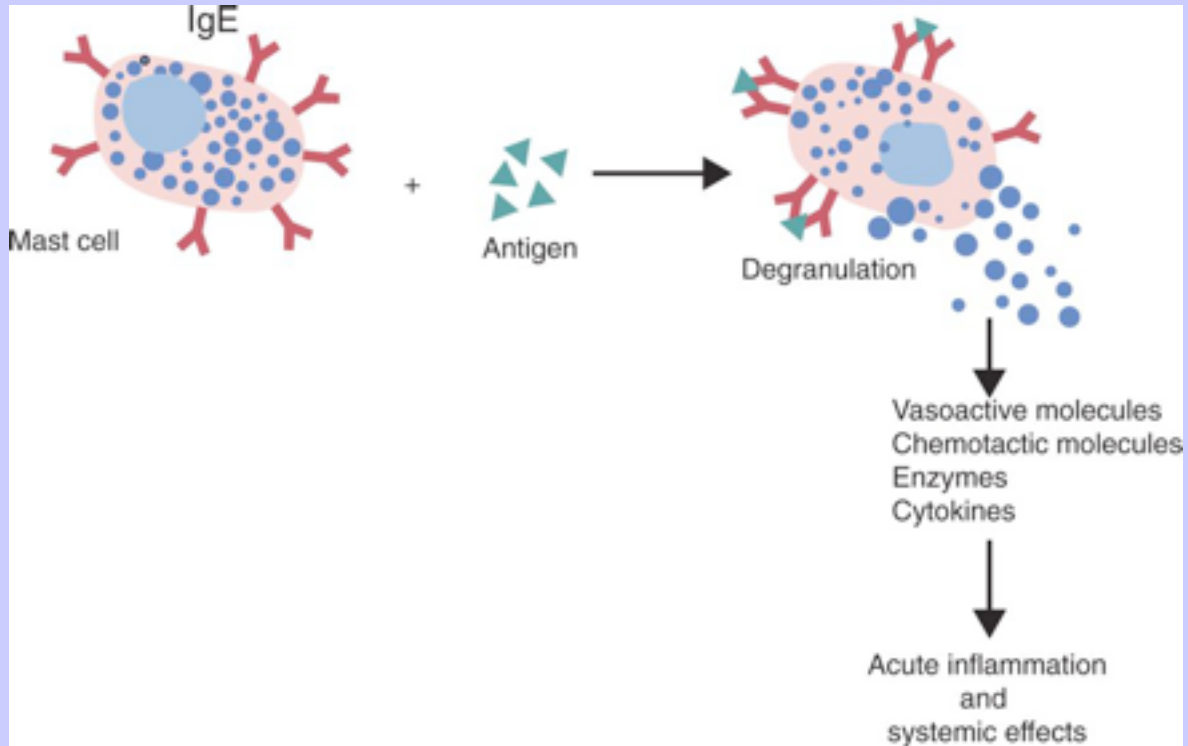
The benefits of this type of inflammation are unclear, but it is of major clinical significance in veterinary medicine (Box 25-1).

25.2 Box 25-1 Nomenclature

Immunoglobulin E mediates immediate hypersensitivity reactions, so called because they develop within seconds or minutes after exposure to antigen. This type of hypersensitivity reaction is also commonly called an allergy. Antigens that stimulate allergies may be called allergens. If an immediate hypersensitivity reaction is systemic and life-threatening, it is called allergic anaphylaxis or anaphylactic shock. Sometimes an animal may have a reaction that is similar to allergic anaphylaxis but is not immunologically mediated. This type of reaction is described as anaphylactoid.

25.3 INDUCTION OF TYPE I HYPERSENSITIVITY

All animals are exposed to environmental antigens in food and in inhaled air. Most normal animals respond to these antigens by producing IgG or IgA antibodies, and there is no obvious clinical consequence. Some animals,

however, may respond to environmental antigens by mounting an exaggerated Th2 response and producing excessive amounts of IgE antibodies. These animals develop type I hypersensitivity reactions or allergies. The excessive production of IgE is called atopy, and affected individuals are said to be atopic. The development of atopy and type I hypersensitivity depends on the interaction of genes and environmental factors. The genetics of atopy and allergy are complex. Thus if both parents are atopic, most of their offspring will also be atopic and will suffer from allergies. If only one parent is atopic, the percentage of atopic offspring varies. There is also a breed predisposition to atopy in dogs. For example, atopic dermatitis is most commonly observed in Terriers (Bull, Welsh, Cairn, West Highland White, Scottish), Dalmatians, and Irish Setters, although nonpurebred dogs may also be affected. The heritability of atopic dermatitis in Labrador and golden retrievers is estimated to be a relatively high 0.47. In horses, high levels of IgE are associated with certain major histocompatibility complex (MHC) DRB haplotypes.

Environmental factors such as childhood infections also influence the development of atopic diseases. Thus children who have had multiple infections when young appear to be less likely to develop allergies than those not exposed to such infections. On the other hand, contact with allergens on the first day of life predisposes puppies to develop significantly higher IgE levels than puppies sensitized at 4 months of age.

Normal animals infested by parasitic worms and insects also produce large amounts of IgE. It is believed that the IgE response may have evolved specifically to counteract these organisms. Chitin, the biopolymer that confers structural rigidity to fungi, insects, and helminths, induces the accumulation of cells such as eosinophils and basophils in tissues and may be a key trigger of some of these allergic reactions. Indeed, the self-cure reaction seen in parasitized sheep has long been the only well-characterized beneficial feature of type I hypersensitivity (Box 25-2) (see Chapter 24). It is of interest to note that atopic and parasitized dogs may have reduced IgA levels, an observation supporting the concept that a deficiency of IgA may predispose to a compensatory increase in IgE production (see Chapter 19).

25.3.1

> ## Box 25-2 Vertical Transmission of Allergies in Dogs?
>
> There is some evidence that the allergic status of parent animals, especially mothers, directly influences the development of allergies in their offspring. Thus in one experiment, two litters of newborn puppies from ragweed-allergic beagles were compared with two litters from nonallergic beagles. (The genetic differences between the parent animals were minimal.) The puppies were repeatedly exposed to ragweed pollen in their inhaled air beginning 1 week after birth. By 40 weeks of age, the puppies from allergic parents had produced high levels of total IgE and ragweed-specific IgE. The puppies from nonallergic parents had produced only IgG antibodies to ragweed. The puppies from allergic parents had eosinophils in their lung washings and developed asthmatic responses to inhaled ragweed pollen. The puppies from nonallergic parents did not. The mechanisms of this effect are unknown. It is possible that factors ingested with the allergic mother's colostrum may favor the switch to a Th2 response in their puppies.
>
> Data from Barrett EG, Rudolph K, Bowen LE, Bice DE: Immunology 110: 493-500, 2003.

25.4

IMMUNOGLOBULIN E

IgE is an immunoglobulin of conventional four-chain structure with a molecular weight of about 200 kDa (see Chapter 14, Figure 14-7). It is found in serum in exquisitely small quantities (9 to 700 mg/ml in dogs), and its half-life there is only 2 days. Most of the body's IgE is not found in the bloodstream but is firmly bound to Fce receptors on tissue mast cells, where it has a half-life of 11 to 12 days. Some IgG subclasses may also bind to mast cell receptors and mediate type I hypersensitivity reactions. For example, IgG4 is associated with atopic dermatitis in

the dog. However, the affinity of these subclasses for mast cells is much lower than that of IgE, and they are of much less clinical significance.

25.4.1 IgE Production

Atopic individuals are predisposed to generate Th2 cells. The Th2 cells produce interleukin-4 (IL-4) or IL-13. These cytokines, together with co-stimulation from CD40, trigger B cell IgE synthesis. IL-4 is also produced in significant amounts by stimulated mast cells. This mast cell–derived IL-4 may alter the helper cell balance and enhance yet more Th2 cell production and IL-4 release (Figure 25-2). Some allergic humans over-express IL-4, leading to excessive Th2 cell activity and enhanced IgE production.

25.4.2 IgE Receptors

There are two types of IgE receptors: high-affinity FceRI and low-affinity FceRII (CD23). There are two forms of FceRI. One form is found on mast cells, basophils, neutrophils, and eosinophils. This form consists of four chains, one a, one b, and two γ chains (abg_2) (Figure 25-3). The a chain binds IgE, the β chain stabilizes the complex, and the γ chains serve as signal transducers. (This same γ chain is also a signal transducer in FcγRI, FcγRIII, and γ/δ T cell antigen receptor.) The affinity of FceRI for IgE is very high (10^{-10} M), so they bind almost irreversibly. The presence of FceRI ensures that mast cells are constantly coated with IgE.

The second form of FceRI consists of three chains, one a and two γ chains (ag_2). It is found on antigen-presenting dendritic cells and monocytes. When an antigen binds to this IgE, it is ingested and treated as exogenous antigen. The expression of FceRI on antigen-presenting cells is enhanced by IL-4 from Th2 cells. Thus a positive feedback loop (the allergy loop) develops (Figure 25-4). The antigen-processing cells present antigen more effectively to Th2 cells. The Th2 cells then secrete IL-4 and enhance IgE production.

The second type of IgE receptor, FceRII (CD23), is a selectin found on B cells, natural killer cells, macrophages, dendritic cells, eosinophils, and platelets. In addition to being an IgE receptor, FceRII also binds the complement receptor CR2 (CD21) (Figure 25-5). Thus B cells expressing FceRII will bind CR2 on other B cells, T cells, and dendritic cells. By linking B cells to dendritic cells, FceRII enhances B cell survival and promotes IgE production.

25.5 THE RESPONSE OF MAST CELLS TO ANTIGEN

When IgE binds to FceRI on the surface of mast cells, it has no obvious immediate effect on the cell. The mast cell is, however, primed to bind antigen and can reside in tissues with its attached IgE acting like a mine

FIGURE 25-2 The role of interleukin-4 *(IL-4)* in induction of immunoglobulin E *(IgE)* responses. IL-4 is produced by Th2 cells. Once released, it promotes the development of more Th2 cells, which are major sources of this cytokine and promote IgE responses. The degranulation of mast cells also releases IL-4, which further promotes this reaction. Natural killer cells may also serve as an initial source of IL-4. The response to IL-4 is inhibited by interferon-γ *(IFN-γ)* and IL-12.

