Virus Associated Immune and Pharmacologic Mechanisms in Disorders of Respiratory and Cutaneous Atopy

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ABSTRACT

Anaphylaxis represents non-atopic immediate hypersensitivity, whereas manifestations of atopic immediate hypersensitivity include bronchial asthma, hay fever, allergic rhinitis, chronic urticaria, and atopic dermatitis. In spite similar antigen exposure, only a minority of the population shows some form of atopic disease. Atopic disease with its spontaneous pattern of familial occurrence cannot be induced at will.

The exact pathogenesis of atopy is yet to be elucidated. Two theories prevail: 1) atopy is a primary disorder of the immune system with sequelae in the various effector tissues; and 2) a concept of atopy as a primary autonomic imbalance, essentially beta adrenergic in character, with sequelae in effector cells, including those engaged in the production of antibodies. The autonomic imbalance is perceived as caused not by some disorder of the autonomic nervous system itself but by a defector functioning of its effector cells. These two concepts are not mutually exclusive. The IgE antibody, which mediates allergic reactions, is essentially identical with atopic reagin in various animal species.

The beta adrenergic theory regards atopic disorders (i.e., perennial and seasonal allergic rhinitis, bronchial asthma, and atopic dermatitis) not as immunologic diseases but as unique patterns of altered reactivities to a broad spectrum of immunologic, psychic, infectious, chemical and physical stimuli. The antigen-antibody interaction is given the same role as that of a broad category of nonspecific stimuli that function only to trigger the same defective homeostatic mechanism in the various effector cells involved in immediate hypersensitivities. Current evidence favors the possibility that there are inherited and/or acquired multiple abnormalities in the receptor – adenylate cyclase – cyclic AMP system of all effector cells that are critical in the organization of immune reactivities.

Atopic abnormality may be 1) acquired by functional receptor regulatory shifts caused by hormonal changes, infection (viral, bacterial, etc), allergic tissue injury or other event; 2) genetically determined; or 3) caused by autoimmune disease. One, two or all three of these effector mechanisms may be operative in a particular disease.

There is an important relationship between asthma and viral respiratory infection. A history of childhood viral respiratory illness is a risk factor for the development of chronic obstructive

airway syndromes in later life. Asthmatic attacks occurred only when the infection produced fever, malaise, cough or coryza. The dominant role of fever in these episodes immediately suggests the profound involvement of adrenergic effector mechanisms. The presence of autoantibodies to beta-adrenoceptors in patients correlated well with a reduced beta - and an increased alpha-adrenergic responsiveness. Virus infections can elicit autoantibody formation.

In patients with atopic dermatitis an increased susceptibility and abnormal host response to viral infections in general. Defective cytotoxic T cells, abnormally functioning macrophages and natural killer cells, a reduced production of IFNα in children, and of IFNγ in atopic patients with food allergy has recently been demonstrated. Lymphocytic cyclic AMP-phosphodiesterase, that destroys cyclic AMP, is increased in atopic dermatitis and in allergic respiratory disease of adults, and this increased activity correlated closely with histamine release from basophils. Peripheral blood leukocytes and lymphocytes in atopic dermatitis have frequently demonstrated impaired beta adrenergic reactivity.

Allergic tissue injury may be initiated by antigen-specific IgE antibodies that combine with Fcε receptors on various cell types and trigger mediator release upon encounter with the antigen. Various noxious agents that are capable of triggering asthma are capable of releasing inflammatory mediators from the same target cells. Accounting only for those pharmacologic mediators where the cell-type has been identified, the spectrum of mediator-storing, synthesizing, or transporting cells includes neutrophil leucocytes, basophilic leucocytes eosinophilic leucocytes; mast cells, "chromaffin-positive" mast cells, enterochromaffin cells, chromaffin cells ; platelets, neurosecretory cells and nerve cells that potentially produce all amine-mediators as well as prostaglandins and kinins.

1. INTRODUCTION

This chapter describes some immune and pharmacologic mechanisms associated with viral infections in certain immunologic diseases that belong into the group of the so-called immediate hypersensitivities. The term *immediate hypersensitivity* denotes an immunologic sensitivity to antigens that manifests itself by tissue reactions occurring within minutes after the antigen combines with its appropriate antibody. Such a reaction may occur in any member of a species *(non atopic immediate hypersensitivity)* or only in certain predisposed or hyperreactive members *(atopic immediate hypersensitivity)*.

The prototype of the non-atopic immediate hypersensitivity is localized or generalized anaphylaxis, whereas manifestations of atopic immediate hypersensitivity include bronchial asthma, hay fever, allergic rhinitis, chronic urticaria, and atopic dermatitis.

The discussions that follow shall be confined to the *atopic form of immediate hypersensitivities* in general, and to their respiratory and cutaneous manifestations, in particular. Of the latter, bronchial asthma, and its cutaneous equivalent, atopic dermatitis, shall serve as the *"model" immunologic* manifestations for our analysis below.

2. ATOPIC IMMEDIATE HYPERSENSITIVITIES (DISEASES OF ATOPIC ALLERGY)

Only a minority of the population shows some form of atopic disease in spite of the fact that, by and large, identical conditions of antigens must be presumed to exist for all members of the

population. The nature of the constitutional basis of atopy, that is, of the underlying determinant for the development of atopic disease, is as yet unexplained.

Many theories of the constitutional basis of atopy have been proposed since Coca and Cooke's original definition. Only two general ideas, however have survived: 1) the perception of atopy as a primary disorder of the immune system with sequelae in the various effector tissues; and 2) a concept of atopy as a primary autonomic imbalance, essentially beta adrenergic in character, with sequelae in effector cells, including those engaged in the production of antibodies. The autonomic imbalance is perceived as caused not by some disorder of the autonomic nervous system itself but by a defector functioning of its effector cells.

These two concepts are not mutually exclusive. In fact, they may be interdependent. Although the immune features of atopic disease can be understood within the framework of a basic adrenergic disorder of various effector cells, many if not most of the nonimmune features of atopic conditions are not readily explicable of the basis of the primary immune abnormality.

3.   THE ORIGINAL CONCEPT OF ATOPY

At the time when the original concepts of atopy were being developed, it had long been known that hay fever and asthma often occurred together in the same individual and both of them showed a marked familial tendency. Similarly, it has been recognized that acute and chronic urticaria as well as gastrointestinal manifestations of idiosyncrasy to a specific food were more common in patients with these diseases than in the general population, and a relation to infantile eczema *(Besnier's prurigo, neurodermatitis)* also was observed. Eczema was found to occur more frequently in the children of patients with hay fever or asthma, and individuals who had eczema in infancy showed an usual incidence of hay fever and asthma later in life.

These diseases were, therefore, considered together by Cooke and Vander Veer as a special group of diseases of human sensitization with a hereditary background, and these authors concluded that such "sensitized individuals transmit to their offspring not their own specific sensitization, but an unusual capacity for developing bioplastic reactivities to any foreign proteins". With further progress in determining additional characteristics of "human sensitization" in contrast to those of experimental anaphylaxis in laboratory animals, Coca and Cooke concluded that a clear distinctions must be made between two types of hypersensitivity manifestations: 1) the anaphylactic type of allergic response to abnormal substances 2) the atopic type of response to substances that are generally innocuous. As they stated:

"This latter sub-group evidently needs a special term by which it may be conveniently designated and this need is satisfactorily met with the term atopy, which was kindly suggested by Professor Edward D. Perry of Columbia University. The Greek word, from which the term was derived, was used in the sense of a strange disease. However, it is not, on that account, necessary to include under the term all strange diseases; the use of the term can be restricted to the hay fever and asthma group."

