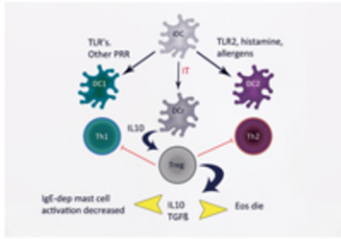
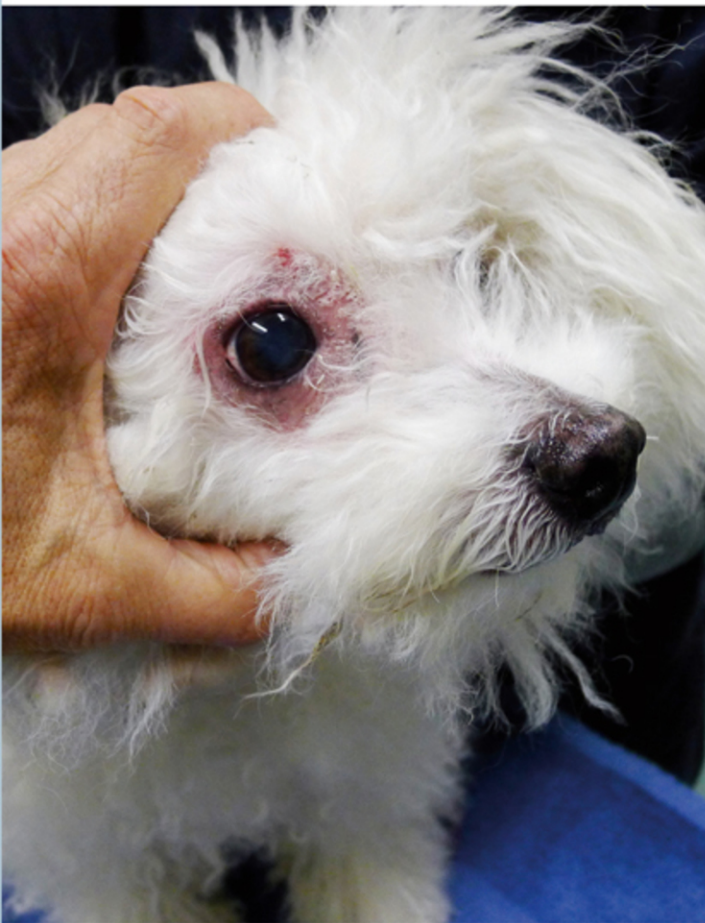


Veterinary Allergy

Edited by Chiara Noli, Aiden Foster
and Wayne Rosenkrantz



WILEY Blackwell

Veterinary Allergy

In memory of my dear colleague and friend Stefano Toma, who is greatly missed. (CN)

I dedicate this book to Susan Shaw in recognition of her great enthusiasm and ability to share with me, as for many vets, her considerable knowledge and understanding of veterinary medicine and dermatology. (AF)

To my cherished friend and mentor, Peter Ihrke, who first introduced me to this wonderful specialty and continues to be an inspiration to all. (WR)

Veterinary Allergy

Edited by

Chiara Noli (canine) (Italy)

Aiden Foster (feline, large animals, exotics) (UK)

Wayne Rosenkrantz (equine) (USA)

WILEY Blackwell

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It has taken three years to bring the original concept to print, and we hope that readers will find this book useful; as editors it has been an enjoyable learning experience, working together and with the authors.

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Foreword

The term ‘allergy’ was introduced by the Austrian physician Clemens von Pirquet in 1906 [1], however with a somewhat different meaning to that of today. He was studying the immune response to tuberculosis and diphtheria, and was thus working at the interface between immunity and hypersensitivity. He proposed the use of the term ‘allergy’ to imply ‘altered reactivity’ in the host. Thus allergy was not a disease *per se*, but rather a state that would result in a hypersensitivity reaction if appropriately challenged. This concept was gradually discarded despite some attempts to keep it alive. Tremendous advances in the understanding of the science behind allergy in man—now used synonymously with hypersensitivity, were made between 1920 and 1940. Notable were the studies by Prausnitz and Küstner [2] who described the skin-sensitizing antibody that was responsible for many allergic reactions. Then in the 1930s Coca [3] introduced the term ‘atopy’ which was derived from the Greek and translated literally as ‘strange disease’, to encompass the triad of the familial diseases of allergic asthma, allergic rhinitis, and atopic dermatitis. They also applied the term ‘reagin’ to the skin-sensitizing antibody of Prausnitz and Küstner. Anyone who reads these early publications cannot but marvel at the painstaking and insightful work, undertaken without the aid of modern-day techniques and at the generally sound conclusions that were reached. The next major step forward was the demonstration by Ishizaka and colleagues that the reagin belonged to a hitherto undescribed antibody class that they termed ‘IgE’ [4].