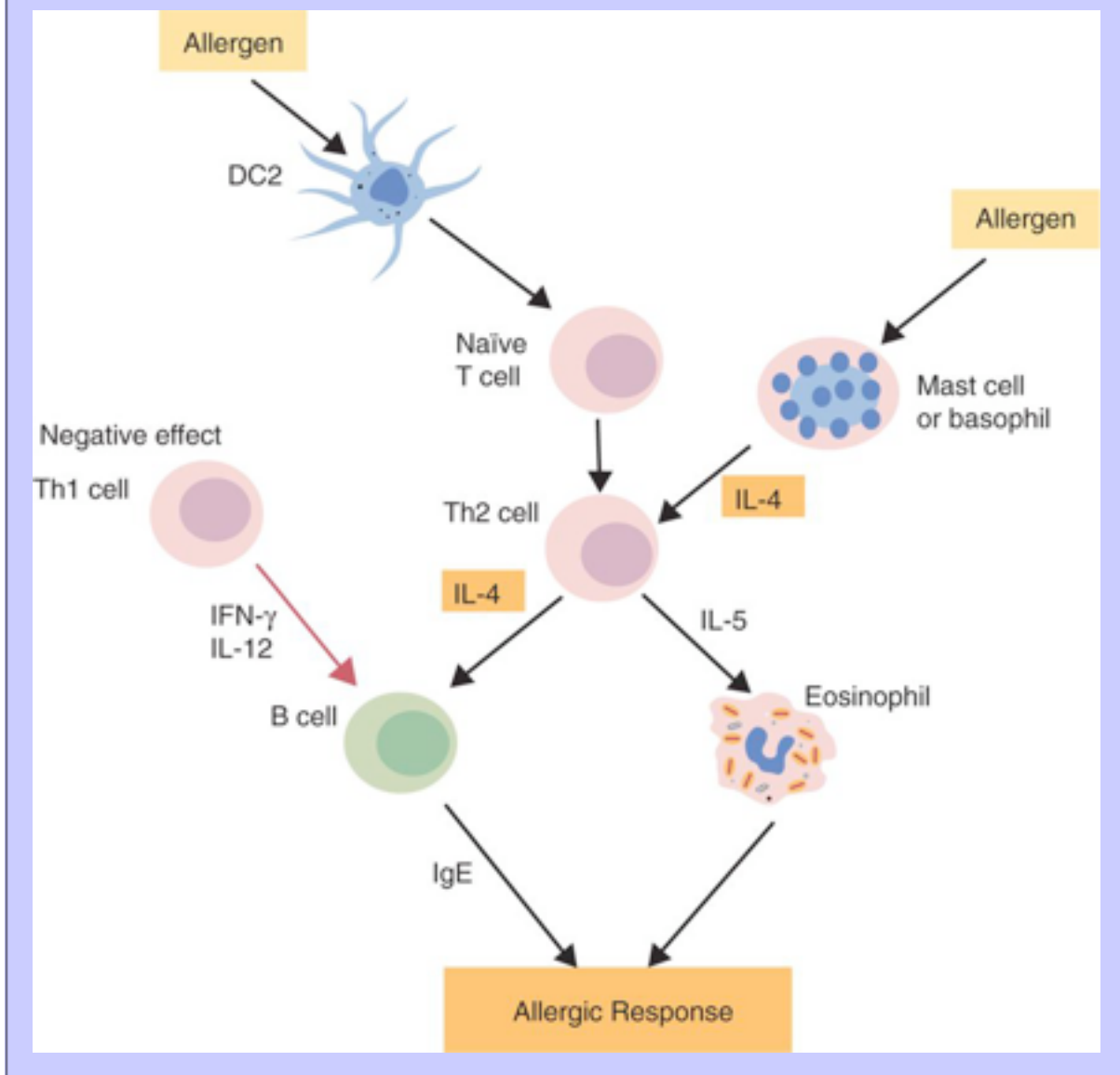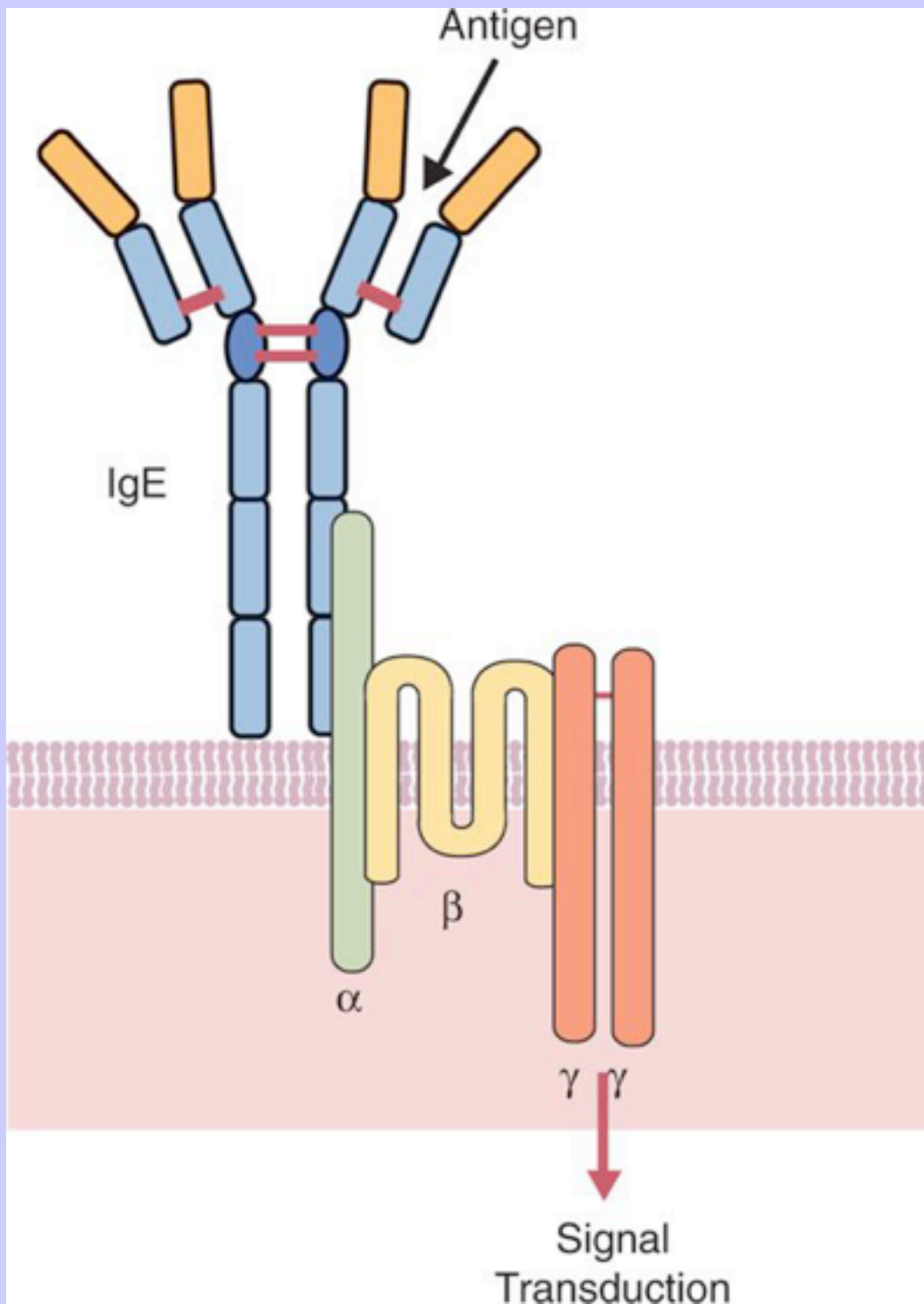FIGURE 25-3 The structure of FceRI. The tetrameric form containing two γ chains is found on mast cells and basophils.

in a minefield. If an antigen enters the tissue, encounters the mast cell, and cross-links two of these bound IgE molecules, the mast cell will be triggered to release the contents of its secretory lysosomes and inflammatory mediators into the surrounding tissues (Figure 25-6).

This triggering of rapid exocytosis is initiated when an antigen molecule cross-links two FcεRI and activates several protein tyrosine kinases. These, in turn, activate phospholipase C, leading to the production of diacylglycerol and inositol triphosphate. These mediators then increase intracellular calcium and activate more protein kinases. These protein kinases phosphorylate myosin in the cytoskeleton and make the secretory lysosomes move to the cell surface. Their membranes then fuse with the plasma membrane, and their contents are released into the extracellular fluid.

Cross-linking of two FceRI by an antigen also activates phospholipase A, which acts on membrane phospholipids to produce arachidonic acid. Other enzymes then convert the arachidonic acid to leuko-trienes and prostaglandins (see Chapter 2, Figure 2-19). Finally, the protein kinases promote transcription