To these, Wise and Sulzberger then added neurodermatitis under the new designation of "atopic dermatitis". Based on the close association of this condition with other atopic manifestations, Wise and Sulzberger concluded that the skin lesions of this disorder were cutaneous analog of hay fever and asthma and suggested that the name atopic dermatitis replace disseminated neurodermatitis.

Several characteristics of the atopic state emerged from these early concepts: atopy was felt to be a hereditary manifestation, subject to a dominant gene, a peculiarly human disorder with

ι reacting serum element different from classic antibodies and reminiscent of the Wasserman reagin (hence the name, atopic reagin). Atopic antibodies, furthermore, seemed to occur only n humans, many times without any demonstrable prior exposure to incitant substances and nduced by agents that often appeared to be nonantigenic (atopens of Grove and Coca)

Over the years, most of these postulated differences between atopy and anaphylaxis were gradually eliminated. Thus, Ishizaka discovered an antibody, which is essentially identical with atopic reagin in various animal species. Moreover, atopic disease was shown by Patterson to occur in animals. Some of the other distinctions between anaphylaxis and atopy were also amenable to various alternative explanations, indicating that these conditions may not be separated by wide and irreconcilable differences, as the originators of the concept of atopy believed it. Nevertheless, some differences remained, and other important new differences remain, and other new differences emerged, making it imperative that a concept of atopy be reformulated.

I. THE REFORMULATED CONCEPT OF ATOPY

Since the 1960's, it has become increasingly evident that in addition to some of the remaining immunologic difference between anaphylaxis and the immediate hypersensitivities of the atopic and non-atopic type. Thus, it appears that in anaphylaxis we are dealing with a normal (physiologic) antibody response to an unnatural exposure to antigen, whereas in atopic allergic an "abnormal" antibody response to natural antigenic exposure seems to be involved. Anaphylactic reactivity of the sensitized individual depends on the release of an amount of pharmacologically active effector molecules sufficient to be toxic for most members of the same species. In contrast, individuals with atopic disease possess a quantitatively and qualitatively abnormal reactivty to otherwise nontoxic concentrations of endogenously released or exogenously administered pharmacologic mediators. Furthermore, the quantitative change consistently is in the direction of a decreased response when beta-adrenergic agents are the agonists and consistently in the direction of an increased response when any one of the other pharmacologically active effector molecules are involved.

Another essential difference between the atopic and non-atopic varieties of immediate hypersensitivities is the major contributory role played by infection in atopy, whereas infection has not been shown to be causally related to anaphylactic allergy anaphylaxis, the Arthus reaction, or serum sickness. Moreover, atopic conditions can be precipitated by a number of unrelated stimuli, whereas only the specific antigen can bring about anaphylaxis. Finally, the latter conditions may be produced artificially, but atopic disease with its spontaneous pattern of familial occurrence cannot be induced at will. Acute human pulmonary anaphylaxis, which can include asthmatic features, for example, has never been reported to lead to the development of bronchial asthma or atopic disease.

In the reformulation of the original concept of atopy by Szentivanyi [1] the essential difference between immediate hypersensitivities of the non-atopic and atopic varieties is that the former conditions are mediated by normal immune and pharmacologic mechanisms, whereas atopy is based on abnormal immune and pharmacologic mechanisms. This difference between anaphylaxis and atopy is regarded as fundamental. In this view, furthermore, it is the altered pharmacologic reactivity that is considered as the uniformly present, single atopic characteristics of pathognomonic significance.

5.   THE DEVELOPMENT OF THE BETA-ADRENERGIC APPROACH TO THE
     STUDY OF THE CONSTITUTIONAL BASIS OF ATOPY

Authentic atopy cannot be produced at will in animals or humans, neither induced directly
nor transferred passively. In addition to animal models of anaphylaxis, there are a number of
experimental models simulating human atopy as well as isolated systems suitable for studying
segmented areas of atopic reactivity. As such, they are useful for the analysis of some of the
individual events (i.e., mediator release in the human reaction). Nevertheless, these in vivo and
in vitro models are anaphylactic variants and represent immunologically and pharmacologically
normal reactivities. Therefore, they cannot be used for the study of the constitutional abnormal-
ity in atopy.

6.   THE TWO EXPERIMENTAL MODELS FOR THE STUDY OF THE CONSTITU-
     TIONAL BASIS OF ATOPY

The search for a laboratory model was guided by the premise that, if it is to be meaningful, the
model must be able to imitate not only the immunologic but also the pharmacologic abnormality
of the atopic state. The latter is manifested against substances that, in mammalian physiology,
serve as the natural chemical organizers of autonomic action. It seemed likely, therefore, that an
abnormal reactivity to these agents could be most effectively produced through some alteration
of normal autonomic regulation significant enough to result in an autonomic imbalance.

7.   THE HYPOTHALAMICALLY " IMBALANCED" ANAPHYLACTIC GUINEA PIG

The first attempts to establish a more meaningful experimental counterpart of the atopic state
were made by Filip and Szentivanyi in the years from 1952 to 1958 during studies of hypotha-
lamically "imbalanced" anaphylactic guinea pigs. Briefly, by electrolytic removal of one
hypothalamic division or electric stimulation of the antagonistic division, it was possible to alter
profoundly the anaphylactic reactivity of guinea pigs both immunologically and pharmacologi-
cally. From both the immunologic and pharmacologic standpoints, the conditions so produced
more closely approximated those of the human atopic state than does anaphylaxis. Nevertheless,
it was felt that the artificiality of such surgically induced hypothalamic imbalance is far removed
from the natural setting, (involving various inherited or acquired factors or both) that may sur-
round the development of an atopic state. In their efforts to discover an accurate representation
of those naturally occurring conditions some of which (i.e., infection) may conceivably serve as
a developmental background for atopy. Szentivanyi and Fishel in the early 1960's found that the
Bordetella Pertussis – induced hypersensitive state served as a more appropriate model.

8.   THE BORDETELLA PERTUSSIS-INDUCED HYPERSENSITIVE STATE OF MICE
     AND RATS

Injection of live or killed *Bordetella Pertussis* organisms into certain strains of mice and rats
modifies the normal reaction of these animals to a number of various stimuli. The possible
applicability of the results of these investigations to atopy is implied by the following principal

features of the *B. Pertussis* induced altered responsiveness: 1) hypersensitivity to endogenously released or exogenously administered histamine, serotonin, bradykinin, slow-reacting substance A, some prostaglandins, and at least in two strains, to acetylcholine; 2) hypersensitivity to less specific stimuli, such as cold, changes in atmospheric pressure, and respiratory irritants; 3) in contrast to these increased sensitivities, a reduced beta adrenergic sensitivity to catecholamines and concerning some metabolic parameters, a reversal of normal beta-adrenergic activity; 4) enhanced antibody formation in general (adjuvant activity) and facilitated production in quantity of antibodies of the IgE class; and 5) presence of a marked eosinophilia.

