# IMMUNOLOGICAL DISEASES

Third Edition

Volume II

Max Samter, M.D., Editor

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# Volume I

# Volume II

# PART THREE: THE ATOPIC DISEASES

## *K. Frank Austen, Editor*

"Atopy," in its original definition, described an altered state of reactivity which occurs in families and leads to the development of "reagins" and disease after "natural" exposure to specific allergens.

Like other terms which served a healthy purpose during the early part of the century because they emphasized the heterogeneity of altered reactivity, "atopy" has come to raise more questions than it answers.[1] Some of these questions attempt to clarify the genetic make-up of atopic patients, clearly recognized by William Sherman in the second edition of this text, and brought up to date by Marsh and Bias in Chapter 45. Genetics, however, might not only refer to specific immune response genes, but also determine the level of total IgE, and even the affinity of IgE for allergen and for mast cell receptors. Consequently, investigations of atopy must extend to the regulation of mediator generation and release as well as to the extracellular controls of mediator function. While this brings the atopic diseases closer to the "diseases of immediate hypersensitivity," the atopic diseases have a sufficient number of characteristics of their own that, at least for the time being, the term *atopic diseases* should be retained.

[1]Samter had previously questioned the legitimacy of the term "atopy" (*Med. Clin. North Am.* 58:233, 1974).

"For years, the definition remained unchallenged, even though it failed to explain common clinical observations. For instance, technicians in laboratories might become sensitive to dander of guinea pigs, rats, rabbits, and dogs, but not to ragweed pollen, even in areas in which hay fever is far more prevalent than sensitivity to animal dander. On the other hand, the hay fever patient, once pollen-sensitive, would remain pollen-sensitive after years of transfer to a pollen-free area, even though the half-life of IgE turned out to be days or weeks, not years.

"Even today, the patient who has life-long and often overwhelming sensitivity—associated with circulating IgE and positive skin reactions—to a single antigen, e.g. to crustacea, defies classification. Can he be atopic, in the absence of any sensitivity to common allergens? Some say "yes" and apply the term atopy to any clinical entity which can be traced to IgE, but most of us prefer to limit it to those conditions which have a familial component. Infestation with ascaris and trichinella spiralis might induce synthesis of IgE and massive eosinophilia, but they are non-atopic diseases: the point, however, has not been settled, and our terminology must be tightened."

# 42. The Atopic Diseases: Definition and Comment

*K. Frank Austen*

Early studies of allergy focused on the relationships of hay fever and asthma in humans to experimental anaphylaxis in animals [4] on the assumption that the observed species differences were attributable to the structure of the antigens, the route and form of their administration, and the nature of the subject's subsequent encounter with the antibody [43]. Indeed, "naturally" sensitized humans who developed hay fever or asthma upon exposure to horses, and humans sensitized by prior injections with horse serum containing diphtheria antitoxin exhibited the same anaphylactic response to administration of a therapeutic dose of horse serum [23]. Both routes of sensitization were associated with the presence of skin-sensitizing antibodies which could be passively transferred to nonsensitive recipients, but the injection of horse serum produced an additional specific antibody of the IgG class [13]. The subsequent recognition of spontaneous asthma due to environmental allergens in dogs and the demonstration that their anaphylactic response to allergen is indistinguishable from that of actively sensitized dogs challenged with specific proteins [52, 53] supported the early view that the immunological mechanisms recognized in human allergic rhinitis and asthma bore some relationship to those studied experimentally in animals. However, as Sherman has pointed out [68], the animal models lacked the genetic considerations central to the human diseases, failed to manifest the characteristics of atopic dermatitis, and generally involved heat-stable homocytotropic antibodies [6].

The association of allergic rhinitis and asthma in the same patient, often with a familial background, and the presence in the serum of passive transfer activity led Coca and Cooke in 1923 [12] to introduce the term "atopy" for the familial tendency of patients to become sensitive to "allergens" and to develop, alone or in combination, such clinical conditions as bronchial asthma, rhinitis, urticaria and eczematous dermatitis (atopic dermatitis). Specific IgE, however, can develop without an atopic setting (e.g., in certain forms of urticaria and in the anaphylactic syndrome), and heat-stable homocytotropic antibodies have now been recognized in humans with reversible airway disease [7].

Most terms are broad when they are coined and narrowed as our experience grows: "allergy"—as conceived by von Pirquet in 1906 [75]—described "altered reactivity" which could be either injurious or beneficial to the host. Common usage eventually made allergy synonymous with "hypersensitivity"; and the term "atopy," in general, was applied to the "classic" diseases of allergy. It seems likely that the unrestricted term "allergic diseases" or the restrictive connotation of "atopic diseases" might be replaced by a more precise definition which must account for the unexplained clinical course of atopic dermatitis [5] or the chronic hyperirritability of the airways demonstrable in an asymptomatic asthmatic subject [45].