Over the years, a wide range of diseases of man mediated by diverse immunological mechanisms were described that could be ascribed to hypersensitivity reactions; Gell and Coombs believed that it was necessary to introduce a system of classification [5]. They proposed four categories, namely Type 1 hypersensitivity (IgE mediated), Type 2 (cytotoxic), Type 3 (immune complex), and Type 4 (cell-mediated). Robin Coombs was in fact a veterinarian, and although he never practised, he was responsible for training a number of veterinary immunologists who passed through his laboratory in Cambridge. However useful this classification undoubtedly was, it has become clear that few allergic diseases are caused exclusively by one type of hypersensitivity and most result from a combination. In the last three decades, and aided by the advent of molecular biological tech-

niques, the science of allergy has advanced exponentially to become a highly sophisticated science and a major branch of human medicine.

In contrast, veterinary allergy (now defined as ‘a hypersensitivity reaction initiated by a specific immunological response to an allergen and mediated by antibodies or cells’ [6]) was slower to emerge as a recognized discipline. In large measure this can be ascribed to fewer resources for research, but also to the fact that we are concerned with multiple species, each one of which requires the development of species-specific reagents. And, of course, no formal specialist status exists for the discipline in any country. Nonetheless, its importance in everyday veterinary practice is unquestioned—indeed it is unlikely that a day will pass by in the life of a busy practitioner, no matter what the species of emphasis, without allergy being involved in one or a number of cases.

Much of the early work on veterinary allergy was undertaken by physicians who were largely concerned with the characterisation of potential animal models for allergic diseases of man. The lack of full veterinary involvement did lead to some incorrect deductions—including one that what we now know as canine atopic dermatitis was primarily a respiratory disease, with any dermatological signs being of secondary significance [7]. But the last three decades have witnessed significant advances, all of which are detailed in this text. These have been the result of single individuals or small groups who have made in-depth studies of systems in specific species of veterinary interest. These advances however have been patchy, rather than on a broad front, and significant knowledge gaps still exist in some major body systems of important species.

The current state of knowledge on this increasingly important subject is beautifully described in this, the first truly comprehensive text of allergic diseases affecting the major veterinary species. It will be an invaluable guide to students, clinicians and researchers alike. However, most importantly, whilst it quite naturally concentrates on what is known, it also draws attention to what is not yet known. In so doing it will hopefully provide the necessary stimulus for future research so that this fascinating subject will continue to advance.

Richard E.W. Halliwell
Edinburgh, 2013

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Introduction: the immunological basis of allergic diseases

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Introduction

In 1963, P.G.H. Gell and R.A.A. Coombs published their seminal text *Clinical Aspects of Immunology*, in which they described and classified immunological hypersensitivity reactions [1]. The Gell and Coombs classification of hypersensitivity remains the cornerstone for modern human and veterinary clinical immunology. It is significant that Robin Coombs (1921–2006), one of the founding fathers of this discipline, was a veterinary surgeon [2].

Hypersensitivity, as described classically, involves the immunological sensitization of an individual (man or animal) by repeated exposure to the causative antigen (allergen) over time. A sensitized individual may, on subsequent exposure to the allergen, react in an immunologically excessive or inappropriate manner, leading to tissue pathology and clinical changes of hypersensitivity or allergic disease. The allergens involved are often ubiquitous environmental substances to which only genetically susceptible individuals will react in an inappropriate fashion.

The Gell and Coombs classification describes four major forms of hypersensitivity reaction [1]:

- 1 type I (immediate) hypersensitivity involving tissue inflammation mediated by mast cell degranulation subsequent to cross-linking of surface membrane immunoglobulin (Ig) E molecules by allergen;
- 2 type II (cytotoxic) hypersensitivity involving destruction of a target cell via the effects of antibody (generally IgG or IgM) and molecules of the complement pathway;
- 3 type III (immune complex) hypersensitivity in which immune complexes of antigen and antibody form locally in tissue (when antibody is in excess) or circulate systemically (when antigen is in excess), leading to local or multisystemic inflammatory pathology; and
- 4 type IV (delayed-type) hypersensitivity (DTH) mediated not by antibody, but by sensitized mononuclear

inflammatory cells (particularly T lymphocytes and macrophages) releasing specific proinflammatory and regulatory, soluble signalling proteins (cytokines).

Now, 50 years since this classification scheme was proposed, there is much greater understanding of the molecular basis of the fundamental mechanisms involved in these key immunological reactions. Although we most often consider these hypersensitivity mechanisms in the context of immune-mediated disease, in evolutionary terms they most likely developed in order to make appropriate immune responses to coevolving pathogens. For example, the type I reaction also underpins the host immune response to parasitic infestation and the type IV reaction is intrinsic to the control of obligate intracellular bacterial or protozoal pathogens. Therapeutic management of allergic disease should therefore ideally be allergen-specific in order not to impair appropriate immune responses to infectious challenge.