As described by Szentivanyi, the major advance in these experiments that has paved the way for a meaningful analogy to atopic disorders has been the finding that hypersensitivity of the pertussis-sensitized mouse to pharmacologic mediators may be due to an acquired or genetically determined autonomic imbalance caused primarily by a reduced functioning of the adenylate cyclase coupled beta adrenergic receptors and the associated cyclic AMP system.

9. THE BETA-ADRENERGIC THEORY OF ATOPIC DISORDERS: UPDATED FORMULATION AND POSSIBLE EFFECTOR MECHANISMS

The previously discussed considerations and conclusions of the two consecutive series of animal experiments have culminated in the postulation of the original beta adrenergic theory of atopic disorders as published by Szentivanyi in 1968 [ ]. This theory regarded those disorders (i.e., perennial and seasonal allergic rhinitis, bronchial asthma, and atopic dermatitis) not as immunologic diseases but as unique patterns of altered reactivities to a broad spectrum of immunologic, psychic, infectious, chemical and physical stimuli. This view gives to the antigen-antibody interaction the same role as that of a broad category of nonspecific stimuli that function only to trigger the same defective homeostatic mechanism in the various effector cells of the biochemical reaction sequence of immediate hypersensitivities.

Activation of the same defective mechanism by such a broad spectrum of unrelated stimuli is believed to be made possible by the unusual character of the pharmacologic mediators as biological distinct class of natural substances. These mediators, when viewed from the standpoint of their probable physiologic function, are the chemical organizers of autonomic action as well as of immunoregulation, that is, of homeostatic control. Consequently, regardless of the immunologic or non-immunologic nature of the triggering event, its chemical realization would be expected to be brought about by essentially the same mediators.

Homeostatic adjustment to these influences requires, among other things, mobilization of the adrenergic neurotransmitters and their balanced (uninhibited) interaction with their effector systems. The theory postulated that the constitutional basis of atopy lies in the reduced function of the beta adrenergic effector system, irrespective of what the triggering event may chemically be in a particular case (e.g., immunologic, infectious, or psychic). In this situation, the adrenergic neurotransmitters are released in the face of relatively unresponsive beta-adrenergic effector system, and the resultant autonomic imbalance deprives the effector tissues of their normal counter regulatory adjustment. This constellation of mediators and effectors then lead to a unique pattern of quantitatively and qualitatively altered reactivity to the chemical organizers of autonomic action, mostly in response to trivial trauma.

When the theoretical scheme is applied to respiratory or cutaneous atopy, at least six levels of responses critical in these diseases are expected to be influenced by the beta-adrenergic sub sensitivity in question:

1. A reduction in the normal beta adrenergic inhibition of lysosomal enzyme release, chemotaxis, phagocytosis, antibody dependent cellular cytotoxicity, increased expression of FC IgE receptors, and prostaglandin E synthesis to stimulation with histamine-induced suppressor factor, that is effector mechanisms that are known to play an important role in immunologic inflammation.
2. A reduction in lymphocytic beta-adrenergic sensitivity resulting in abnormality decreased (lymphocyte transformation, E-rosette forming cells, T cells, suppressor cell function) and abnormally increased (IgE-producing B cells, Fc receptor-bearing lymphocytes) lymphocyte reactivities.
3. Mast cell mediator release to immunologic or non-immunologic stimuli, ordinarily suppressed by beta-adrenergic stimulation would become sub sensitive to the same, while both cholinergic and alpha-adrenergic enhancement of mediator release would be exaggerated.
4. Beta-adrenergically mediated bronchial smooth muscle dilation is reduced, while cholinergically and alpha- adrenergically mediated constriction is augmented.
5. Increased mucous secretion in response to alpha adrenergic and cholinergic stimulation, while sodium and water fluxes into tracheobronchial secretions in response to beta-adrenergic stimulation would be reduced.
6. The beta adrenergically mediated eosinopenia would be reduced and replaced by eosinophilia.

All these theoretically predictable manifestations do in fact exist, and represent the cardinal features of atopic disease. Similarly, they all point to the most critical of the malfunctioning effector system that is to the adenylate cyclase-coupled beta-adrenergic receptor and the associated cyclic nucleotide complex. It follows, therefore, that the fundamental abnormality common to all atopic persons may lie in an inherited or acquired lesion that causes defective functioning of this intracellular messenger system.

These reduced responses to catecholamines would reflect alterations to any of a number of sites, including 1) changes in the affinity of catecholamines and their receptor sites; 2) decreases in the number or reactivities of beta receptors; 3) "interconversion" of adrenergic receptors from beta to alpha; 4) alterations in the efficiency of coupling of activated receptors to the catalytic units of adenylate cyclase; and 5) reductions in the concentrations of adenylate cyclase. Alternatively, the postulated lesion may occur at a point beyond the cAMP generation step in the biological sequence leading to the adrenergic end response; in a cAMP related pathway; in a complementary interacting or modulating system such as that provided by acetylcholine, histamine, the prostaglandins, leukotrienes, the interleukins, and a large group of lymphokines, monokines, and cytokines; or in an intracellular messenger system with counter regulatory potential, such as that associated with cyclic GMP. The currently available evidence seems to favor the possibility that there are inherited and/ or acquired multiple abnormalities in the receptor – adenylate cyclase-cyclic AMP system of essentially all effector cells that are critical in the organization of immune reactivities.

Progression of the disease process from subclinical to a clinical form conceivably requires the operation of preparatory or triggering factor. The preparatory factor involves the postulated abnormality, and it may be familial (presumably hereditary) or acquired in nature; however, in either case, it must set the stage for a functional imbalance. The triggering event must be appropriate to result in an increase in the rate of firing of adrenergic neurons, or in any conceivably mediator constellations suitable to make the latent abnormality clinically manifest. However, the preparatory and triggering factors need not be separate or unrelated entities. Infection (probably viral), for example, could serve in both capacities.

With the exception of non-nucleated erythrocytes, the adenylate cyclase system has been found in all animal cells examined to date. Its ubiquitous character suggests, that the ultimate clinical manifestation of the fundamentally same atopic abnormality will be determined by the type of cell primarily involved, that is, by effector cell system that primarily harbors the postulated abnormality (cells of bronchial tissue versus those of nasal mucosa and skin and the circulating cells of blood).

For the extensive analysis of the experimental evidence supporting the validity of the beta-adrenergic theory of atopic disorders, and its updated formulation, the reader is referred to major reviews [2,3].

10. DEVELOPMENTAL MECHANISMS OF BETA ADRENERGIC SUBSENSITIVITY IN RESPIRATORY AND CUTANEOUS ATOPY

With respect to the apparent central feature of the atopic abnormality, that is the beta-adrenergic subsensitivity of the effector cells that participate in the cellular organization of the atopic response, the question could be raised as to how such an abnormality could develop. At present, at least three major developmental mechanisms can be envisaged. The abnormality may be 1) acquired by functional receptor regulatory shifts caused by hormonal changes, infection (viral, bacterial, etc) allergic tissue injury or other event; 2) genetically determined; or 3) caused by autoimmune disease. In case of a given atopic disorder, one two or all three of these effector mechanisms may be operative. Because of the orientation of this chapter only the role of viral infection, the allergic tissue injury, and auto-immunity due to anti-receptor antibodies will be discussed below.