FIGURE 25-4 The allergy loop. Dendritic cells express trimeric FceRI and as a result can bind antigen bound to immunoglobulin E *(IgE)*. This antigen, once processed, stimulates Th2 responses. These Th2 cells in turn secrete cytokines, which further promote the IgE response.
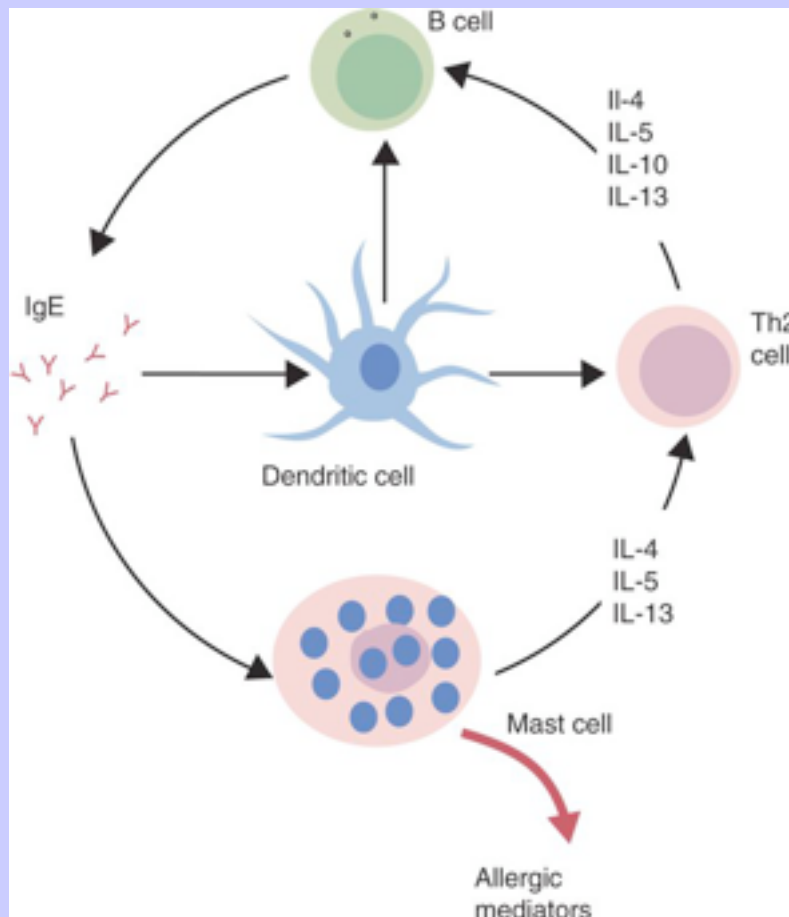
FIGURE 25-5 The combination of the Fcε receptors with their ligands stimulates a variety of different responses in mast cells depending on the nature of these stimuli.
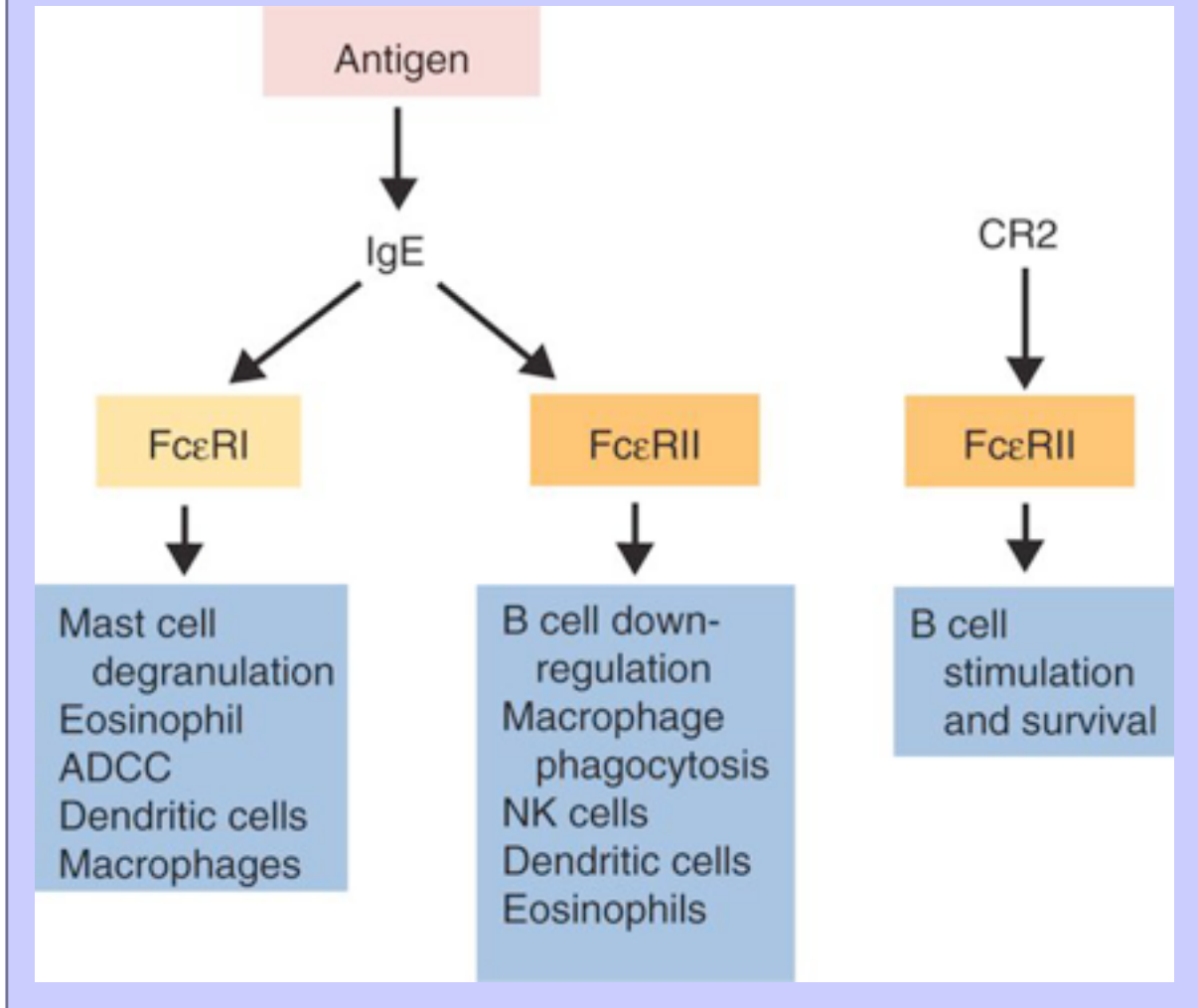
FIGURE 25-6 A simplified view of mast cell signal transduction. The process is triggered by cross-linking two bound immunoglobulin E *(IgE)* molecules with antigen. The combined signal eventually leads to degranulation (granule exocytosis), leukotriene and prostaglandin synthesis, and cytokine production.
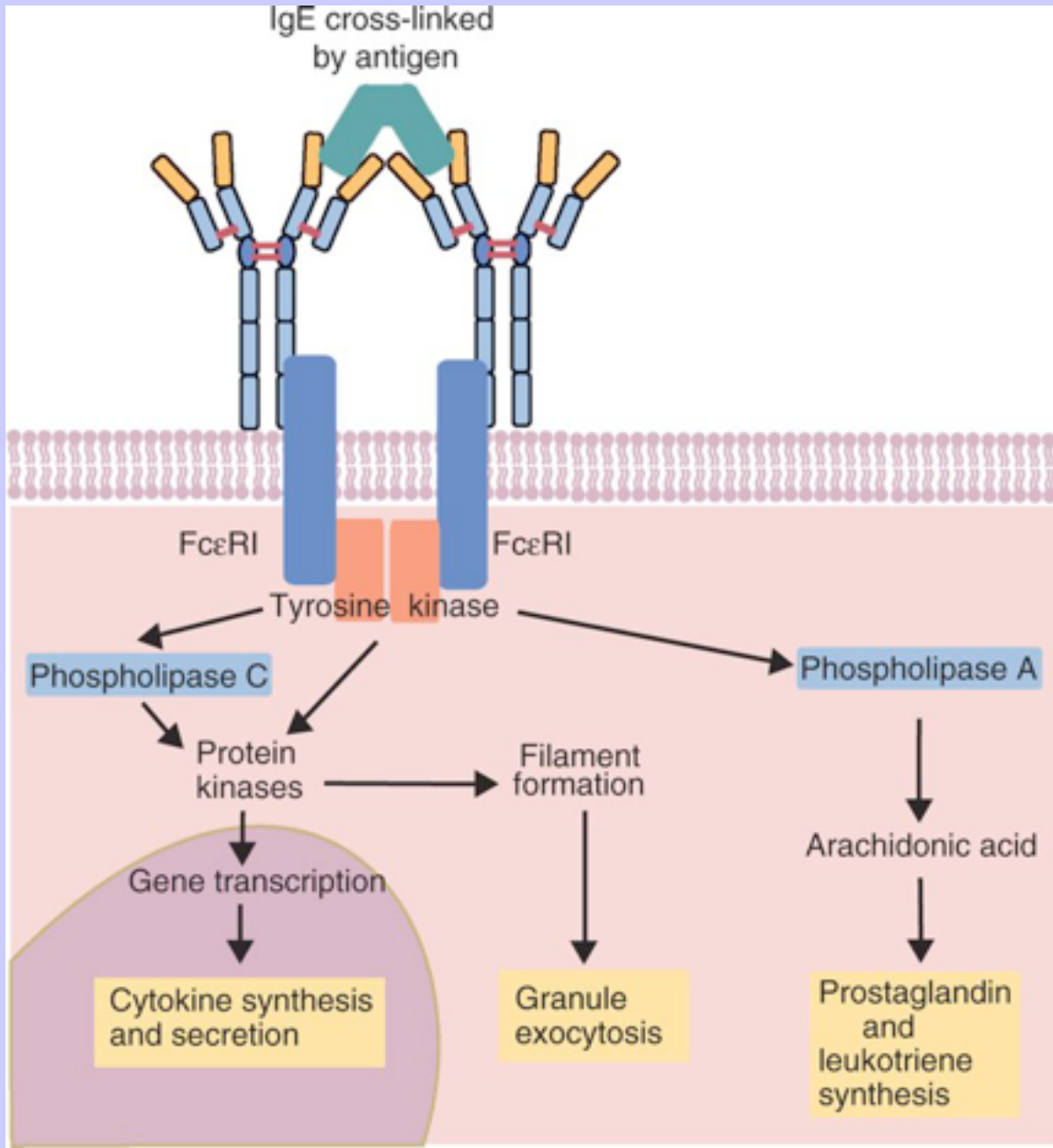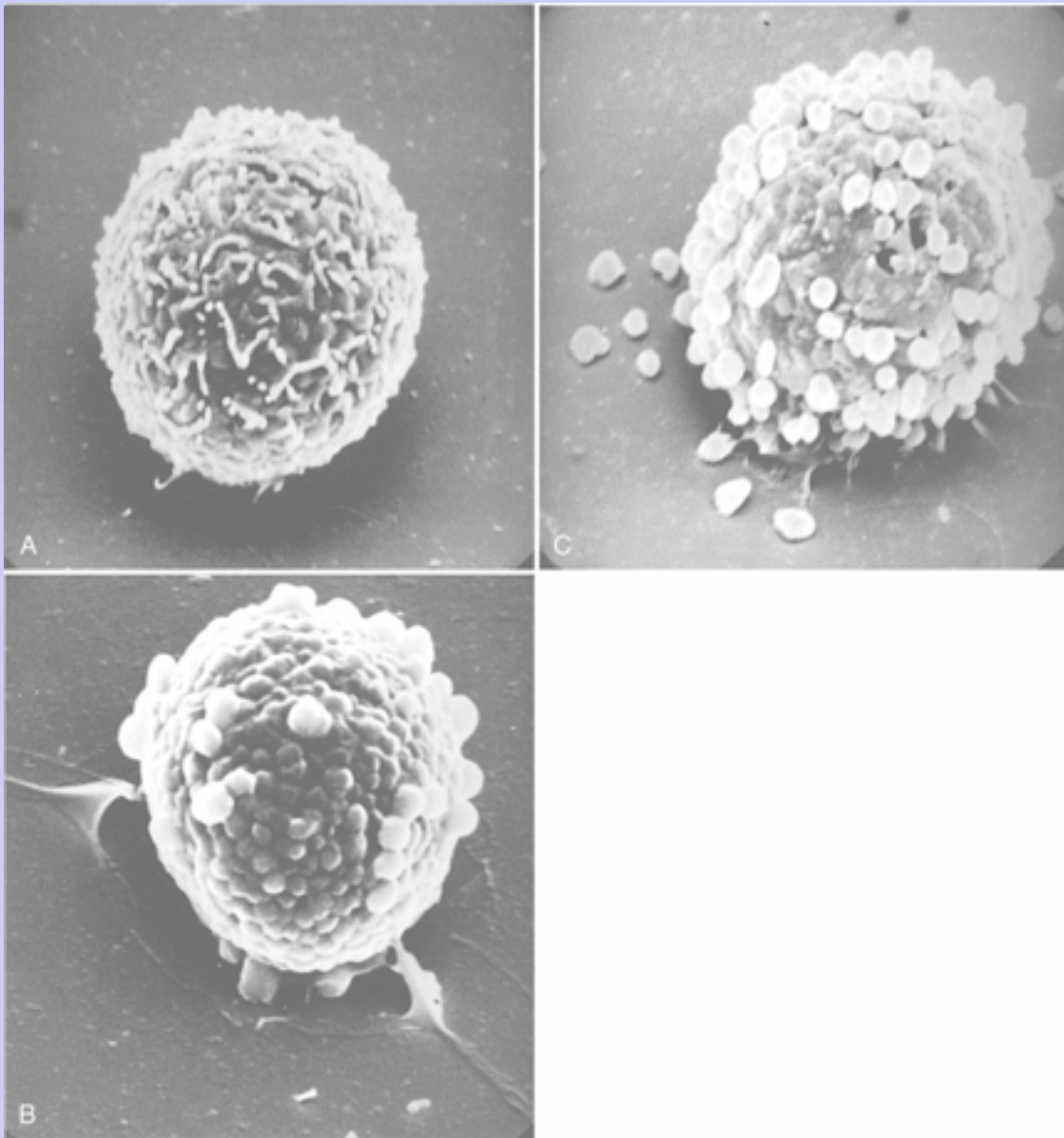

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FIGURE 25-7 Scanning electron micrographs showing the rapid exocytosis of granucles from stimulated mast cells. **A,** A normal rat mast cell. **B,** A sensitized mast cell fixed 5 seconds after exposure to antigen. **C,** A sensitized mast cell fixed 60 seconds after exposure to antigen (×3000). (From Tizard IR, Holmes WL: *Int Arch Allergy Appl Immunol* 46:867-879, 1974.)

and expression of genes coding for many different cytokines as well as the genes for cyclooxygenases and lipoxygenase.

These mast cell responses are extremely rapid. For example, granules are released within seconds after antigen binds to IgE (Figure 25-7). Because the release is rapid and extensive, sudden acute inflammation develops. Degranulated mast cells do not die but, given time, will regenerate their granules.

25.5.1 Mast Cell–Derived Mediators

Mast cells are loaded with a complex mixture of inflammatory mediators, enzymes, and cytokines. Triggering of receptor-bound IgE by antigen causes the mast cells to release all these molecules and triggers the productions of many others. All these molecules (both preformed and newly synthesized) generate the acute inflammation characteristic of type I hypersensitivity response (Figure 25-8). These molecules have been described in detail in Chapter 2. The most important include histamine, serotonin, prostaglandins, and leukotrienes. Mast cells secrete IL-4, IL-5, IL-6, IL-13, IL-16, chitinases, tumor necrosis factor-α (TNF-α), and the chemokine CCL3. These cytokines either are proinflammatory or promote Th2 responses, or both. High levels of these cytokines may therefore be found in tissue fluids in allergic reactions. It is likely no coincidence that mast cells also produce and secrete chitinases. Chitin is characteristically found in insects, fungi, and helminths, and the pro-duction of chitinases supports the hypothesis that allergic reactions may have evolved to combat these invaders.