This book will review in great detail the immunopathology, clinical presentation, and management of allergic diseases of the skin, respiratory tract, and gut of dogs, cats, and horses. It is the aim of this introductory chapter to overview the fundamentals of the allergic immune response. Many of the basic concepts presented here will be expanded in the pages that follow.

The multifactorial nature of allergy

Immune-mediated diseases (allergic, autoimmune, immunodeficiency, or neoplastic diseases) are by definition complex and multifactorial in nature. Allergic diseases will only become expressed clinically in individual people or animals in which there is an optimum combination of underlying predisposing and triggering factors at play. The key factors are genetic background, environmental influences, and immunological dysregulation (Figure 0.1).

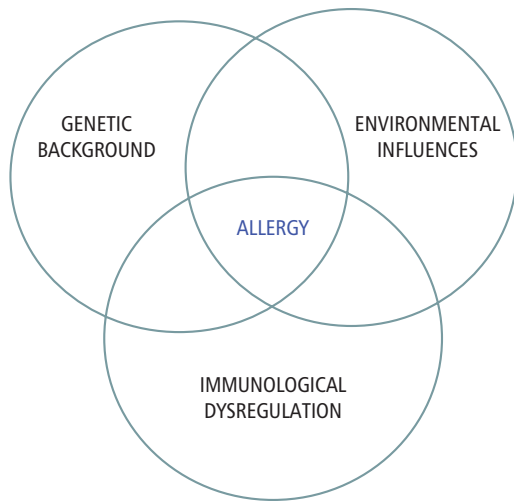


Figure 0.1 The multifactorial nature of allergy. Clinical manifestations of allergy will only become apparent when an individual person or animal has in place an optimum number of background predisposing and triggering factors. The three most important of these are genetic background, environmental influences, and immunological dysregulation.

Genetic background

There is no doubt that allergic disease runs through human families and therefore has a heritable component. Given that we now live in the ‘postgenomic era’, it might be assumed that the genetic basis of human allergy is well defined and that polymorphisms in specific allergy-associated genes are fully characterized. However, despite intensive research, the precise genetic basis of allergic diseases of man is not yet understood [3,4]. It is also clear that allergic disease has greater prevalence in certain breeds of dog and runs through canine pedigrees [5,6]. Clear examples of this phenomenon come from observations of the predisposition of the West Highland white terrier [7] and golden retriever [8] to atopic dermatitis. Again, despite publication of the canine genome in 2005 [9], the genetic basis of allergy in this species is not yet defined. Gene expression microarrays applied to samples of atopic dog skin have indicated a range of likely candidate genes [10] but early genome-wide association studies (GWAS) [11] and candidate gene investigations [12] have not provided clear data. At the time of writing, we await the outcome of GWAS of canine atopic dermatitis performed under the European Union-funded ‘LUPA’ project [13].

There is far less evidence for a genetic predisposition to allergy in the cat and the best example of breed-associated equine allergic disease is the predisposition of the Icelandic pony to *Culicoides* spp. hypersensitivity (‘insect bite hypersensitivity’ (IBH), ‘sweet itch’) [14].

Environmental influence

Simply inheriting a susceptibility genotype does not guarantee that an individual will go on to develop allergic disease. It is now very clear that the environment and personal lifestyle factors impact strongly on predisposition to allergy. At the simplest level, contact with potential allergens, to allow sensitization and subsequent hypersensitivity, is important. Allergen exposure may be geographical (e.g. the global distribution of particular plants and their pollens; the climatic influence on the distribution of ectoparasites) or related to the balance between an indoor and outdoor lifestyle. For example, in most developed nations the dominant allergens responsible for canine atopic dermatitis are traditionally indoor in nature (particularly of house dust mite origin); however, in some areas there is anecdotal suggestion that the prevalence of pollens as causative allergens may be increasing subsequent to climate change and more accessible outdoor lifestyle. Icelandic ponies do not develop IBH unless they are exported from Iceland where *Culicoides* spp. midges do not exist, but even then only 50% of exported horses are susceptible, suggesting a genetic component to susceptibility [14].