11. VIRAL INFECTIONS AS A DEVELOPMENTAL MECHANISM OF BETA ADRENERGIC SUBSENSITIVITY IN BRONCHIAL ASTHMA

Upper respiratory tract infection has frequently been shown to precipitate or exacerbate the asthmatic condition and to produce or increase airway hyperreactivity to bronchospastic agents [4]. In an earlier era when whooping cough was common, *Bordetella Pertussis* infection was considered a frequent cause of asthma or recurrent bronchospasm. Even today, there is evidence of that *Hemophilus influenzae* infection is present in the deeper respiratory tract of asthmatic patients [5]. Since this bacterium was shown to produce in animal experiments [6–8] beta adrenergic impairment and/or an increased cyclic GMP level, the relationship between H. influenzae infection and the pharmacologic abnormality in asthma may be an authentic one.

In the meantime, in contrast to bacterial pathogens, viral respiratory infection was shown to have a more significant role in the pathogenesis of asthma. During the Asian Pandemic in the late 1950s severe exacerbations of bronchial asthma were found to be among the more frequent complications of this infection [9]. Since then numerous reports have appeared describing an important relationship between asthma and viral respiratory infection. Recent refinements in epidemiologic methods, microbiologic isolation techniques, and pulmonary function testing have provided new opportunities to characterize the relationship more precisely [10]

A review of the available information indicates that: 1) experiments in animal models [11] and observations in children [12] suggest that the expression of atopy occurs during a period termed *"allergic breakthrough"* which may follow viral infections; 2) a history of childhood viral res-

iratory illness is a risk factor for the development of chronic obstructive airway syndromes in ater life; 3) if such infection lead to obstructive airway disease, the resultant manifestation is kely to be a *"wheezy"* or asthmatic type of obstructive airway disease; 4) viral as opposed to acterial respiratory pathogens commonly herald the onset of wheezing in childhood and pre-ispose to the development of atopy, although bronchial pharmacologic hyperreactivity after iral illness may also proceed independent of immunologic mechanisms in bronchospasm; and inally 5) no matter what the ultimate effect of respiratory infection in infancy on the subsequent evelopment of asthma may be, there is little doubt that respiratory viruses commonly induce xacerbations of bronchospasm in the older child, and adults with known asthma.

The significance of one or another respiratory virus in causing asthma or its exacerbations ppears to depend on the age of the patient. Thus, in preschool age (0–4 years) the predominant gent is respiratory syncytial virus followed by parainfluenza types 1–3, influenza, rhinovirus nd corona virus. In the school age (5–16 years), rhinovirus leads the list followed in descend-ıg order of incidence by influenza, parainfluenza types 1–3, and respiratory syncytial virus. In dults, the order of relative significance changes again with the dominance of the influenza virus ollowed by rhinovirus and respiratory syncytial virus [4,10,12].

Another dimension of viral influences involves the problem of bronchial hyperactivity or labil-:y in asthma. It has been recognized for some time that normal subjects exhibit relatively short ved bronchial hyperirritability to inhaled histamine when they have a viral respiratory infec-.on [13] and as stated above asthma may worsen during and after viral respiratory infection. In ome of these situations the documented release in airway resistance could be partially or fully locked by atropine aerosol prompting the hypothesis that damage to the epithelial surface of ıe upper airways by viral infection exposes and thereby sensitizes the rapidly adapting sensory ritant receptors in the upper airways to various inhaled irritants, causing reflex parasympathetic agal bronchoconstriction [14].

There are, however, several considerations that discount the significance of a parasympatheti-ally oriented interpretation of virus induced asthmogenecity:

) Not all viruses can be implicated in this phenomenon. For instance, adenoviruses herpes virus hominis, influenza Type B virus, and enteroviruses do not show a relationship to episodes of asthma [15,16]. Studies of rhinovirus suggest that only a few rhinovirus subtypes are asso-ciated with asthmogenicity. This is a finding that is difficult to reconcile with the damaged epithelium hypothesis (assuming equivalence of infection) and raises the question of other possible mechanisms related to the biochemical properties of the virus [17,18].

) Conversely, influenza Type A virus that is clearly associated with increased asthma [16] affects lung function largely through an effect on small ways [4] whereas the aforementioned rapidly adapting sensory irritant receptors are primarily distributed in the larger upper air-ways [19].

) The hypothesis of a cholinergic hyperactivity as a consequence of epithelial damage presup-poses the de facto presence of an active viral infection, which is the cause of the respiratory inflammation, leading to the disruption of the airway epithelial barrier and activating of the subepithelial rapidly adapting sensory irritant receptors. Indeed, the characteristic histologic finding in viral respiratory infection is epithelial destruction. Welliver et al. [20] has shown that IgE was bound to exfoliated nasopharyngeal epithelial cells in most patients during the acute phase of infection with respiratory syncytial virus. They also found that a continued presence of cell bound IgE was more common in patients with bronchiolitis or asthma than in those with mild upper respiratory tract infection. In this regard, it has been established in avian species that experimentally induced viral laryngotracheitis results in disruption of

airway epithelium, with resultant increased permeation of horseradish peroxidase [21] and possibly increased uptake of inhaled antigens. Furthermore, Ida and associates [22] have demonstrated that interferon elaborated during viral infections from leukocytes harvested from patients with ragweed allergy may induce histamine release suggesting that atopic patients may experience bronchial hyperreactivity, if specific antigen exposure occurs at the time of viral infection.

Under these circumstances, it is important to mention that evidence is available that actual respiratory infection with influenza Type A virus is not a necessary condition for the development of increased airway irritability in patients with asthma. Thus, administration of killed influenza virus vaccine to asthmatic patients caused a significant increase in bronchial sensitivity to methacholine aerosol, reaching a maximum after one day and persisting for three days [23]. Normal subjects did not develop the heightened response to methacholine, and no evidence of allergy to the vaccine was detected. These investigators suggested that the effect might be explained by an endotoxin-like action of influenza vaccine. Indeed, endotoxin sensitization of human bronchial smooth muscle to alpha-adrenergic agonists has been reported. Phenylephrine-induced contractions were enhanced two to ten times in normal lung and 1000 times in lungs from a patient with chronic bronchitis. Endotoxin also caused a decrease in cyclic AMP of the tissue [24]. These observations are complemented by recent findings obtained through vaccination with a purified LPS preparation from E. coli that resulted in a decreased number of beta-adrenergic receptors in guinea pig lung [25].

) There are other observations calling into question the requirement of an active viral infection in the production of bronchial hyperactivity as mediated by cholinergically activated irritant receptors. Thus, pulmonary function abnormalities in adults with viral respiratory illness are generally more pronounced seven to ten days after the onset of symptoms, a time when the clinical manifestations and manifestations of viral inflammation are waning [26]. Also, the abnormalities of pulmonary function are generally prolonged well beyond what we now recognize as the period of viral shedding. Furthermore, administration of the antiviral agent, amantadine hydrochloride, although clinically effective, has no effect on the magnitude or duration of airway hyperactivity [27]

) In one longitudinal study, Minor et al. [16] found that simple colonization of the respiratory tract by virus was not sufficient to provoke asthma: such attacks occurred only when the infection produced symptoms of fever, malaise, cough or coryza. The dominant role of fever in these episodes immediately suggests the profound involvement of adrenergic effector mechanisms.