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FIGURE 25-8 The soluble mediators released from degranulating mast cells. These fall into three categories: molecules released from exocytosed granules, lipids (eicosanoids) synthesized within minutes, and proteins synthesized over several hours.
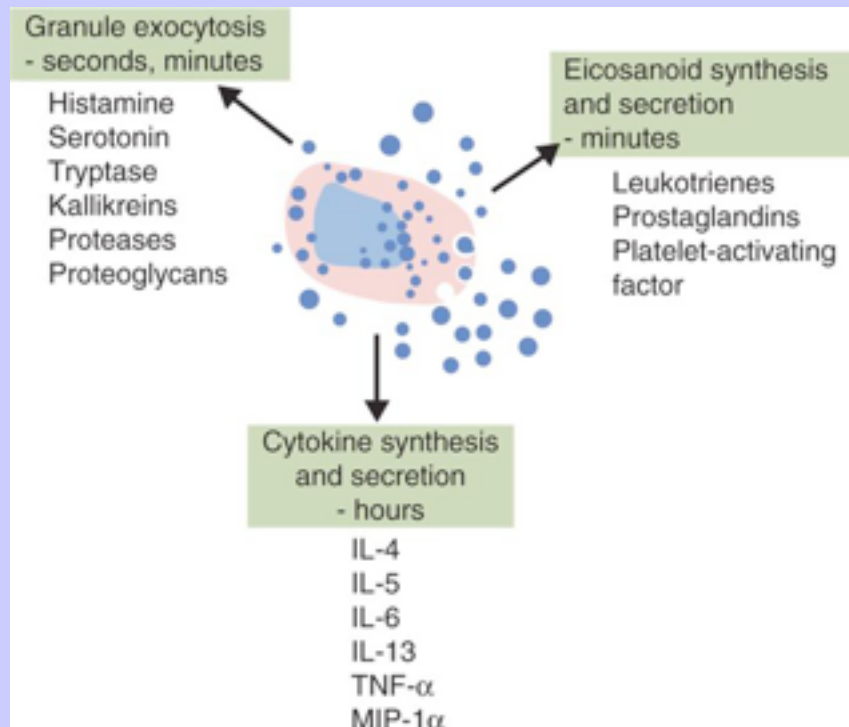
Table 25-1 Effects of Stimulating α and β Adrenoceptors

System	α Receptor Stimulation or β Blockade	β Receptor Stimulation or α Blockade
Mast cells	Enhances degranulation	Suppresses degranulation
Smooth muscle	Contracts	Relaxes
Blood vessels	Constricts	Dilates

25.5.2 Regulation of Mast Cell Degranulation

Mast cells express two surface receptors for cate-cholamines called α and β adrenoceptors. These G-protein–linked receptors have opposing effects. Thus molecules that stimulate the a adrenoceptors (such as norepinephrine and phenylephrine) or block the β adrenoceptors (such as propranolol) enhance mast cell degranulation (Table 25-1). In contrast, molecules that stimulate β receptors or block a receptors inhibit mast cell degranulation. β stimulants include isoproterenol, epinephrine, and salbutamol and are widely used in the treatment of allergies. β-receptor blockers enhance mast cell degranulation and promote allergies. Some respiratory pathogens such as *Bordetella pertussis* or *Haemophilus influenzae* can cause β blockade. As a result, the airways of infected animals are more likely to become severely inflamed because of mast cell degranulation. These infections may also predispose animals to the development of respiratory allergies.

25.5.3 Regulation of the Response to Mast Cell Mediators

The α and β adrenoceptors are found not only on mast cells but also on secretory and smooth muscle cells throughout the body. Alpha stimulators cause vasoconstriction and may be of use in treating severe allergic reactions, reducing edema, and raising blood pressure. Beta stimulators mediate smooth muscle relaxation and may therefore reduce the severity of smooth muscle contraction. Pure α and β stimulators are of only limited use in the treatment of allergic diseases because each alone is insufficient to counteract all the effects of mast cell–derived factors. Epinephrine (or adrenalin), on the other hand, has both α and β adrenergic activity. In addition to causing vasoconstriction in skin and viscera, its β effects cause smooth muscle to relax. This combination of effects is well suited to combat the vasodilation and smooth muscle contraction produced in type I hypersensitivity. Ideally, epinephrine should be available whenever potential allergens are administered to animals.

25.5.4 The Late-Phase Reaction

When antigen is injected into the skin of an allergic animal, two distinct inflammatory responses occur. There is an immediate acute inflammatory response that occurs within 10 to 20 minutes as a result of mast cell degranulation. This is followed several hours later by a late-phase reaction, which peaks at 6 to 12 hours and then gradually diminishes. This late-phase reaction is characterized by redness, edema, and pruritus. It is believed that this late reaction results from the release of inflammatory mediators by eosinophils and neutrophils attracted to the site by mast cell–derived chemotactic factors.
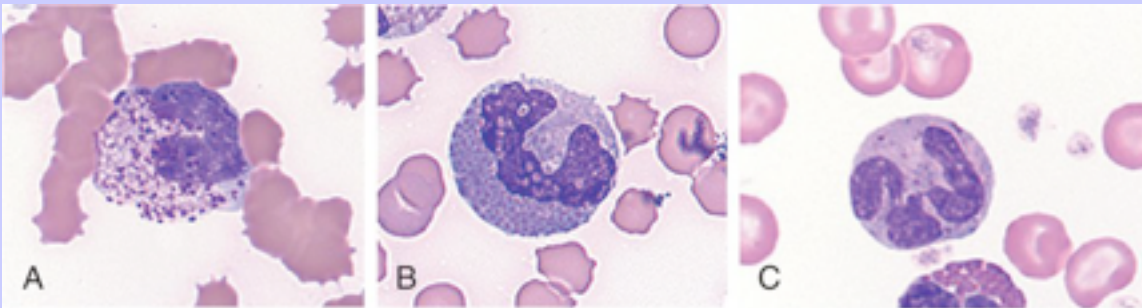
^{25.6} BASOPHILS

The least numerous granulocytes, the basophils, are so called because their cytoplasmic granules stain intensely with basic dyes, such as hematoxylin (Figure 25-9). Basophils constitute about 0.5% of blood leukocytes. They are not normally found outside the bloodstream but may enter tissues under the influence of some T cell–derived chemokines. Basophil granules contain a complex mixture of vasoactive molecules similar to those found in mast cells.

The precise relationships between basophils and mast cells have long been a matter of controversy. Thus while the functions of both cell types are clearly

FIGURE 25-9 Light photomicrographs of peripheral blood basophils from a horse **(A),** cat **(B),** and dog **(C).** These cells are about 10 μm in diameter; all were photographed at the same magnification. Giemsa stain. (Courtesy Dr. M.C. Johnson.)

very similar, their morphological characteristics and tissue distribution are very different. In mice, basophils and mast cells share a common stem cell. This stem cell is also the source of both connective tissue and mucosal mast cells.

^{25.7} EOSINOPHILS

Tissues undergoing type I hypersensitivity reactions characteristically contain large numbers of eosinophils. These cells are attracted to sites of mast cell degranulation, where they degranulate and release their own biologically active molecules. Eosinophils may be considered the terminal effector cells of the allergic response.

Eosinophils are polymorphonuclear cells, slightly larger than neutrophils, with cytoplasmic granules that stain intensely with the red dye eosin (Figure 25-10). They originate in the bone marrow and spend about 30 minutes circulating in the bloodstream before migrating into the tissues, where they have a half-life of about 12 days. The proportion of eosinophils among the blood leukocytes varies greatly since it is affected by the presence of parasites. Normal values range from 2% in dogs to about 10% in cattle.

Eosinophils contain two types of granule (Figures 25-11 and 25-12). Their small, primary granules contain arylsulfatase, peroxidase, and acid phosphatase. Their large crystalloid granules have a core of major basic protein (MBP) surrounded by a matrix containing eosinophil cationic protein, eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin.

25.7.1 | Eosinophil Activation

Three mechanisms are involved in mobilizing eosinophils (Figure 25-13). First, both Th2 cells and mast cells produce IL-5 and the chemokines known as eotaxins that stimulate the release of eosinophils from the bone marrow. Thus Th2 cells mobilize eosinophils at the same time that they stimulate IgE responses. Second, these eosinophils are attracted to sites of

FIGURE 25-10 Light photomicrographs of peripheral blood eosinophils from a horse **(A),** cat **(B),** and dog **(C).** Each cell is about 12 μm in diameter. Giemsa stain. (Courtesy Dr. M.C. Johnson.)
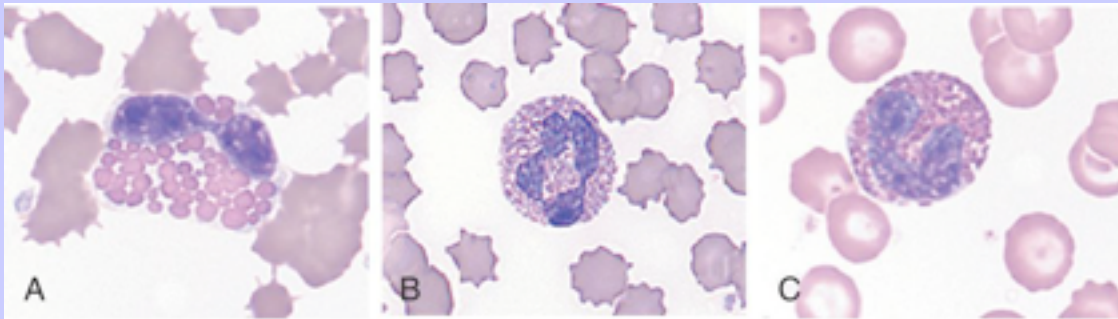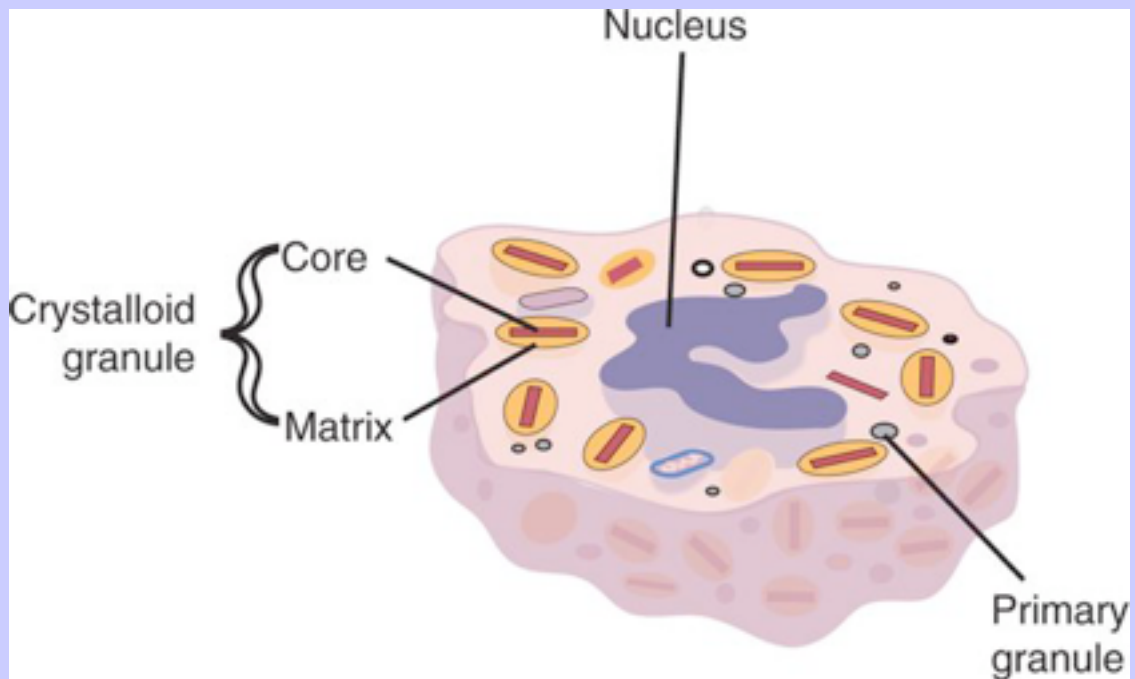

FIGURE 25-11 The major structural features of an eosinophil.