Of greatest impact in this area of allergy research has been discussion of the ‘hygiene hypothesis’ [15]. The hygiene hypothesis seeks to explain the fact that the prevalence of allergic (and autoimmune) disease in the human population of developed nations has increased exponentially since the 1960s. This epidemiological observation has been linked to changes in human lifestyle and the impact of these changes on the immune system. In the past five decades, people (and particularly children in whom allergy is particularly prevalent) live an increasingly indoor and ‘sanitized’ lifestyle based around modern technology. Numerous such lifestyle factors are implicated in the hygiene hypothesis, including: indoor carpeting, central heating or air-conditioning; frequency of use of indoor cleaning agents; ingestion of highly processed diets; increased use of childhood vaccination; smaller family size; and lack of exposure to infectious agents in the natural environment. Immunologically, these effects are collectively believed to impair the number or function of ‘natural regulatory T cells’ (natural Tregs; see section ‘Immunological basis’) that are important in the suppression of allergen-specific or autoantigen-specific T cells that may promote allergic or autoimmune disease [16]. Other investigations have demonstrated the protective effects of exposure to environmental infectious agents or the ability of such agents to modulate allergic disease. For example, it is clear that living in a rural environment on a farm is protective from developing allergic disease [17] and that

this protective effect may also impact on the fetus *in utero* [18]. One of the most potent means of stimulating or restoring Treg function is by intestinal exposure to probiotic bacteria or helminth parasites, and human clinical trials support use of these novel therapies [19–21].

It is clear that some elements of the ‘hygiene hypothesis’ might also potentially impact on the prevalence of allergic disease in indoor dogs and cats that have contemporaneously been exposed to more widespread use of processed diets, vaccination, and endoparasite control. The latter serves an important role in human public health, but the link between parasitism, Treg amplification, and control of allergic disease has not been lost on the veterinary research community, where already clinical trials of ‘parasite therapy’ have been performed in atopic dogs [22].

Immunological basis

The chapters that follow will describe the major allergic diseases of dogs, cats, and horses as they affect the skin (e.g. canine and feline atopic dermatitis and flea allergy dermatitis, equine atopic dermatitis, and IBH), respiratory tract (e.g. feline asthma and equine recurrent airway obstruction), and intestinal tract (e.g. dietary hypersensitivity). Immunologically, the majority of these disorders are suggested to have an underlying type I hypersensitivity pathogenesis, although there remain unproven, suggestions that other mechanisms might sometimes be involved (e.g. type III and IV reactions in dietary hypersensitivity [23]). True ‘contact allergic dermatitis’ is relatively uncommon in animals, but involves a classical type IV hypersensitivity reaction. Following is a generic summary of type I hypersensitivity as it might be applied to many of the specific diseases discussed throughout this text.

Immunological sensitization to allergen of a susceptible individual living in an appropriate environment is a complex affair (Figure 0.2). Sufficient environmental loads of allergen must be present and placed in contact with the cutaneous, respiratory, or intestinal surface. It is generally presumed that some form of ‘barrier defect’ affects the covering epithelium and that this permits greater access of the allergen to deeper levels of the epithelial barrier [24]. For example, many human atopic patients have mutations in the profilaggrin gene (*FLG*), which encodes a precursor of the filaggrin protein that is important in maintaining structural integrity of the upper epidermis [25]. Both human and canine atopic patients have now been shown to have increased transcription of genes encoding antimicrobial peptides (e.g. cathelicidins, β -defensins) within lesional skin, although the significance of this finding remains

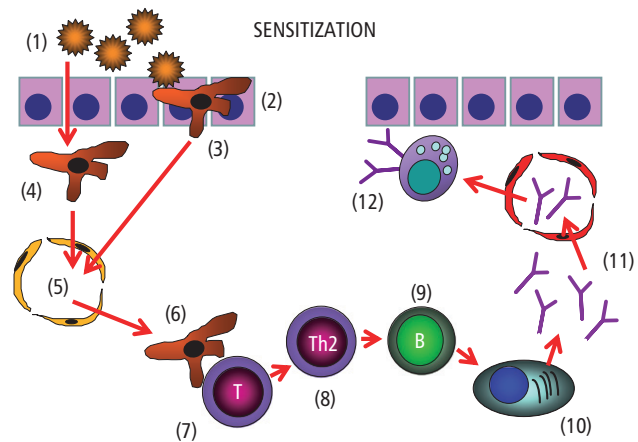


Figure 0.2 The sensitization phase of type I hypersensitivity.

- (1) Allergen is deposited onto or into the epithelial barrier (i.e. epidermis, bronchial, or intestinal mucosa).
- (2) Loss of barrier integrity permits penetration of the allergen.
- (3) Allergen encounters an epithelial resident dendritic cell (e.g. epidermal Langerhans cell).
- (4) Allergen encounters a subepithelial dendritic cell. These encounters may involve conserved allergenic structures and dendritic cell pattern-recognition receptors.
- (5) Dendritic cells migrate within lymphatic vessels to the regional draining lymph node.
- (6) Dendritic cells localize to the paracortex of the lymph node and present allergenic peptide in the context of MHC class II molecules.
- (7) A naïve T cell recognizes the combination of allergenic peptide and MHC via its T-cell receptor.
- (8) Dendritic cell co-stimulation directs differentiation towards the Th2 phenotype.
- (9) The activated Th2 cell enters the lymph node follicle to provide co-stimulation to the allergen-specific B cell.
- (10) The activated B cell differentiates to become a plasma cell, likely committed to the synthesis of allergen-specific IgE or IgG subclass.
- (11) Plasma cells secrete allergen-specific antibodies that enter the circulation.
- (12) Allergen-specific IgE (or IgG subclass) binds Fc ϵ receptors on circulating basophils or tissue mast cells. At this stage the individual is ‘sensitized’ by allergen and primed to mount a hypersensitivity reaction on subsequent exposure to the allergen.