Additional support for the important effect of viral infections on adrenergic mechanisms in asthmatic patients came from the extensive studies of Busse and his associates [18]. In their experiments human granulocytes served as a convenient *in vitro* model for the systematic study of virus incubation on the pharmacologic agonist response. At first, it was described [18] that an impairment of the inhibitory action of a beta adrenergic agonist (isoproterenol), normally observed on lysosomal enzyme release, occurred in granulocytes taken from asthmatic patients (lysosomal enzymes are known to play a major role in bronchial immunologic inflammation) [28]. The beta adrenergic impairment of lysosomal enzyme release was significantly greater if the cells were obtained during upper respiratory infection. Following these observations, Busse and colleagues have consistently reported virus-induced impairment of several neutrophil mechanisms, which normally mediate inhibition of enzyme release. Impairment occurred after incubation in vitro with live influenza virus [29] and with live rhinovirus 16 (RV 16) [30], a finding also observed following infection of normal sub-

jects with RV 16 [31]. Both studies reported an impairment of the normal functioning of the beta adrenergic, histamine H_2 and PGE receptors, all responsible for inhibition of lysosomal enzyme release through stimulation of adenylate cyclase, resulting in cyclic AMP formation [32]. Interference with granulocyte beta-adrenergic receptor activity by influenza virus has subsequently been confirmed by Lee [33] and extended to include lymphocytes, resulting in decreased inhibition of E-Rosette formation to beta-adrenergic stimulation by isoproterenol. Another important study by Buckner et. al. [17] showed that parainfluenza 3-virus infection in vivo causes a selective blockade of the beta-adrenergic inhibition of antigen induced contraction of isolated airway smooth muscle. These abnormalities moreover are not limited to those with known atopy but may also be demonstrated in cell systems from normal subjects. Viral infections therefore, may have important inhibitory effects on beta-adrenergic responsiveness in the course of bronchoconstriction. This area has recently been extensively reviewed by Norris and Eyre [34].

Up to this point an analysis of the evidence against a parasympatheticlly (cholinergically) oriented virus induced asthmogenecity included arguments based on information obtained from the current state of our understanding of some aspects of virology, immunology, immunologic inflammation, and the cyclic nucleotide system. In the discussion below, these arguments will be extended to include some basic principles of neurophysiology and neuropharmacology, which also contradict the basic validity of the hypothesis of Nadel and his associates [14].

For the purpose of establishing an appropriate framework for this discussion, the basic tenets for this hypothesis will be restated as follows. In the past two decades, Nadel, Boushey, Holtzman, and their associates have accumulated evidence indicating that stimulation of rapidly adapting epithelial nerve receptors of the airways by mechanical, chemical and pharmacologic stimuli, reflexly increases the output of acetylcholine by the vagus nerves, causing a reflex bronchoconstriction. In particular it was shown that, although histamine is capable of constricting airway smooth muscle directly, most of its bronchoconstrictor effect *in vivo* is indirect, and due to this reflex mechanism. This is accomplished both by direct stimulation of these epithelial receptors, and also by decreasing their firing threshold to other introduced stimuli. Thus, when histamine is injected into dog bronchial arteries, most of the airway constriction can be blocked by atropine. In otherwise healthy subjects, viral upper respiratory tract infections, through damage to the bronchial epithelium cause transient bronchial hyperactivity to inhaled histamine and citric acid, a phenomenon that is also abolished by anticholinergic drugs. On the basis of this and similar observations as well as the fact that bronchial hyperactivity is associated with a decrease in cough threshold, these workers suggested that airway epithelial damage with sensitization of airway nerve endings causes exaggerated cough and bronchomotor responses. With this background, Nadel, Boushey, Holtzman, and their associates, further postulated that bronchial asthma is a constellation involving two ingredients: release of pharmacologic mediators, and sensitization of airway epithelial nerve receptors providing a positive feedback system for increasing bronchomotor tone. This mechanism in fact probably contributes to the bronchial obstructive process in asthma. The altered pharmacologic reactivity in atopy, however, is not restricted to airway epithelial effectors, but it is a universal atopic trait. In fact, as explained earlier, the altered pharmacologic reactivity is the uniformly present, single atopic characteristic, which by its very nature must be explained by any theory attempting to elucidate the constitutional basis of atopy [3,35, 36]. For the reasons below, cholinergic overactivity cannot serve in this capacity. Using spontaneously breathing, unanesthetized guinea pigs, it has been found that the vagal reflex component in histamine bronchoconstriction is small and probably a consequence rather than

a cause of the constriction. In histamine-sensitive and histamine-insensitive strains of guinea pigs it has been demonstrated that the ease of *in vivo* histamine-induced reduction in lung compliance in the guinea pig is inversely related to its *in vitro* tracheal sensitivity to isoproterenol, revealing the primary homeostatic importance of the tracheobronchial beta- adrenergic receptors rather than that of cholinergic control, in determining the sensitivity of this effector tissue to histamine [37–39]. In harmony with these findings are the extensive studies carried out in humans in the past 20 years [40–49]. The most recent findings by O'Byrne et al. [50] further support the conclusions of these long series of observations indicating not only that blockade of the muscarinic cholinergic receptors has only a small effect on the response to inhaled histamine but also the observations that such a blockade elicits only a minor degree of protection against the response to inhaled allergen [46], exercise [44] and inhalation of cold air [48] in subjects with asthma. Taken together, these experiences indicate that the bronchial effect of histamine is exerted not by reflex bronchoconstriction but through stimulation of H_1 receptors on airway smooth muscle. Therefore, hyper-responsiveness to histamine in asthma is not primarily caused by a defect in the parasympathetic nervous supply to the airway.

Furthermore, no reproducible evidence of elevated levels of acetylcholine in tissues or body fluids of atopic individuals is available. This, in fact, is not surprising when the issue of cholinergic overactivity is examined in the broader biologic context of the general nature of cholinergic versus adrenergic control. Thus, the sympathetic system is distributed to effectors throughout the body, whereas the parasympathetic distribution is much more limited. For instance, sympathetic postganglionic fibers also innervate smooth muscles and glands of somatic (non visceral) regions; no comparable distribution has been established for the parasympathetic division. Moreover, the sympathetic fibers ramify to a much greater extent, and their preganglionic terminals make contact with a large number of postganglionic neurons. In general, the ratio of preganglionic to postganglionic axons may be about 1:20 or more. In addition, there is an overlapping of synaptic innervation so that one ganglion cell is supplied by several pre- ganglionic fibers. By contrast, the parasympathetics are more discrete in their action, i.e., there is a closer to a 1:1 relation between pre- and postganglionic neurons [51]. Also the parasympathetic nervous system has no reinforcing mechanism comparable to that of the adrenal medulla for the sympathetic division.

Usually, when any part of the sympathetic nervous system is stimulated, the entire system, or at least major portions of it, is stimulated at the same time, a phenomenon called *mass discharge*. Norepinephrine and epinephrine, therefore, are almost always released by the adrenal medulla at the same time that the different tissues are being stimulated directly by the sympathetic nerves. The two means of stimulation support each other and either can actually substitute for the other. Without any stimulation, however, the normal resting rate of secretion by the adrenal medulla is sufficient to maintain blood pressure almost to normal even if all direct sympathetic pathways to the cardiovascular system are removed. Another important value of the adrenal medulla is the capability of catecholamines to stimulate structures of the body that are not innervated by sympathetic fibers. In contrast, the characteristics of parasympathetic reflexes are discrete. For instance, they usually act only on the heart to increase or decrease its activity, or frequently cause secretion only in the mouth or, in other instances, secretion only by the stomach glands.