FIGURE 25-12 A transmission electron micrograph of a rabbit eosinophil. (Courtesy Dr. S. Linthicum.)
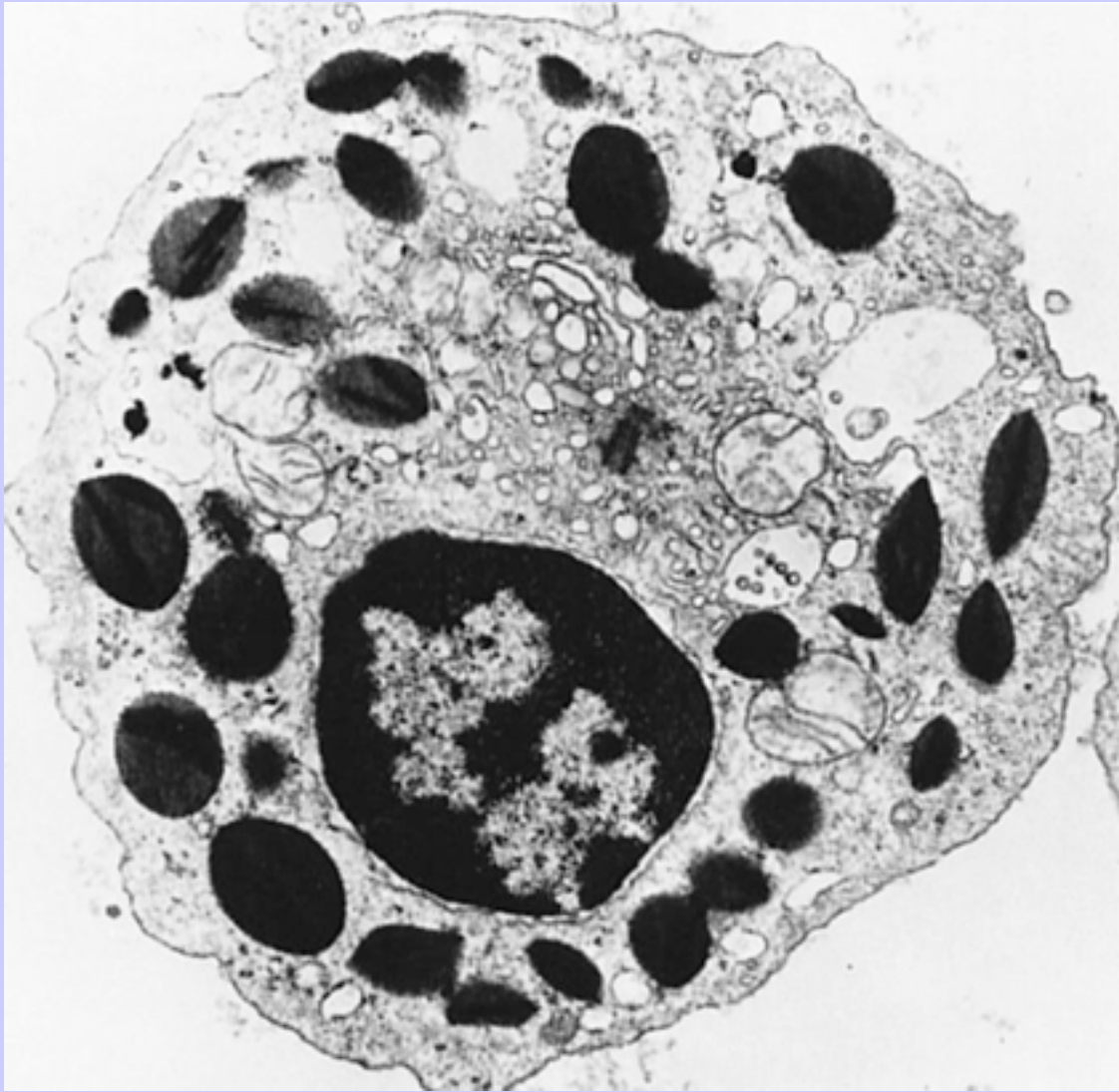
mast cell degranulation by molecules such as the eotaxins, histamine and its breakdown product imidiazoleacetic acid, leukotriene B_4, 5-hydroxytryptamine (5-HT), and platelet-activating factor (PAF). Activated eosinophils are especially attracted by CXCL8 (IL-8) complexed to IgA. Third, some common allergens directly activate eosinophils, stimulating their chemotaxis and upregulating CR3 expression. Once they reach sites of mast cell degranulation, the eosinophils are activated by these same molecules. The mobilization and activation of eosinophils enhances their ability to kill parasites and supports the contention that the major function of the IgE-mediated responses is the control of helminth parasites (see Chapter 24). Activated eosinophils express MHC class II molecules and can serve as antigen-presenting cells. These eosinophils also express the immunosuppressive enzyme IDO (see Chapter 17). IDO suppresses local Th1 responses but may promote Th2 responses.

25.7.2 | Eosinophil Degranulation and Mediators

Although eosinophils can phagocytose small particles, they are much more suited to extracellular destruction

FIGURE 25-13 The regulation of eosinophil mobilization, chemotaxis, and activation.
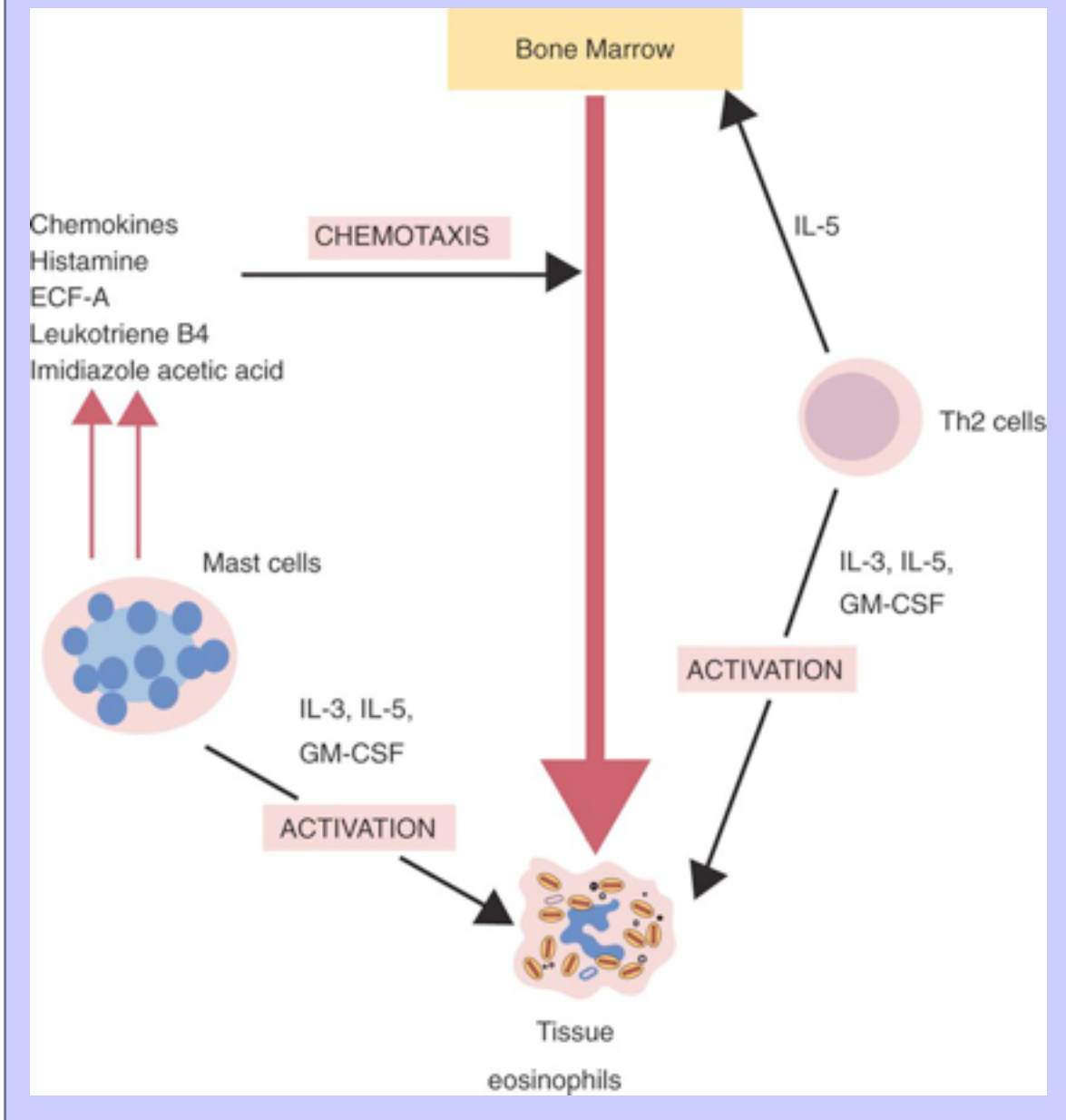

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FIGURE 25-14 Eosinophils release a complex array of molecules that contribute to the acute inflammatory process. It is clear that on balance, eosinophils exacerbate the inflammation triggered by mast cells.

ENZYMES
Phospholipase D
Lysophospholipase
Histaminase
Catalase

OXIDANTS
O_2^-
H_2O_2

CHEMOKINES
CXCL8
CCL3
CCL5

LIPID MEDIATORS
Prostaglandins
Leukotrienes
PAF

CATIONIC
GRANULE
PROTEINS
Major basic protein
Eosinophil cationic protein
Eosinophil neurotoxin
Eosinophil peroxidase

CYTOKINES
IL-1α
IL-2   TGF-α
IL-3   TGF-β
IL-4   TNF-α
IL-6   GM-CSF
IL-10   PDGF
IL-16
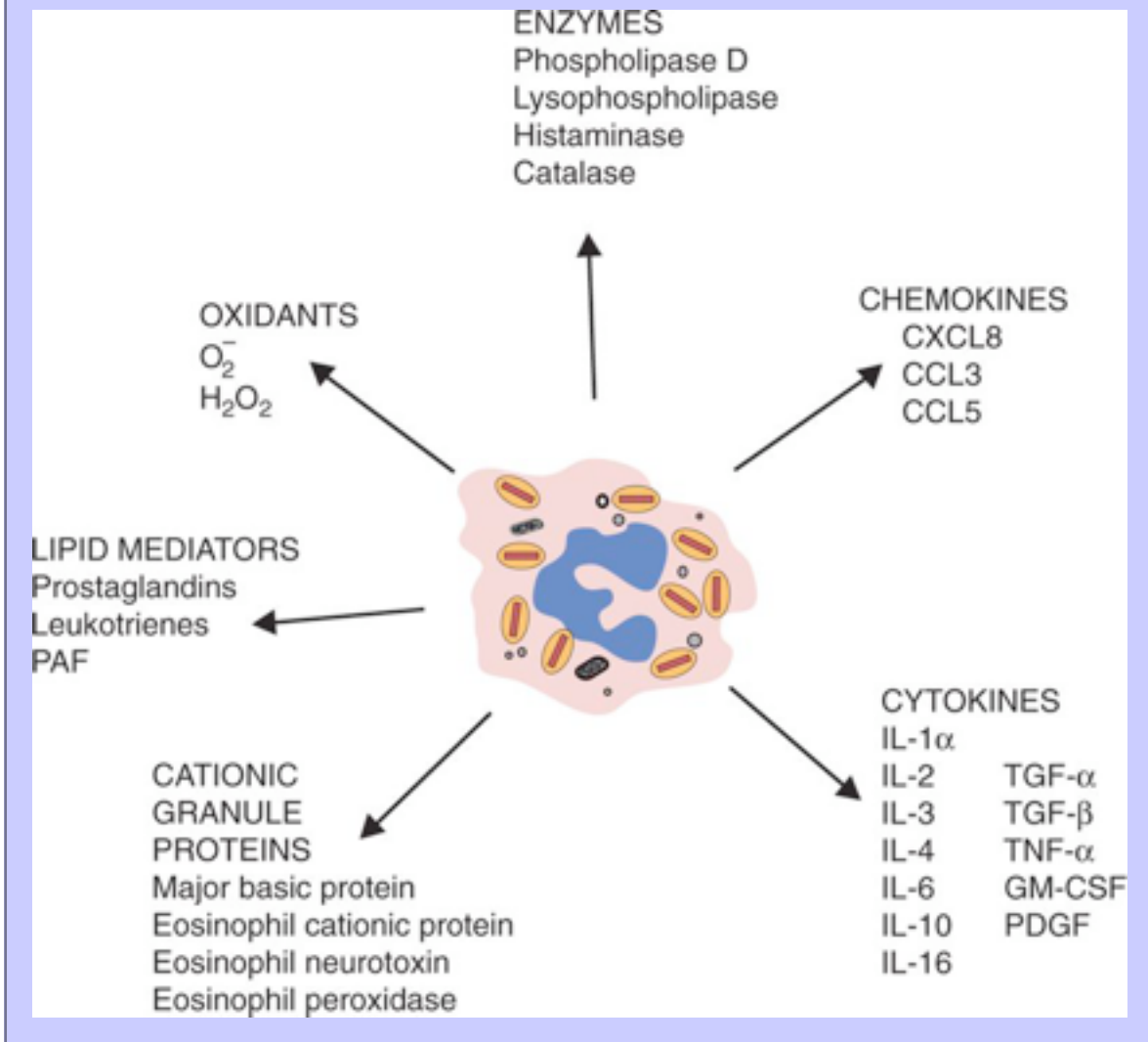
of large parasites since they can degranulate into the surrounding fluid. Eosinophils undergo piecemeal degranulation. In this process small vesicles bud off the secondary granules and are released into the tissues. This degranulation occurs in response to IgE-coated parasites, antigen-bound IgE, many chemokines, PAF, and C5a.