undetermined [26]. Defects in epithelial adhesion molecules forming interepithelial tight junctions (e.g. E-cadherin, claudins, and α -catenin) have been proposed as mechanisms of mucosal epithelial barrier dysfunction in airway or intestinal disease; however, it is not always clear whether these defects are pre-existing or a consequence of the inflammatory response. For example, the *Dermatophagoides pteronyssinus* cysteine protease allergen Der p 1 is known to enzymatically disrupt respiratory epithelial tight junctions [27]. Once allergen

penetrates the barrier it must come into contact with an epithelial-resident (e.g. cutaneous Langerhans dendritic cell) or subepithelial dendritic cell. In the case of the intestinal tract, dendritic cells that lie immediately beneath the enterocyte monolayer may extend cytoplasmic processes between adjacent enterocytes and into the intestinal lumen to achieve antigen sampling. The recognition of allergen by the dendritic cell may have specificity if the allergen bears some form of conserved molecular sequence ('pathogen-associated molecular pattern'; PAMP) that interacts with ligands on the dendritic cell surface ('pattern recognition receptors', PRRs; or 'Toll-like receptors', TLRs).

Dendritic cells capture antigen and transport it via lymphatics to the nearest organized secondary lymphoid tissue (i.e. subcutaneous, bronchial, or mesenteric lymph nodes) where these cells largely remain within the T-cell areas of the tissue (i.e. the paracortex). Such dendritic cell migration has been shown in murine models in which fluorochromes are painted onto the skin and labelled dendritic cells detected subsequently in draining lymph nodes [28]. Concomitant with migration, dendritic cells also 'process' their captured exogenous antigen through a lysosomal compartment within the cytoplasm of the cell. Allergen processing involves enzymatic degradation of the allergen to small peptide fragments and 'loading' of these peptides to the antigen-binding region of a class II molecule of the major histocompatibility complex (MHC). Antigen-loaded MHC II molecules are then expressed on the surface of the dendritic cell during 'antigen presentation' for repeated inquisition by different T lymphocytes (via their T-cell receptors, TCRs) that pass by the relatively stationary dendritic cell.

In a clinically normal individual, the 'default' immune response to allergens (and autoantigens) is to ignore them (immunological tolerance). Tolerance may be achieved through the combination of particular forms of tolerogenic or 'immature' dendritic cell, activated via particular PRR events to deliver signals that stimulate and maintain populations of Treg cells. Dendritic cells expressing the molecule CD103 have tolerogenic function at mucosal sites [29]. Natural Tregs are characterized by the production of the cytokine interleukin (IL)-10 and expression of the transcription factor Foxp3. Should any allergen-specific T cells be inappropriately activated in the normal individual, they would be largely controlled by the circulating complement of natural Tregs that are designed to prevent allergic or autoimmune pathology. Allergic individuals of many species have now been shown to lack adequate numbers of Tregs and this is believed to be a key immunological feature of the allergic response [30].

Therefore, in the presence of a significant allergen load, a barrier defect, a non-tolerogenic dendritic cell, and lack of Treg inhibition, presentation of allergenic peptides by dendritic antigen presenting cells (APCs), together with provision of appropriate co-stimulatory cytokines and surface molecular interactions, may permit the inappropriate activation of CD4⁺ helper T cell (Th) subsets that promote the allergic response; in particular, the Th2 cell characterized by production of IL-4, IL-5, IL-9, and IL-13 and expression of the transcription factors signal transducer and activator of transcription (STAT)-6, suppressor of cytokine signalling (SOCS)-3 and GATA binding protein (GATA)-3.

In parallel to the dendritic cell–T cell interaction, intact allergen particles must be translocated to the same lymph node to enter the B-cell areas of the tissue (the follicles) and interact with the B-cell receptor (BCR) or surface membrane Ig (SmIg). Allergen-specific B cells cannot be fully activated until they receive co-stimulatory signals (e.g. IL-4, IL-13) from allergen-specific Th2 cells that migrate from the paracortex into the follicles to permit this interaction. Activated allergen-specific B cells with high affinity receptors will divide and undergo genetic rearrangement of genes known as the 'immunoglobulin class switch'. In the case of allergen-specific B cells the outcome of this process is that the cell commits to production of IgE or IgG antibodies of particular subclasses (in dogs most allergen-specific IgG antibodies are either IgG1 or IgG4) and transforms to become an antibody-secreting plasma cell.