Acetylcholine (ACh), i.e., the cholinergic transmitter released by parasympathetic fibers, is almost instantaneously destroyed in the junctional clefts by an unusual enzyme, acetylcholinesterase (true cholinesterase, AChE). The principal evidence for this is the decay time of the end plate current, which is more rapid than diffusion of ACh out of a synaptic cleft would allow. Also, the most recent preparation of AChE hydrolyzed 960 nmoles ACh per mg of protein per

hour, thus placing it among the enzymes having the highest turnover number that is known [51]. This powerful destructive capacity is reinforced by a battery of butyryl cholinesterases ("pseudo" or nonspecific cholinesterases), which destroy most of whatever acetylcholine may have escaped into the blood stream. Thus, it is doubtful whether acetylcholine can reach non-innervated cells or is present in the extracellular space in regulatory concentrations for cells with immunologic significance such as the antigen-sensitive lymphocytes. There is no comparable system of rapid destruction for the catecholamines, a fact that accounts in part for the widespread nature of sympathetic action.

Another way to determine whether we are dealing with a primary cholinergic overactivity in atopy is to examine whether there is any evidence for an enhanced guanylate cyclase activity in cells obtained from patients with atopic disease. This is all the more necessary, since as mentioned earlier, cholinergic and alpha-adrenergic agents activate guanylate cyclase, and markedly reduced adenylate cyclase-cyclic AMP responses to beta-adrenergic stimulation have been shown to be present in atopic individuals.

Under these circumstances, it is highly significant that the available evidence shows not an enhanced but a reduced cholinergic responsiveness in lymphocytes of atopic individuals. Thus, it was found that in normal subjects alpha-adrenergic stimulations with norepinephrine plus propranolol, and cholinergic stimulation with acetylcholine evoked significant increases in cyclic GMP formation. In contrast, the lymphocytic guanylate cyclase activity did not show a significant response to the same agents in patients with acute asthma, but the normal guanylate cyclase responsiveness was found to be partially restored in patients in remission [52]. Similarly, Lang, Goel, and Greico[53], in their study on adrenergic and cholinergic responses of peripheral lymphocytes in the *"active"* E rosette assay, demonstrated not only a subsensitivity of T lymphocytes to beta adrenergic but also to cholinergic stimulation in patients with bronchial asthma. In the same experiments, phenylephrine, an alpha-adrenergic agonist, showed no difference between the normal and asthmatic groups in enhancing the "active" E rosette formation. A subsensitive beta adrenergic and cholinergic system with a normal alpha adrenergic effector system may produce a state of relatively enhanced alpha adrenergic activity, a circumstance which may explain some of the findings showing that by giving alpha receptor blockers one can restore beta adrenergic responsiveness toward normal in lymphocytes of asthmatics [54,55]. There are additionally at least three major arguments against cholinergic overactivity as the primary mechanism of atopy. First, neither pulmonary sympathectomy nor pulmonary vagotomy produces any lasting improvement in bronchial asthma. Second, as discussed in detail elsewhere [3,35,36] it is never the excessive presence of a neurohumor, but if anything, it is its prolonged lack that is likely to result in the development of chronic effector hypersensitivities. Consequently, it is inconceivable that cholinergic overactivity could produce a hypersensitivity to acetylcholine or similar mediators of immediate hypersensitivities. On the contrary, cholinergic overactivity would be expected to lead to desensitization of the cholinergic receptors, as has been extensively demonstrated in numerous preparations such as the skeletal muscles of the frog, the hearts of vertebrates and invertebrates, the Renshaw cells, the neurons of mollusks, etc. [56]. This is in harmony with more recent findings obtained in non-obstructed, non-reversibly obstructed, and reversibly obstructed (asthma) patients. Using H^3-quinuclidinyl benzilate, a stereospecific radioligand for muscarinic cholinergic receptors a significant reduction in receptor density was found in the lung preparations of asthmatics, and no difference in the numbers of such receptors in lung specimens derived from the non-reversibly obstructed and non-obstructed groups as shown by Szentivanyi et al.[57] . An important question of course is how can one possibly find a reduction in the number of muscarinic cholinergic receptors in lung membranes derived from patients

with reversible obstruction (asthma) in the simultaneous presence of an exquisite bronchial hyperreactivity to cholinergic agents? At the time of this writing, we can only offer two possible interpretations. One is that the bronchial hyperreactivity to cholinergic agents in asthma is not mediated through cholinergic mechanisms, but is basically due to the beta adrenergic abnormality, which is also responsible for the atopic feature of the disease. The second possibility is that the reduction in muscarinic receptor densities is caused by a heightened vagus activity resulting in a cholinergic "downturn" and ultimately producing a pharmacological "denervation supersensitivity" to cholinergic agents [51,58]. Whether one or the other, or both of these interpretations will prove to be correct, it is evident that they represent important evidence against the validity of Nadel's [14] reflex hypothesis of the virally induced mechanisms of bronchoconstriction in asthma. Finally, if the atopic state were to be due to cholinergic overactivity produced by viruses through the postulated reflex mechanisms, then anticholinergic agents should have a far more demonstrable therapeutic effect than what we are able to observe in asthma [40–42,44] let the other atopic conditions were they are useless.

12. VIRAL INFECTION AS A DEVELOPMENTAL MECHANISM OF BETA-ADRENERGIC SUBSENSITIVITY IN ATOPIC DERMATITIS

The most typical viral infection that affects children with atopic dermatitis is Kaposi's herpetic eruption. It is caused by herpes simplex, type 1 or 2, and also the virus coxsackie A16 can mimic perfectly the eruption caused by a herpetic virus. Other viruses associated with this disease include herpes zoster, vaccinia, warts, and molluscum contagiosum. While it has long been known that recurrent viral cutaneous infections are more prevalent in atopic dermatitis, there is now growing evidence for recurrent cold sores and upper respiratory infections in this condition. Serological studies have also revealed that atopic dermatitis patients display significantly higher serum levels of antibodies against Epstein Barr virus (EBV) than their non-atopic controls. It appears therefore, that the increased susceptibility to viral infections is not restricted to dermatotropic viruses but rather reflects an abnormal host response to viral infections in general [59, 60].

Host defense against most viral infections is dependent to a large extent on cell-mediated immune mechanisms, and there is abundant clinical and experimental evidence of defective cell-mediated immunity in atopic dermatitis. In early studies, a reduction in the number of T cells was found which correlated with the severity of the disease, and these findings were later complemented by the demonstration of a defective functioning of these cells. Soon it was also shown that the T cell defect is particularly evident in suppressor/cytotoxic T cell subsets [61–65].

Defective cytotoxic T cells and also the association of abnormally functioning macrophages [66] and natural killer cells [67], appear to have an important role in the impaired host defense against viral infections in atopic dermatitis. Since these cell types produce, or are capable of producing interferon, a deficient production of this agent may at least be partly responsible for the increased susceptibility to viral infections in atopic dermatitis. A reduced production of interferon alpha in children with atopic dermatitis [68] as well as of interferon-gamma in atopic patients with food allergy has recently been demonstrated [60].