Eosinophil granules contain a mixture of inflammatory and toxic mediators, including cationic proteins, peroxidase, and MBP. Eosinophils also produce lipid mediators such as leukotrienes and PAF. Particles bound to eosinophil receptors trigger a powerful respiratory burst. The EPO uses bromide in preference to chloride, thus producing OBr^-. The peroxidase generates nitric oxide and nitrotyrosine, both potent oxidizing agents.

The proteins released by degranulation include MBP, cationic protein, and peroxidase. All of these can kill helminths and bacteria and are important mediators of tissue pathology. They all, for example, damage respiratory epithelium. Eosinophils also synthesize and secrete many different cytokines, including IL-1α, IL-3, IL-4, IL-5, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, transforming growth factor-α (TGF-α), and TGF-β. The production by eosinophils of multiple Th2 cytokines as well as IDO inhibits local Th1 responses and ensures that a "Th2 environment" is maintained in regions of eosinophil accumulation. Eosinophils can produce their own CCL5 and CCL11 so that additional eosinophils can be attracted to the inflammatory focus (Figure 25-14).

25.7.3 Regulation of Eosinophil Degranulation

Mast cells and eosinophils interact extensively in allergic reactions. Thus eosinophil-derived basic proteins activate mast cells to release histamine. Mast cells in turn release eosinophil chemotactic agents, activate eosinophils, and enhance the expression of eosinophil receptors. Mast cells can synthesize and secrete IL-3, IL-5, and GM-CSF, all of which promote eosinophil degranulation, growth, and survival.

25.8 PLATELETS

While it has long been accepted that immediate hypersensitivity results from the IgE-mediated degranulation of mast cells, it has recently been shown that fatal allergic responses may be induced in mast cell–deficient mice. Analysis indicates that these may be mediated by platelets. Antigen-challenged, sensitized, mast cell–deficient mice failed to show increased vascular permeability in skin but did so in skeletal muscle. The effect was blocked by antiplatelet serum. Given our uncertainties about the pathogenesis of allergic skin disease or anaphylaxis in birds, it seems that studies on the role of platelets in these conditions would likely be rewarding.

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25.9 CLINICAL TYPE I HYPERSENSITIVITY

The clinical signs of type I hypersensitivity result from the abrupt and excessive release of inflammatory mediators from mast cells, eosinophils, and basophils. The severity and location of these responses depend on the number and location of these cells; this, in turn, depends on the degree of sensitization of an animal, the amount of antigen involved, and its route of administration. In its most extreme form, antigen administered rapidly to a sensitized animal will cause generalized mast cell degranulation and massive mediator release. If the rate of release of vasoactive molecules from these mast cells exceeds its ability to respond to the rapid changes in the vascular system, an animal will undergo allergic anaphylaxis and may die.

25.10 ALLERGIC ANAPHYLAXIS

Allergic anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity reaction. Its precise clinical signs (Table 25-2) are determined by organ system involvement, which differs among the major domestic animals. Many of the symptoms are a result of vasoactive molecules making smooth muscle contract in the bronchi, gastrointestinal tract, uterus, and bladder.

The major shock organs of horses are the lungs and the intestine. Bronchial and bronchiolar constriction leads to coughing, dyspnea, and eventually apnea. On necropsy, severe pulmonary emphysema and peribronchiolar edema are commonly seen. In addition to the lung lesions, edematous hemorrhagic enterocolitis may cause severe diarrhea. The major mediators of anaphylaxis in horses are probably histamine and serotonin.

In cattle the major shock organ is the lung. Allergic anaphylaxis is characterized by profound systemic hypotension and pulmonary hypertension. The pulmonary hypertension results from constriction of the pulmonary vein and leads to pulmonary edema and severe dyspnea. The smooth muscle of the bladder and intestine contract, causing urination, defecation, and bloating. The main mediators of anaphylaxis in cattle are serotonin, kinins, and the leukotrienes. Histamine is of much less importance. Dopamine acts in bovine anaphylaxis by enhancing histamine and leukotriene release from the lung, thus exerting a form of positive feedback. Because of the anticoagulant properties of heparin from mast cells, blood from animals

FIGURE 25-15 Severe urticaria in a Boxer stung by three wasps. (Courtesy Dr. G. Elissalde.)

experiencing anaphylaxis may fail to coagulate. In cattle, in contrast to the other species, beta stimulants such as isoproterenol potentiate histamine release from leukocytes, whereas alpha stimulants, such as norepinephrine, inhibit histamine release. In addition, epinephrine potentiates histamine release in the bovine. The significance of these anomalous effects is unclear.

Table 25-2 Anaphylaxis in the Domestic Species and Humans

Species	Shock Organs	Symptoms	Pathology	Major Mediators
Horse	Respiratory tract	Cough	Emphysema	Histamine
	Intestine	Dyspnea	Intestinal hemorrhage	Serotonin
		Diarrhea		
Ruminants	Respiratory tract	Cough	Lung edema	Serotonin
		Dyspnea	Emphysema	Leukotrienes
		Collapse	Hemorrhage	Kinins
				Dopamine
Swine	Respiratory tract	Cyanosis	Systemic hypotension	Histamine
	Intestine	Pruritus		
Dog	Hepatic veins	Collapse	Hepatic engorgement	Histamine
		Dyspnea	Visceral hemorrhage	Leukotrienes
		Diarrhea		Prostaglandins
		Vomiting		
Cat	Respiratory tract	Dyspnea	Lung edema	Histamine
	Intestine	Vomiting	Intestinal edema	Leukotrienes
		Diarrhea		
		Pruritus		
Human	Respiratory tract	Dyspnea	Lung edema	Histamine
		Urticaria	Emphysema	Leukotrienes
Chicken	Respiratory tract	Dyspnea	Lung edema	Histamine
		Convulsions		Serotonin
				Leukotrienes

In sheep, pulmonary signs predominate in allergic anaphylaxis as a result of constriction of the bronchi and pulmonary vessels. Smooth muscle contraction also occurs in the bladder and intestine with predictable results. The major mediators of type I hypersensitivity in sheep are histamine, serotonin, leukotrienes, and kinins.

In pigs, allergic anaphylaxis is largely the result of systemic and pulmonary hypertension, leading to dyspnea and death. In some pigs the intestine shows signs of involvement, whereas in others no gross intestinal lesions are observed. The most significant mediator identified in this species is histamine.

Dogs differ from the other domestic animals in that the major shock organ is not the lung but the liver, specifically the hepatic veins. Dogs undergoing allergic anaphylaxis show initial excitement followed by vomiting, defecation, and urination. As the reaction progresses, the dog collapses with muscular weakness and depressed respiration, becomes comatose, convulses, and dies within an hour. On necropsy, the liver and intestine are massively engorged, perhaps holding up to 60% of the animal's total blood volume. All these signs result from occlusion of the hepatic vein due to a combination of smooth muscle contraction and hepatic swelling. This results in portal hypertension and visceral pooling, as well as a decrease in venous return, cardiac output, and arterial pressure. Identified mediators include histamine, prostaglandins, and leukotrienes.

In cats, the major shock organ is the lung. Cats undergoing allergic anaphylaxis show vigorous scratching around the face and head as histamine is released into the skin. This is followed by dyspnea, salivation, vomiting, incoordination, collapse, and death. Necropsy reveals bronchoconstriction, emphysema, pulmonary hemorrhage, and edema of the glottis. The major pharmacological mediators in the cat are histamine and the leukotrienes.

25.11 SPECIFIC ALLERGIC CONDITIONS

Although allergic anaphylaxis is the most dramatic and severe type I hypersensitivity reaction, it is more common to observe local allergic reactions, the sites of which are referable to the route of administration of antigens. For example, inhaled antigens (allergens) provoke inflammation in the upper respiratory tract, trachea, and bronchi, resulting in fluid exudation from the nasal mucosa (hay fever) and tracheobronchial constriction (asthma). Aerosolized antigen will also contact the eyes and provoke conjunctivitis and intense lacrimation. Ingested antigens may provoke diarrhea and colic as intestinal smooth muscle contracts violently. If sufficiently severe, the resulting diarrhea may be hemorrhagic. Antigen reaching the skin causes local dermatitis. The reaction is erythematous and edematous and is described as an urticarial type (*urtica* is Latin, meaning "stinging nettle") (Figure 25-15). Urticarial lesions are extremely irritating because of the histamine released; consequently, scratching may mask the true nature of the lesion.

25.11.1 Milk Allergy

Jersey cattle may become allergic to the a casein of their own milk. Normally, this protein is synthesized in the udder, and provided that the animals are milked regularly, nothing untoward occurs. If milking is delayed, however, the increased intramammary pressure forces milk proteins into the bloodstream. In allergic cattle, this may result in reactions ranging from mild discomfort with urticarial skin lesions to acute anaphylaxis and death. Prompt milking can treat the condition, although some seriously affected animals may have to go for several lactations without drying-off because of the severe reactions that occur on cessation of milking.

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25.11.2 Food Allergy

About 2% of ingested protein is absorbed as peptide fragments large enough to be recognized as foreign. This antigen may travel in the blood and reach mast cells in the skin within a few minutes. It has been claimed that up to 30% of skin diseases in dogs are due to allergic dermatitis and that responses to ingested allergens may account for 1% of cutaneous disease in dogs and cats, although its true prevalence is unknown. The clinical consequences of food allergies are seen both in the digestive tract and on the skin.

It is important not to confuse *food allergy,* an immunologically mediated reaction to food allergens, with *food intolerance*. The American Academy of Allergy and Immunology has defined *food intolerance* as "those adverse reactions to foods that are not immunologically mediated." These reactions can include food idiosyncrasies, in

which an animal responds abnormally to a food; metabolic reactions, in which a food component affects the metabolism of the animal; pharmacological reactions, in which some food components may act like drugs; and food poisoning, in which the adverse reaction is caused by a toxin or organism.

About 10% to 15% of dogs with food allergies have gastrointestinal problems. The intestinal reaction may be mild, perhaps showing only as an irregularity in the consistency of the feces, or it may be severe, with vomiting, cramps, and violent, sometimes hemorrhagic, diarrhea occurring soon after feeding. About half of affected dogs have a nonseasonal pruritic dermatitis. The skin reactions are usually papular and erythematous and may involve the feet, eyes, ears, and axillae or perianal area. The lesion itself is highly pruritic and is commonly masked by self-inflicted trauma and secondary bacterial or yeast infections. This pruritus tends to respond poorly to corticosteroids. In chronic cases the skin may be hyperpigmented, lichenified, and infected, leading to a pyoderma. A chronic pruritic otitis externa may also develop. The foods involved vary but are usually protein-rich such as dairy products, wheat meal, fish, chicken, beef, or eggs. In pigs, fishmeal and alfalfa have been incriminated. Immunoblots of serum from dogs that are allergic to beef and cow's milk showed that they produce IgE against bovine IgG heavy chains.