In the final stages of immunological sensitization, this allergen-specific IgE (and to a lesser extent the IgG subclasses) circulates in the bloodstream and engages with Fcε receptors on the surface of circulating basophils, and, more importantly, on the surface of tissue mast cells. The IgE-coated mast cells are most often resident immediately beneath (or sometimes within) the epithelial surface of the skin, respiratory tract, or gut. They are generally located in close proximity to small capillaries in the subepithelial matrix. At this stage, the individual is classically 'sensitized' to allergen. Of note is the fact that concentrations of serum allergen-specific IgE or IgG do not necessarily correlate with clinical allergy, as shown repeatedly for atopic cats [31] and dogs with atopic dermatitis [32] and dietary hypersensitivity [33].

The clinical manifestation of allergy becomes apparent on the next occasion that the sensitized individual is exposed to the same allergen (Figure 0.3). At this time, allergen that penetrates the epithelial barrier encounters IgE-coated mast cells. Where adjacent membrane IgE molecules bind epitopes on the same allergenic particle, those IgE molecules are said to be 'cross-linked'. The process of cross-linking leads to physical movement of

Fcε receptors and initiation of complex intracellular signal transduction pathways. The end result of this is classical rapid (within minutes) mast cell degranulation with release of preformed bioactive mediators, resulting in the combination of vasodilation, local tissue oedema, leucocyte exocytosis, interaction with neural receptors, and the induction of cutaneous pruritus, and, in the case of airway disease, bronchoconstriction following smooth muscle contraction.

Although regarded as an 'immediate' phenomenon it is now clear that this early pathology is followed by the subsequent 'late-phase response' (between 4 and 24 hours) during which there is infiltration of eosinophils, macrophages, and Th2 CD4⁺ T lymphocytes into the inflamed tissue microenvironment (Figure 0.3). Plasma cells (presumptively allergen-specific) may also be present within lesional tissue and expression of Th2-

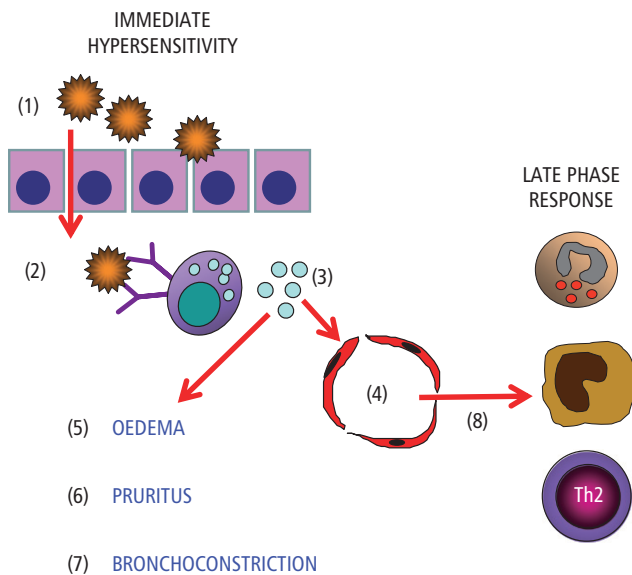


Figure 0.3 The immediate and late-phase hypersensitivity response.

- (1) Allergenic re-exposure occurs to a sensitized individual.
- (2) Allergen penetrates the epithelial barrier and encounters allergen-specific IgE on the surface of a subepithelial mast cell. Two IgE molecules are cross-linked by binding to epitopes on one allergen molecule.
- (3) Signal transduction leads to mast cell degranulation and release of potent preformed biological mediators.
- (4) There is vasodilation of capillaries. Other effects of mast cell degranulation include: (5) tissue oedema, (6) cutaneous pruritus, and (7) airway bronchoconstriction (depending upon the anatomical location of allergen challenge).
- (8) Between 4 and 24 hours later there is an influx of eosinophils, macrophages, and lymphocytes comprising the 'late-phase response'.

related genes (e.g. IL-4, IL-13) has been shown in early-stage canine atopic skin. It is also apparent that in many patients, allergic disease becomes chronic in nature and compounded by other immunological events (Figure 0.4). This is particularly the case in atopic dermatitis which may become complicated by the secondary effects of staphylococcal or yeast infections.