## Mast Cells and Mediators

The importance of the presence of specific IgE in atopic diseases by implication involves tissue mast cells as the target cells of the antigen challenge and mast cell-derived mediators as the effector principles of the symptom complex. Although reversible bronchospasm [67] of hyperresponsive airways [14, 18, 50, 73] is the hallmark of natural and experimentally induced bronchial asthma, the functional abnormalities are now understood to include not only increases in bronchomotor tone and gas trapping [57] but also a decrease in static compliance [42, 59]. Further, the characteristic pathological features include edema of the submucosa and mucosa; thickening of the basement membrane; infiltration with polymorphonuclear leukocytes of the eosinophilic and neutrophilic type; and a bronchiolar exudate of shed epithelial cells, viscid mucus, and a serous transudate [1, 19]. In order to implicate mast cell-mediated events in such a disorder it is necessary to establish acces-

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sibility to environmental stimuli and capacity to elicit both acute *pathopharmacological* and subacute/chronic *inflammatory* tissue changes [2].

The presence of mast cells in the bronchial mucosa and lumen of rhesus monkeys and humans [48, 54], the antigen reactivity of comparable cells from the bronchial lumen of dogs [55], and the intraepithelial location of IgE-bearing mast cells in the tonsils, adenoids, and nasal polyps of humans [20] indicate that initial mediator release may occur without involvement of interstitial mast cells. Subsequent alterations in mucosal impermeability to allergens or in delivery of allergen after absorption might account for the decrease in total numbers of detectable mast cells and the prominence of disrupted cells with scattered granules throughout the bronchial connective tissue in acute allergic asthma [66]. Although measurements of systemic release of mediators in spontaneous and experimentally induced asthma are generally lacking, it appears that such measurements could be made, since recent studies [37, 70] have confirmed earlier findings [61] of the release into the venous effluent of chemical mediators during cold-induced urticaria-angioedema, as demonstrated with newly available specific and sensitive techniques for analyzing complex biological fluids.

*Mast Cell Regulation*
Mast cell-dependent phenomena are regulated at many levels: by the intensity of the mast cell-activating event, by the endogenous determinants of the ratio of preformed and newly generated mediators released, by the receptor binding and responsiveness of target cells to released mediators, and by the rate at which released mediators undergo biodegradation. An example of each of these control levels has been recognized in in vitro systems, which serves to emphasize that the pathobiological considerations of immediate type hypersensitivity reactions need not be limited to a focus on specific IgE alone. At the first level, a minimal IgE-mediated stimulus may cause intracellular SRS-A generation without release of SRS-A or histamine. At the second level, histamine, a primary preformed mediator, acting via an H2 receptor to activate adenylate cyclase, increases cellular levels of cyclic 3′,5′-adenosine monophosphate (cyclic AMP), thereby suppressing further mediator release [39]. At the third level, the $NH_2$- and COOH-terminal tripeptides of ECF-A block the chemotactic response of eosinophils to ECF-A by reversible competition for the receptor and irreversible deactivation, respectively [26]; such tripeptides would be readily derived from the eosinophilotactic tetrapeptides [24] (ECF-A) by cleavage with carboxypeptidase A and aminopeptidase M. Conversely histamine, in minimally chemotactic doses [11], facilitates the response of the eosinophil to the eosinophilotactic tetrapeptides [25].[1] Finally eosinophils, concentrated by directed migration, inactivate released primary mediators such as SRS-A [77], histamine [78], and a platelet-activating factor [38] because of their content of arylsulfatase B, histaminase, and phospholipase D, respectively. Biodegradation is not dependent wholly on responding and infiltrating cells in that in the human lung arylsulfatase B, which predominates over arylsulfatase A in that organ, inactivates SRS-A in a reaction comparable to that achieved with the eosinophil-derived enzyme [76].

Level two is the point at which regulation has been extensively considered in atopic patients in regard to a possible functional impairment of the $\beta$-adrenergic receptor [71]. A selective defect in responsiveness of peripheral blood leukocytes to $\beta$-adrenergic agonists does appear to be acquired by some patients and to be more prominent with increased disease severity [49]; this might represent receptor shedding, as noted for lymphocytes cultured with insulin [22] and for human fibroblasts grown in the presence of various $\beta$-adrenergic agonists [21]. Even without administration of $\beta$-receptor agonists [46], an impaired response of peripheral leukocytes to $\beta$-agonists in vitro has been reported in studies of cells from untreated patients who have bronchial asthma [51] and atopic dermatitis without respiratory symptoms [60]. While endogenous catecholamine release from the adrenal glands by histamine [58] could be a factor, urinary excretion of catecholamines in atopic dermatitis has been normal [31].