Thus, IgG is the major allergen in cow's milk. It is likely that it triggers hypersensitivity to lamb as a result of cross-reactivity with sheep IgG. A second major antigen in lamb and beef extracts has been identified as phosphoglucomutase.

Food allergies have been reported in the horse but are uncommon. Wild oats, white clover, and alfalfa have been recognized as allergens in this species. The most reliable test for suspected food allergies is to remove all potential allergens and then feed a hypo-allergenic diet. These elimination diets usually contain meat and carbohydrates from sources to which the animal is unlikely to have been exposed. Examples include mutton, duck, venison, or rabbit with brown rice or potato. Several commercial hypoallergenic diets are available to facilitate this diagnosis. The diet may be supplemented by adding other ingredients until the allergen is identified by a recurrence of clinical signs. Intradermal skin testing and serological assays (radioallergosorbent test [RAST] or enzyme-linked immunosorbent assay [ELISA]) are of limited usefulness in diagnosing food allergies (p. 344). Treatment involves elimination of the responsible food after correctly identifying it. The development of food allergies may be significantly promoted by the presence of nematode parasites. Thus, an antigen (human serum albumin) was fed to two groups of cats. One group was infected with the roundworm *Toxocara cati;* the other group was worm free. Parasitized cats developed significantly higher levels of antibodies to the antigen. Most importantly, they developed higher levels of IgE antibodies, suggesting that the presence of these parasitic worms in the intestine may well provoke food allergies.

25.11.3 Allergic Inhalant Dermatitis

In dogs and cats, allergy to inhaled environmental antigens most commonly leads to an atopic dermatitis with intense pruritus. Terriers and Dalmatians appear to be predisposed to this, but any breed may be affected. Animals may present with the allergic triad: face rubbing, axillary pruritus, and foot licking, although allergic skin lesions can be found anywhere on the body. The specific lesions are secondary to the pruritus and vary from acute erythema and edema to more chronic secondary changes including crusting, scaling, hyperpigmentation, lichenification, and pyoderma. Some animals may have otitis externa or conjunctivitis. The cutaneous inflammatory infiltrate contains mast cells, γ/δ T cells, dendritic cells, low numbers of eosinophils and neutrophils, and few B cells. The allergens implicated include molds; tree, weed, and grass pollens (especially pollens that are small and light and are produced in very large quantities); house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*); animal danders; and fabrics such as wool. Depending on the source of allergen, the atopy may be seasonal. Hypersensitivity to a single allergen is uncommon, and most

animals develop multiple sensitivities. Diagnosis is based on history and identification of the offending antigens by direct skin testing. Canine allergic dermatitis may be treated by corticosteroids or by hyposensitization therapy. Antihistamines and nonsteroidal antiinflammatory drugs seem to help some of the time, although leukotrienes likely play an important role in this disease.

Nasolacrimal urticaria (hay fever) is an uncommon manifestation of respiratory allergy in dogs and cats. Pollens usually provoke a rhinitis and conjunctivitis characterized by a profuse watery nasal discharge and excessive lacrimation. If the allergenic particles are sufficiently small, they may reach the bronchi or bronchioles, where the resulting reaction can cause bronchoconstriction, wheezing, and recurrent asthma-like paroxysmal dyspnea. It should be noted that basenji dogs have unusually sensitive airways and experience a disease similar to humans with asthma. Cats are also recognized as suffering from asthma manifested by paroxysmal wheezing, dyspnea, and coughing. Although its pathogenesis has not been clarified, asthmatic cats respond well to corticosteroids and inhaled bronchodilators.

A familial allergic rhinitis characterized by extreme nasal pruritus, violent sneezing, dyspnea, mucoid nasal discharge, and excessive lacrimation has been observed in cattle. Depending on the allergen, it may be seasonal. The antigens involved are inhaled and come from a variety of plant and fungal sources. Diagnosis may be confirmed by skin testing. Nasal granulomas may form in chronically affected cattle. These consist of numerous polypoid nodules, 1 to 4 μm in diameter, situated in the anterior nasal mucosa. The nodules contain large numbers of mast cells, eosinophils, and plasma cells.

25.11.4 Atopic Dermatitis

Atopic dermatitis is a chronic, multifactorial syndrome characterized by chronically inflamed and itchy skin. It is very common in dogs (as many as 15% are affected) and has been recognized in cats, horses, and goats. Canine atopic dermatitis has a major breed predilection, being most common in Retrievers, Setters, Terriers, Beagles, Cocker Spaniels, Boxers, Bulldogs, and Shar-Peis. It is commonly associated with reactions to environmental allergens such as house dust mites, pollens, and molds such as the yeast Malassezia pachydermatis. However, the etiology of atopic dermatitis is complex and not all cases are associated with IgE antibodies to environmental antigens. Affected dogs commonly present with pruritus. Initially there may be no obvious skin lesions, but this progresses to diffuse erythema. Chronic licking and scratching leads to hair loss, papules, scaling, and crusting. Hyperpigmentation and lichenification may occur. Skin lesions occur most commonly on the ventral abdomen and in the inguinal and axillary regions. About half of affected dogs have otitis externa. Dogs may develop focal "hot spots." The cellular infiltrate within the lesions contains mast cells, Langerhans cells, and γ/δ T cells. There are low numbers of eosinophils and neutrophils and very few B cells. Secondary bacterial or yeast infections complicate the disease. Depending on the inducing allergen, the disease may be seasonal and relapsing. Once it starts, it tends to get progressively worse unless treated. Control of both allergies and secondary infection is critical.

Atopic dermatitis is provoked by environmental, food, and respiratory allergens that enter animals by the oral, respiratory, or percutaneous routes. The importance of the latter route is reflected by the frequency of lesions on contact areas such as the face, feet, and ears. Affected animals commonly show positive skin test responses to intradermally injected allergens. However, serological assays such as the ELISA or RAST, which measure IgE antibodies to the offending allergens, rarely correlate with disease severity or the levels of IgE in the skin and are of limited usefulness. Blood IgE levels may drop to undetectable levels while levels in skin and skin reactivity remain high. The many false-negative results probably reflect the fact that the immunological reactions such as the presence of reactive Th2 cells and elevated IL-4 levels are largely restricted to affected skin. Affected skin contains more IL-4, IFN-γ, TNF-α, and IL-2 and less TGF-β compared with healthy skin. Allergen avoidance is

the best treatment. Specific desensitization therapy gives good responses in up to 80% of cases, but secondary problems such as bacterial or yeast (Malassezia) infections or flea infestations must also be controlled. It may take several months before the benefits of immunotherapy become apparent. Topical therapy such as bathing with emollient shampoos helps considerably. Antihistamines are of limited usefulness but may be of benefit in mild cases. Sources of essential fatty acids such as n(W)3 (fish oil) and n(W)6 (evening primrose oil) help some cases of atopic dermatitis, possibly by affecting lipid synthesis in the skin and promoting the synthesis of antiinflammatory eicosanoids. Glucocorticoids, such as prednisolone, produce rapid remission but may cause significant side effects. They should be used only as a last resort and given, preferably, by the oral route. Treatment with the prostaglandin analog misoprostol has given encouraging results. The immunosuppressive agents cyclosporine and azathioprine have also been effective in some cases of nonseasonal atopic dermatitis, as has the phosphodiesterase-inhibitor pentoxifylline.

25.11.5 Allergies to Vaccines and Drugs

An IgE response may result from the administration of any antigen, including vaccines. It is most likely to occur in vaccines that contain trace amounts of fetal calf serum, gelatin, or casein. This must always be taken into account when animals are vaccinated. Severe allergies have been associated with the use of killed foot-and-mouth disease, rabies, and contagious bovine pleuropneumonia vaccines in cattle. IgE responses may also occur following administration of drugs. Most drug molecules are too small to be antigenic, but many can bind to host proteins and then act as haptens. Penicillin allergy, for example, may be induced in animals either by therapeutic exposure or by ingestion of penicillin-contaminated milk. The penicillin molecule is degraded in vivo to several compounds; the most important of these contains a penicilloyl group. This penicilloyl group can bind to proteins and provoke an immune response. In sensitized animals, injection of penicillin may cause acute systemic anaphylaxis or milder forms of allergy. Feeding of penicillin-contaminated milk to these animals can lead to severe diarrhea. Allergies to many drugs, especially antibiotics and hormones, have been reported in the domestic animals. Even substances contained in leather preservatives used in harnesses, substances in catgut sutures, or compounds such as methylcellulose or carboxymethylcellulose used as stabilizers in vaccines may provoke allergies.

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25.11.6 Allergies to Parasites

The beneficial role of the IgE–mast cell–eosinophil system in immunity to parasitic worms was first observed in the self-cure phenomenon. Helminths preferentially stimulate IgE responses, and helminth infestations are commonly associated with many of the signs of allergy and anaphylaxis; for example, animals with tapeworms may show respiratory distress or urticaria. Anaphylaxis may be provoked by rupture of a hydatid cyst during surgery or through transfusion of blood from a dog infected with *Dirofilaria immitis* to a sensitized animal.

Allergies are also commonly associated with exposure to arthropod antigens. Insect stings account for many human deaths each year as a result of acute anaphylaxis following sensitization to venom. Anaphylaxis can also occur in cattle infested with the warble fly *(Hypoderma bovis)*. The pupae of this fly develop under the skin on the back of cattle after the larvae have migrated through the tissues from the site of egg deposition on the hind leg. Because the pupae are so obvious, it is tempting to remove them manually. Unfortunately, if they rupture during this process, the release of coelomic fluid into the sensitized animal may provoke an anaphylaxis-like response that may kill the animal.

In horses and cattle, hypersensitivity to insect bites may cause an allergic dermatitis variously called Gulf Coast itch, Queensland itch, or sweet itch. The insects involved include midges (*Culicoides* spp.), black flies (*Simulium* spp.), stable flies *(Stomoxys calcitrans)*, mosquitoes, and stick-tight fleas *(Echidnophaga gallinacea)*. If animals

are allergic to antigens in the saliva of these insects, biting results in the development of urticaria accompanied by intense pruritus. The itching may provoke severe self-mutilation with subsequent secondary infection that may mask the original allergic nature of the lesion.

In mange due to *Sarcoptes scabiei* in dogs and due to *Octodectes cyanotis* in cats, allergies may contribute to the development of skin lesions. The infested dermis is infiltrated with mast cells, lymphocytes, and plasma cells, and an intradermal injection of mite antigen leads to an immediate wheal-and-flare response. Infested animals may also make precipitating antibodies to mite antigens so that immune complexes may contribute to the development of lesions.

Animals do not inevitably respond to arthropod allergens with a type I hypersensitivity. Thus, responses to Demodex mites and to components of flea saliva may be cell-mediated (type IV hypersensitivity; see Chapter 28). Flea-bite allergic dermatitis is the single most important allergic skin disease. There is no breed or gender predisposition, but atopic animals as well as those exposed to fleas on an intermittent basis tend to get more severe disease. Continual exposure to fleas at an early age appears to result in a form of hyposensitization. Pruritus is a consistent feature, as is a history of flea infestation. Affected animals, in addition to the characteristic clinical signs, show a reaction to intradermally injected flea antigen. Most positive animals will respond within a few minutes, but up to 30% may show a delayed reaction at 24 to 48 hours. Hyposensitization therapy has not been shown to be successful in treating flea allergy. Flea allergy can be successfully treated only by total flea control.