Microbial 'superantigens' (e.g. staphylococcal toxins) may non-specifically activate leucocytes and amplify tissue pathology; microbe-specific Th1 or Th17 effector immune responses may be engendered with infiltration of these T cells into the affected tissue. Th1 cells are characterized by the production of the cytokine interferon (IFN)-γ and expression of transcription factors STAT-4, SOCS-5, and T-bet. Th17 cells are characterized by production of IL-17 and IL-22 and use of the transcription factors STAT-3 and retinoic acid receptor-related orphan receptor (Ror) γt and Rorα and are proposed to amplify innate immune and inflammatory responses in allergic disease [34]. It has also been proposed that a separate Th subset, the IL-9-producing

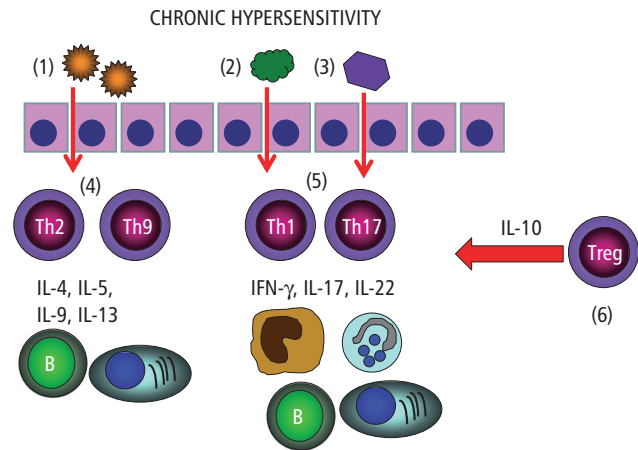


Figure 0.4 The chronic phase of type I hypersensitivity.

- (1) Continued exposure to allergen may be compounded by secondary infection by (2) bacteria and (3) yeasts.
- (4) Allergen exposure drives Th2 cells producing IL-4, IL-5, IL-9, and IL-13 to expand B cell and plasma cell activity. In chronic allergy there may also be differentiation of a population of Th9 cells that preferentially produce IL-9.
- (5) Additional exposure to microbial pathogens now induces a Th1 and Th17 response with recruitment of macrophages and neutrophils. Th1 cells may provide help for antibody responses of a different IgG subclass to those subclasses involved in the immediate phase.
- (6) Although IL-10 producing Tregs are recognized at sites of chronic hypersensitivity, they are unable to successfully down-regulate the active immune response.

Th9 cell (which uses PU.1 as a transcription factor), may play a role in perpetuating the chronic stages of the cutaneous and respiratory allergic response [35,36]. Some studies have suggested that there is a dominance of Th1-related genes (IFN- γ , IL-12, IL-18) in canine chronic atopic skin, but, in reality, in most canine lesional skin there is a complex mix of Th1, Th2, and Treg cells, as indicated by gene expression studies [37]. A complex immunopathology is also suggested for canine cutaneous lesions of adverse food reactions in which there are more CD8⁺ T cells than CD4⁺ cells and expression of genes encoding IL-4, IL-13, Foxp3, and SOCS-3 [38].

Future progress

Although we have come a long way in the understanding of allergic disease, there remain many areas for future research in human and animal allergy. Knowledge of susceptibility genotypes may allow controlled breeding programmes in predisposed canine breeds, although it is likely that allergic diseases will prove to be complex multigenic disorders. Recognition of the contribution of the environment and lifestyle factors might permit recommendations to be made for avoidance of triggering factors and further definition of immunological pathways will lead to development of targeted therapeutic approaches that affect only the allergen-specific elements of the host immune system. In this respect, it is now known that the likely mechanism underlying allergen-specific immunotherapy (ASIT) is amplification of the effects of Tregs to control the aberrant immune response [39–41]. Further approaches targeting deficient Treg activity (e.g. the use of parasite-derived molecules [42], development of refined ASIT using recombinant allergens [43] or DNA vaccines [44], administration of ASIT via novel approaches such as sublingual delivery [45]) should be a focus of future developments.

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Part 1

Canine Allergy

(Editor: Chiara Noli)

Section 1

Canine Atopic Dermatitis

Introduction: canine atopic dermatitis as an evolving, multifactorial disease

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Conflict of interest: none declared.

Canine atopic dermatitis (CAD) has been defined as a genetically predisposed, inflammatory and pruritic, allergic skin disease with characteristic clinical features, most commonly associated with IgE antibodies to environmental allergens [1]. However, this rather simplistic definition belies our incomplete understanding of the complex pathogenesis of the disease and its varied clinical features. In fact, as knowledge increases, CAD is increasingly viewed as a clinical description or syndrome, with a variety of manifestations and potential underlying causes that vary from patient to patient.