[1]Histamine has a positive chemokinetic effect on neutrophilic and eosinophilic polymorphonuclear leukocytes via their H1 or H2 receptors; and H1 agonists augment the response to cell-specific chemotactic factors, whereas H2 agonists block that same response (E. J. Goetzl and K. F. Austen, *Progress in Immunology III.* Australian Academy of Science, 1977. P. 439).

*Mast Cell Function*
The mast cell is the only cell which has a specific recognition unit, IgE, for a foreign substance and is located in the tissues in general rather than in a circulation, hematogenous or lymphatic. It is tempting to speculate that the physiological role of the mast cell in host defense is the recruitment of proteins and cells from the circulation to the reaction site. Once specific antibody and complement, followed in hours by polymorphonuclear leukocytes, have arrived at the reaction site to create the *cellular phase,* the initial or *humoral phase* mediated by substances such as histamine and SRS-A is terminated, not only by local controls but also by the constituents of the cellular phase attracted by such factors as ECF-A and HMW-NCF. Failure to limit the humoral phase creates a *pathopharmacological state* recognized clinically as urticaria, angioedema, exacerbations of rhinitis or asthma, or systemic anaphylaxis. Similarly, an inability to regulate the cellular phase would induce a local *inflammatory state* with attendant implications for long-term low-grade injury in nasal and bronchial tissues of atopic persons. Thus the mast cell and its mediators might be involved in diseases other than those initiated by IgE-dependent mechanisms.

That the mast cell and its constituent mediators have multiple capabilities is demonstrated by the dual, early and late, pulmonary and cutaneous responses to aerosol and intracutaneous administration, respectively, of *Aspergillus* [41, 56] and avian materials [29, 30]. Similar dual responses in sensitive subjects have been observed in skin with *Bacillus subtilis* enzyme preparations [17] and in both skin [72] and airways [10] with grass pollen. Even more telling has been the elicitation of dual responses in normal subjects to crystalline *B. subtilis* $\alpha$-amylase in the P-K reaction and to the $F(ab)_2$ fragment of sheep antihuman IgE [16]. These latter studies reveal that IgE-dependent mast cell activation is sufficient to achieve a clinical local inflammatory response characterized histologically by mast cell degranulation and infiltration with eosinophils and some neutrophils.

Immediate type hypersensitivity is present in patients experiencing metazoal parasite infections, as revealed by specific immediate type skin tests [33] and the release of histamine and ECF-A from peripheral leukocytes interacted with appropriate helminth antigen [64]. The clinical course may include signs compatible with immediate type hypersensitivity reactions [65] and is characteristically marked by a profound elevation in IgE [32, 34, 62], of which only a fraction is specific [15]. In a particularly intriguing study, serum IgE levels and peripheral blood eosinophils were found to be elevated and fecal egg counts of *Necator americanus* substantially reduced in atopic as compared to nonatopic native inhabitants of a hookworm-infested region of New Guinea [27, 28]. The capacity of the tissue mast cell to recruit blood protein and cellular elements in the humoral phase of its response to specific antigen or to a parasitic degranulating factor [74] might be particularly pertinent to the control of the skin-penetrating or gut-attaching phase of a helminth cycle. For example, Ogilvie et al. [47] protected rats against invading cercariae of *Schistosoma mansoni* by intradermal injection of specific reagin-containing serum but not by intraperitoneal administration of much larger quantities of antiserum. *Nippostrongylus brasiliensis* expulsion from the gastrointestinal tract of the rat is associated with macromolecular leak as assessed with Evans blue dye [3] or horseradish peroxidase in electron microscopy [44], suggesting marked release of chemical mediators. Such an event might serve to clear worms already damaged by immune humoral or cellular events and might contribute directly to impairing the integrity of the parasite [63]. In schistosomiasis, killing of the schistosomula in vitro by human and peripheral blood leukocytes has been shown to be an IgG antibody-dependent function of the eosinophil [8, 9], and this has been confirmed in in vivo studies in mice [40].[2] In these circumstances both the humoral and cellular phases of the specific mast cell response might contribute to host resistance. Since both IgE and certain IgG subgroups mediate antigen-dependent mast cell reactions, there is ample opportunity for the mast cell activation to be closely linked to initiation of other effector pathways of host resistance. It is now critical to begin to assess tissue mast cells and their

[2]Non-antibody-dependent eosinophil cytotoxicity for schistosomula occurs via the capacity of the helminth surface to activate the alternative complement pathway (A. Sher, *Nature* 263:334, 1976; F. J. Ramalho-Pinto, D. J. McLaren, and S. R. Smithers, *J. Exp. Med.* 147:147, 1978), and the anaphylatoxic by-products would also recruit mast cell factors.

state of activation in experimental studies of host resistance and in human disease states by quantitative cell counts, ultrastructural techniques, and quantitative measurements of preformed and newly generated mediators [69].

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