25.11.7 The Eosinophilic Granuloma Complex

The eosinophilic granuloma complex is a confusing group of clinical conditions associated with various types of skin lesions (ulcer, plaque, granuloma) in cats. Although their cause is unknown, these conditions have been associated with flea or food allergies or inhalant dermatitis. It has been suggested that they are an allergic response to a feline autoantigen. A seasonal form has clearly been associated with mosquito bites. The eosinophilic plaques in the skin are intensely pruritic. As a result, the lesions may be masked by self-inflicted trauma. Histologically they are associated with a local mast cell and eosinophil infiltration, as well as an eosinophilia. Eosinophilic granulomas, in contrast, are not pruritic, and they present as a line of raised pink plaques. Some may present as scattered individual crusted papules. Eosinophilic ulcers are commonly located in the oral cavity or on the lips. Removal of the offending allergen may result in clinical improvement, and corticosteroid treatment is also of benefit. An idiopathic hypereosinophilic syndrome has been described in humans, cats, and dogs. It is characterized by a prolonged, unexplained eosinophilia, the infiltration of many organs with eosinophils, organ dysfunction (affecting especially the heart, but also the lungs, spleen, liver, skin, bone marrow, gastrointestinal tract, and central nervous system), and death. An eosinophilic enteritis may result from canine hookworm infestation.

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25.12 DIAGNOSIS OF TYPE I HYPERSENSITIVITY

The term *hypersensitivity* is used to denote inflammation that occurs in response to normally harmless material. For example, animals normally do not react to antigens injected intradermally. If, however, a hypersensitive animal is given an intradermal injection of an allergen, this provokes local inflammation. Vasoactive molecules are released within minutes to produce redness (erythema) as a result of capillary dilation, as well as circumscribed edema (a wheal) due to increased vascular permeability. The reaction may also generate an erythematous flare due to arteriolar dilation caused by a local axon reflex. This "wheal and flare" response to an allergen reaches maximal intensity within 30 minutes and then fades and disappears within a few hours. A late-phase reaction sometimes

occurs 6 to 12 hours after injection of an allergen as a result of the release of mediators by eosinophils and neutrophils.

Direct skin testing using very dilute aqueous solutions of various allergens has been widely used for the diagnosis of allergies in animals, especially those with allergic inhalant dermatitis. Following careful intradermal injection of an allergen solution, the site is examined for a local inflammatory response. The results obtained must be interpreted carefully since both false-positive and false-negative responses may occur. For example, the concentration of antigen in commercial skin testing solutions may be too low. Dogs may be up to 10 times less sensitive than humans to intradermal allergens such as pollens, fungi, or danders. False-positive reactions may be due to the presence of preservatives in the allergen solutions. Results of skin testing are affected by steroid treatment. The precise set of allergens used for intradermal skin testing varies among different locations. However, they commonly include an assortment of allergens from trees, grasses, fungi, weeds, danders, feathers, house dust mites, and insects. Intradermal skin testing is less commonly performed in cats because they fail to develop a significant wheal and the reaction is therefore difficult to evaluate.

An experimental technique used to detect IgE antibodies is called the passive cutaneous anaphylaxis (PCA) test. In this test, dilutions of test serum are injected at different sites into the skin of a normal animal. After waiting 24 to 48 hours, the antigen solution is administered intravenously. In a positive reaction, each injection site shows an immediate inflammatory response. The injected antibodies may remain fixed in the skin for a very long period. In the case of the calf, this may be up to 8 weeks. In the PCA test, it is sometimes difficult to detect very mild inflammatory responses. One way to make them more visible is to inject the test animal intravenously with Evans blue dye. The dye binds to serum albumin and does not normally leave the bloodstream. In sites of acute inflammation in which vascular permeability is increased, the dye-labeled albumin enters the tissue fluid and forms a striking blue patch (Figure 25-16). The size of this patch may be used as a measure of the intensity of the inflammatory reaction.

Serological methods of measuring the level of specific IgE in body fluids include the RAST, western blotting, and the ELISA (see Chapter 38). These are not subject to clinical bias, but there has been a poor correlation between the results obtained by serology or skin testing and clinical severity. There is also a poor correlation between ELISA results and intradermal testing. Serological assays are especially prone to a high level of false-positive results (low specificity). A negative ELISA will generally rule out atopy. Best results are obtained by testing for individual allergens rather than for groups of allergens. The reasons for this poor correlation between direct IgE measure

FIGURE 25-16 Passive cutaneous anaphylaxis (PCA) reactions in a calf. Several different sera were tested for PCA activity on the flank of a normal calf. (Courtesy Dr. P. Eyre.)

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ments and in vivo methods such as skin testing are debatable but probably reflect the fact that the skin microenvironment is much more complex than that of the bloodstream. Heavily parasitized dogs may have elevated IgE levels, and this may result in false-positive serological results. It is also possible that immunoglobulins of other classes such as IgG4 may contribute to the development of allergic dermatitis in the dog and not be detected by an ELISA employing anti-IgE. For these reasons many veterinary dermatologists prefer skin testing, despite its drawbacks.

25.13 TREATMENT OF TYPE I HYPERSENSITIVITY

In practical terms, by far the most satisfactory treatment of allergic disease is avoidance of exposure to the allergen. Except for food allergies, however, avoidance may be difficult or impossible. Other treatments such as desensitization therapy may be used (see below). This has the potential to induce stable, long-term remissions, but immunotherapy of this type is not a substitute for avoidance. The principal indications for drug therapy include short-term temporary relief either while waiting to begin immunotherapy or while waiting for it to take effect. Drugs may also be useful for relief of transient recurrences or in animals in which immunotherapy is not possible. Many different drugs are available to treat type I hypersensitivity, although veterinarians tend to employ only a few of these. Corticosteroids are most commonly used to reduce the irritation and inflammation associated with the acute allergic response. These drugs can suppress all aspects of inflammation by inhibiting nuclear factor kappa-B

activity and so blocking the production of prostaglandins and leukotrienes (see Chapter 36). Corticosteroids have a considerable palliative effect on chronic type I hypersensitivities, but it is important to remember that these drugs can have serious side effects. They can be immunosuppressive and can increase an animal's susceptibility to infection (see Chapter 36).
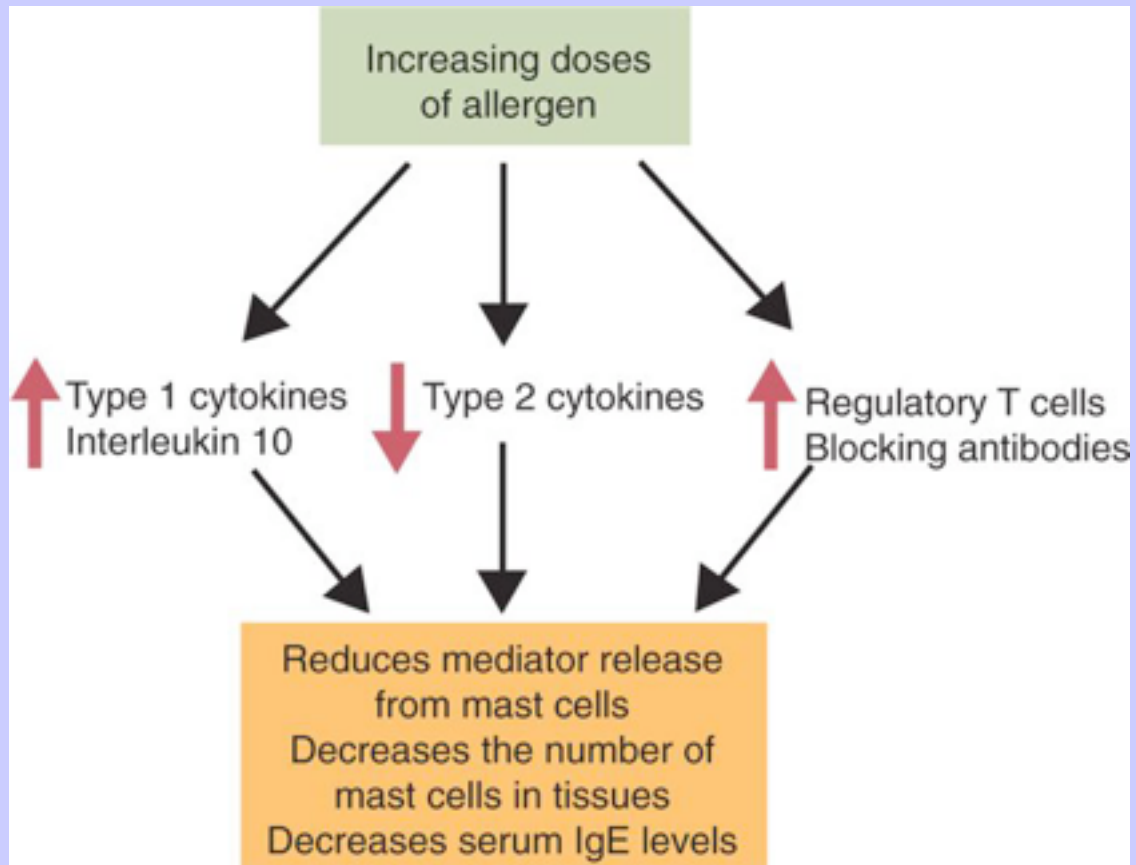
Long-term use of the potent immunosuppressive drug cyclosporine has been reported to be effective and well tolerated as a treatment of canine atopic dermatitis. The skin disease may recur once cyclosporine therapy is terminated.

The β stimulants include epinephrine, isoprenaline, and salbutamol; a antagonists include methoxamine and phenylephrine. All have been used extensively in humans and are available for use in animals. Epinephrine is the most important drug used to treat anaphylaxis. It is rapidly absorbed following intramuscular injection and thus can rapidly reverse the clinical signs of shock. Another group of drugs widely employed in the treatment of type I hypersensitivity reactions are the specific pharmacological inhibitors. These drugs, by mimicking the structure of the active mediators, competitively block specific receptors. Thus H1 antihistamines such as diphenhydramine can effectively inhibit the activities of histamine. However, since histamine is but one of a large number of mast cell–derived mediators, antihistamines possess limited effectiveness in controlling hypersensitivity diseases in animals.

25.13.1 Desensitization Therapy

In many animals, allergic disease may be controlled though the use of "allergy shots"—injections of the offending allergen. These injections promote IgG rather than IgE production and reduce the recruitment of inflammatory cells. In humans, immunotherapy of this type reduces mast cell and eosinophil numbers in the lung, as well as the infiltration of $CD4^+$ T cells and eosinophils in the skin. Desensitization induces a shift in the dominant helper cell response from Th2 to Th1 cells (Figure 25-17). For example, the IFN-γ : IL-4 ratio is low in atopic dogs, indicating a Th2 cytokine profile. After specific immunotherapy, the ratio rises significantly as blood IFN-γ levels increase and the balance shifts toward a Th1 response. This IFN-γ blocks the stimulation of IgE antibody synthesis by IL-4 from Th2 cells. The changes in cytokine production promote a shift in allergen-specific immunoglobulin production from IgE to IgG. It is believed that desensitization may activate CD8 T cells that induce dendritic cells to produce IL-12 and IL-18, which synergize in promoting Th1 responses. Desensitization also stimulates T_{reg} cells to produce IL-10, thus inhibiting IgE production,

FIGURE 25-17 The principles of desensitization therapy. Increasing doses of allergen promote a Th1 response, while at the same time reducing the Th2 response and regulating antibody production.

Increasing doses of allergen

Type 1 cytokines Interleukin 10

Type 2 cytokines

Regulatory T cells Blocking antibodies

Reduces mediator release from mast cells
Decreases the number of mast cells in tissues
Decreases serum IgE levels

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mast cell activation, and histamine and leukotriene release.

In desensitization therapy, small amounts of dilute aqueous solutions of antigen are administered. The first injections contain very little allergen. Over a number of weeks, the dose is gradually increased. If an animal's allergy is seasonal, the course of injections should be timed to reach completion just before the anticipated antigen exposure. It has been estimated that up to 80% of dogs have a good-to-excellent response to desensitization. This would include improvements in clinical signs and a reduction in the amount of medication required. Cats may respond even better. On the other hand, horses with hypersensitivity to biting flies have a poor response to this form of therapy (although, paradoxically, they may show clinical improvement following immune stimulation).

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