Historically, the commonly diagnosed skin disease termed ‘eczema’ in humans was recognized as having allergic origins, and as early as the 1930s veterinarians understood that a similar syndrome also existed commonly in dogs [2]. The exact allergens responsible for ‘canine eczema’ were undefined but often were thought to be either food or parasite related, as with fleas in ‘summer eczema’ [3]. In 1941, a physician allergist named F.W. Wittich provided the first description of a dog with seasonal pollen allergy [4], with successful treatment by desensitization via injections of pollen extracts. Subsequent work in dogs focused on respiratory signs associated with pollen allergy and the possible use of dogs as a model for allergic respiratory disease in human beings. Patterson (also a physician allergist) developed a colony of pollen-sensitive dogs in the 1960s,

which were reported to have allergic rhinitis and dermatitis [5]. The same dogs could be induced to display asthmatic signs if high concentrations of allergen were introduced into the airways. This emphasis on respiratory signs prompted investigators to deem the disease ‘allergic inhalant dermatitis’, as it was assumed that the dermatitis was caused principally by allergen that entered via the respiratory route. The disease in dogs became known by this name, or sometimes by the more general ‘atopic disease’ or ‘atopy’.

On the human front, by the late 1960s, continuing research on the pathogenesis of ‘eczema’ and allergic respiratory disease was pointing to involvement of a newly described and very different type of immunoglobulin, termed immunoglobulin E (IgE), which was capable of binding to the surface of mast cells. Following exposure to the relevant allergen the IgE induced mast cell degranulation, mediator release, and the familiar inflammatory signs. Though Patterson and colleagues [6] were the first to demonstrate that allergic reactivity could be transferred from a sensitive dog to a normal dog with injections of serum—suggesting mediation by an immunoglobulin—it was Halliwell *et al.* who made the final connection, publishing a series of papers in the early 1970s confirming the existence of canine IgE, its antigenic relationship to human IgE, its localization in canine skin, and a complete description of canine atopic disease, including detection of allergen-specific IgE in sera of affected dogs [7–10].

It seems that for many years, we were blissfully content to view ‘canine atopy’ as a rather straightforward disorder of the immune system: simply an IgE-mediated, immediate-type hypersensitivity reaction, caused by exposure to environmental allergens via the inhalant route. Students for decades were taught this mechanism as gospel, in spite of many dogs presenting with extreme dermatitis *without* respiratory signs, reports of human atopic patients with no demonstrable IgE involvement, and ‘classically’ atopic dogs with negative allergy tests. In the 1990s, a new generation of veterinary investigators began to view ‘atopy’ in the light of the explosion in knowledge about the immune system and its complex regulatory mechanisms and to use the more preferred and specific term of ‘canine atopic dermatitis’. The role of cutaneous IgE-bearing antigen presenting cells [11], expression of cytokines by different T-helper lymphocyte populations in the skin [12], and other immunologic details of CAD were uncovered and found to remarkably parallel those of the human atopic disease. From here, a large number of studies extending to the present day have examined such factors as epidermal barrier function and percutaneous allergen penetration as the actual main route of allergen exposure in CAD [13], the important role of skin infections, genetic and environmental influences, and countless other immunologic and molecular details.

The details of these many investigations, and how they fit in the framework of our current understanding, will be the subject of the following chapters in this book. New knowledge about pathogenesis has a direct impact on how we diagnose and treat CAD, and is the basis of new treatments that will arrive on our pharmacy shelves in the future.

In proceeding through these chapters it will be useful for the reader to be aware of some definitions and terminology that describe AD and associated phenomena. This ‘standard terminology’ was originally proposed by the ACVD Task Force on Canine Atopic Dermatitis in 2001 [1] and has been updated since to more accurately express our current understanding [14]. The most common terms that are important to understand, with their current definitions, include the following:

- **Atopy.** Strictly, a genetically predisposed tendency to develop IgE-mediated allergy to environmental allergens. *Atopy* is a term originally and literally meaning ‘strange disease’, reflecting the historical lack of understanding of the disease process. It is a general term that in its adjective form *atopic* can indicate disease of various organ systems, for example *atopic rhinitis*, *atopic asthma*, or *atopic dermatitis*. Though in casual conversation we may refer to a dog as *atopic* or *having*

atopy, it is important to understand (and to explain to students) that the correct and preferred name for the skin disease in dogs is *atopic dermatitis*.

- **Atopic disease.** Any clinical manifestation of atopy. In the dog, *atopic dermatitis* is the most commonly diagnosed atopic disease. Other, less common atopic diseases include *atopic rhinitis*, *atopic conjunctivitis*, etc.
- **Atopic dermatitis.** A genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, associated with IgE antibodies most commonly directed against environmental allergens.
- **Atopic-like dermatitis.** An inflammatory and pruritic skin disease with clinical features identical to those seen in CAD, but in which an IgE response to environmental or other allergens cannot be documented with serological or intradermal methods. From a practical standpoint, this term describes dogs that fit all the clinical criteria for CAD, but who are negative on all allergy tests.

Though these definitions are not perfect and will no doubt be revised again, they represent our best current efforts to describe atopic diseases in dogs in a way that is clinically useful and enables us to establish uniform diagnostic criteria, evaluation schemes and formulate appropriate management plans.

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