Central to the immunologic and other abnormalities (discussed later) is the T cell defect, which to many workers in this field appears to be a primary, inherited feature of atopic disease. In the context of the T cell, therefore, it is important to focus our interest on the gene products, primarily enzymes that affect T cell maturation or function in atopic dermatitis. For the first

time in 1982, it has been reported that the activity of lymphocytic cyclic AMP-phosphodieste-rase (that is the enzyme that destroys cyclic AMP) is increased in atopic dermatitis as well as allergic respiratory disease of adults [69], and that this increased activity correlated closely with histamine release from basophils [70]. When the same enzymatic activity together with histamine release was investigated in the newborn using umbilical cord blood, the significant elevation of phosphodiesterase activity was reconfirmed in newborns with a positive atopic history in first-degree relatives, compared to newborns with a negative history. In contrast to adults, however, there was no correlation between phosphodiesterase activity and histamine release [71]. Elevation of cyclic AMP phosphodiesterase activity in cord blood leukocytes before the development of clinical manifestations of atopy strongly suggests that increased cyclic AMP phosphodiesterase activity plays a primary role in the pathogenesis of atopic disease. The lack of correlation between phosphodiesterase activity and histamine release in neonates further suggests that elevated cyclic AMP phosphodiesterase activity is a primary, genetically linked defect rather than secondary to *in vivo* desensitization by inflammatory mediators such as histamine and prostaglandin E_1 [72].

These considerations complete the full circle of the core argument of this chapter and guide us back to the primary nature of the constitutional basis of respiratory and cutaneous atopic disease. Following the publication of the original beta-adrenergic theory by Szentivanyi, [1], a series of experiments have been carried out to examine the applicability of this theory to atopic dermatitis. Studies of peripheral blood leukocytes and lymphocytes in atopic dermatitis have frequently demonstrated impaired beta adrenergic reactivity as revealed by a loss of regulatory effects on lysosomal enzyme secretion [73,74], by reduced formation of cyclic AMP to beta adrenergic stimulation [74–76], by decreased affinity of binding for radio-labeled beta-adrenoceptor ago-nists [77] and by a shift in the numbers of beta adrenergic receptors to alpha adrenergic receptors resulting in an increased ratio of alpha to beta binding sites [4,78]. More recently, Hannifin has made an extensive effort with his group to determine the lymphocyte and monocyte localization of altered adrenergic receptors, cyclic AMP responses, and cyclic AMP phosphodiesterase in atopic dermatitis [79–84].

In these experiments, the numbers and affinities of beta-adrenergic surface receptors on mononuclear leukocyte subpopulations were measured by the binding of propranolol-displace-able ^{3}H-dihydroalprenolol to cell surfaces. Unfractionated atopic mononuclear leukocytes showed reduced numbers of beta adrenergic receptors per cell together with the absence of a normal, lower affinity subpopulation of high affinity beta receptors. This resulted in a linear Scatchard plot of beta adrenergic binding to mononuclear-leukocytes from atopic patients, instead of the biphasic plot seen in normal control cells. These alterations of surface receptors for cyclic AMP-elevating ligands were localized to T cells and monocytes of patients with atopic dermatitis, whereas atopic B-cell receptor numbers and affinities were identical to those of normal B-cells [79,80]. Of the various subpopulations of T-cells, a lymphocyte subset which is activatable by self Ia-antigen (MHC-II) bearing presenting monocytic cells, has been identified as radiosensitive (functionally dependent upon a proliferative step) OKT4$^+$, T29$^+$ helper/inducer T cell [85–87]. A primary abnormality in the numbers and/or in the intracellular regulation of the cyclic AMP system of the radiosensitive, T29$^+$, helper/inducer T-cells generated by the interaction with autologous Ia antigen presenting macrophages may explain many of the characteristic features of immune dysfunction in atopic dermatitis [81].

For instance, soluble mitogen stimulated proliferation is critically dependent on successful macrophage/T-cell interaction, and can be reduced in patients with atopic dermatitis [88,89]. Development of the pool of blood PWM-recruitable B-cells for in vitro antibody production

requires induction by a radiosensitive T-cell inducer [85,90,91], and indeed, B-cells from patients with atopic dermatitis demonstrate decreased mitogen- stimulated antibody secretion, even when corrected for number or when normal T-cells are used to provide helper function [92]. T-cells associated with suppressor and cytotoxic functions, such as T-cells with FcIgG receptors, OKT8 cells and histamine H_2–receptor-bearing T-cells often show significantly reduced values in patients with atopic dermatitis [87,92–94], which is in accord with findings indicating that the development of mature suppressor and cytotoxic effector T cells requires induction by the aforementioned radiosensitive T-helper cells [95–97]. It may be added that the development of cytoxic T lymphocytes is known to be dependent upon Ia^+ monocyte stimulation of helper T-cell factors such as interleukin-2 [95], and a decrease in the production of interleukin 2 as well as interferon by these abnormal helper/inducer T-cells, or their altered ability to respond to these signals may explain the reduced natural killer activity in atopic dermatitis [67]. Thus, the aforementioned multiple abnormalities of the cyclic AMP system in the helper/inducer T-cells in question may account for the immune dysfunction in atopic dermatitis. Alternatively, each of the immune abnormalities listed could be due to altered immune signal processing by distal effector cells with their own malfunctioning intracellular cyclic AMP systems as will be further pointed out below.

In closing the discussion of viral infection as one of the major developmental mechanisms of beta-adrenergic subsensitivity in cutaneous atopy, we need to briefly revisit the issue of whether the atopic diathesis increases the susceptibility to viral infections, or the viruses themselves may produce the atopic disposition. As stated above, the demonstration of higher serum levels of antibodies against EBV in atopic dermatitis were interpreted in support of the assumption that defective immune mechanisms rather than cutaneous alterations predispose for increased susceptibility to viral infections. Although the findings of raised EBV antibody titers in atopic dermatitis may in fact reflect on abnormal host response to the virus, it cannot be excluded that the cause and effect relationship is the reverse, so that EBV may play a causative role for the development of atopic dermatitis. Thus, EBV is a B- cell mitogen, which may stimulate IgE antibody formation, and infectious mononucleosis, which is caused by EBV, is associated with raised serum levels of IgE [98]. The report of a case of atopic dermatitis developing soon after an episode of infectious mononucleosis suggests that EBV may in fact occasionally precipitate atopic disease [99]. Essentially the same causative role of viral agents has been described for respiratory atopy above.

13.   THE ALLERGIC TISSUE INJURY AS A DEVELOPMENTAL MECHANISM OF BETA ADRENERGIC SUBSENSITIVITY

The allergic tissue injury is another major developmental mechanism of beta-adrenergic subsensitivity. Advances in knowledge of the immune response and immune reactivity achieved since the early 1960's have been accompanied by a more complete understanding of the different pathways of immune tissue injury. Based on this new understanding, the various types of immunopathologic processes have been subdivided by the classification by Coombs and Cell (1962) into the following four basic types:
Type I: Immediate-hypersensitivities
Type II: Cytotoxic tissue injury
Type III: Immune-complex tissue injury
Type IV: Cell-mediated immune tissue injuries

This classification is oversimplified because of the complex interrelationships that exist between the several events that constitute an inflammatory response. Nevertheless, this view represents the closest approximation of the various basic patterns of immune tissue injury, and the classification does not depend on the host species or on the method of antigen exposure. Another valuable feature of the classification is its integrated emphasis on the important central point that in these various patterns of immune injury the tissue damage results from the immune activation of cellular and biochemical mediator systems of the host. The combination of the immune reactants produces only minimal direct effects, but as a trigger mechanism it sets the destructive factors into play.

Because of the subject of this chapter only the general pattern of immunologic tissue injury that occurs in immediate hypersensitivities will be discussed. Furthermore, no distinction will be made between the atopic and non-atopic varieties of immediate hypersensitivities since in both cases the pattern of tissue injury follows the characteristic triphasic reaction sequence of these manifestations.

In these reactivities, following the initiation of antibody production, the cytotropic antibodies (primarily IgE) that are formed disseminate throughout the circulation to become almost selectively and uniquely attached to the cell membranes of basophils in the circulation and mast cells in the tissues. The attachment occurs through a structural area in the Fc part of the antibody molecule to a specific receptor on the basophil or mast cell membrane. Although evidence indicates that subpopulations of monocytes, macrophages, and lymphocytes also express Fc receptors for IgE antibody, of all mammalian cells only basophils and mast cells exhibit an extraordinary binding affinity for this antibody. There is a relative abundance of these IgE molecules bound along the membrane, and they are located close to each other physically. When the IgE becomes attached, the cells are said to be sensitized, and the individual is now in a sensitive state for reactivity on subsequent exposure to the antigen [100].

A second, or subsequent, exposure can occur via many routes, such as inhalation, ingestion, or injection. The antigen must move across membrane and tissue barriers in order to come to the surface of the sensitized cells. When this close encounter occurs with an antigen of sufficient size to react with the antigen-binding sites of two closely adjacent IgE molecules, it produces a "bridging' effect. In this molecular interaction, one antigen molecule combines with two antibody molecules to form a bridge. This bridging brings together two IgE receptor molecules, which results in coformational changes in the receptors, triggering an enzymatic cascade that causes the release of pharmacologically active effector molecules responsible for the clinical symptomatology of immediate hypersensitivities. Accounting only for those pharmacologic mediators where the cell-type has been identified, the spectrum of mediator-storing, synthesizing, or transporting cells, includes the neutrophil leucocyte [slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), enzymes, vascular permeability factors, kinin-generating substances, a complement- activating factor, histamine-releasers, and a neutrophil inhibitory factor (NIF)], basophilic leucocyte [histamine, SRS-A, ECF-A, neutrophil chemo- tactic factor (NCF) and platelet-activating factor (PAF)], the murine basophilic leucocyte (histamine, SRS-A, ECF-A, PAF, and serotonin), the eosinophilic leucocyte (histamine, PAF, and possibly SRS-A), the mast cell (histamine, SRS-A, ECF-A, NCF and PAF), the murine mast cell (histamine, SRS-A, ECF-A, PAF, NCF and serotonin), the "chromaffin-positive" mast cell (dopamine in ruminants; in other mammals possibly norepinephrine), the enterochromaffin cell (serotonin), the chromaffin cell (catecholamines), the platelet (depending on species: histamine, serotonin, catecholamines, and prostaglandins), the neurosecretory cell (histamine, serotonin, catecholamines, acetylcholine, and prostaglandins), and the nerve cell

potentially all amine—mediators as well as prostaglandins and kinins) [101]. Collectively, these pharmacologically active agents produce an increase in blood flow, capillary permeability, constriction of smooth muscles, and secretion of mucous glands, that is manifestations that dominate the clinical picture of immediate hypersensitivities and the associated inflammatory responses.

4. REACTIVITIES OF THE MEDIATOR-STORING CELLS TO ANTIGENIC AND PHARMACOLOGIC INFLUENCES AND THEIR RELATIONS TO CYCLIC NUCLEOTIDES

Depending on concentrations and other experimental conditions, pharmacologically active adrenergic agents can both release as well as inhibit the release of allergic mediators. Thus, amphetamine, phenylethylamine, tyramine, and the like-substances that induce sympathomimetic activity indirectly through the endogenous release of catecholamines are capable of liberating histamine. The same can be accomplished by the exogenous administration of catecholamines and of their specific blocking agents. While all these agents elicit non-immunologic histamine release, they render sensitized mast cells incapable of responding to antigen challenge with histamine release [102–104].

Analysis of these seemingly contradictory findings suggests that 1) adrenergic agents interfere with binding or release of histamine because of their catecholamine-like intrinsic activity, and 2) they operate on a cellular system that is antigen activated and thus central to the mechanism of the allergic reaction.

The first conclusion is supported by the residual agonistic activity of the blocking agents employed, since the only common feature of these directly acting adrenergic compounds is their basic catecholamine structure. The second conclusion is based on the observation that methylxanthine also inhibit immunologic release of histamine [104]. Thus, when ragweed antigen was made to interact in vitro with IgE antibody on the surface of leukocytes from ragweed-sensitive human donors, both methylxanthines and catecholamines inhibited histamine release. The significance of these findings is seen in the fact that methylxanthines are competitive inhibitors of the specific phosphodiesterase that inactivates cyclic 3', 5'AMP; and thereby they may induce adrenergic action" by increasing the intracellular concentration of the compound. Indeed, catecholamines and methylxanthines were found to act synergistically in inhibiting histamine release, and the phosphodiesterase-inhibitory potencies of the various methylxanthines correlated well with their inhibitory effects on histamine release [3]. Of further significance is the fact that the methylxanthines and catecholamines were shown to inhibit only if added to the cells when antigen was present; they had no effect if removed from the environment of the sensitized cells before antigen exposure [104]. The adenylate cyclase system therefore must be considered as a critical regulatory system in allergic histamine release.

In addition to beta-adrenergic agents, allergic release of histamine or of other pharmacologic mediators of immediate hypersensitivity is also inhibited by prostaglandins of the E series, prostacycline, adenosine, and histamine (i.e., by substances that interact with cell membrane receptors that activate adenylate cyclase [105,106]. Inhibition of allergic mediator release by these agents is generally paralleled by an increase in the intracellular concentration of cyclic AMP in the respective cell preparations. Furthermore, since the release-inhibitory activities of these agents are blocked by their specific antagonists, it is presumed that these agents increase cyclic AMP by acting on receptors linked to adenylate cyclase. The mechanism by which cyclic

AMP blocks mediator release is not known, but current evidence suggests that cyclic AMP acts early in the release process, that it is linked to the obligatory inward flux of calcium, and that it related to microtubule function [107]. There are, however, exceptions when changes in cyclic nucleotide levels do not correlate with inhibition of immunologic mediator release [7,108]. The nature of such dissociation between cyclic AMP elevation and inhibition is unclear but may be explained if there are functionally separate intracellular cyclic AMP pools [109] and if a product of the lipoxygenase or some other pathway can block selectively a biochemical sequence linking adenylate cyclase activation to inhibition of mediator release [107]. The effect of changes in intracellular cyclic GMP levels on allergic mediator release has been less extensively studied. In lung tissue, alpha- adrenergic and cholinergic stimulation increase cyclic GMP levels [110 111], and such effects as well as extracellular cyclic GMP derivatives potentiate antigen-induced mediator release [112]. However, cyclic GMP does not enhance release from rat mast cells and has minimal or no effect on immunologic mediator release from basophils [113]. Furthermore, it is not known whether cyclic GMP-induced enhancement of pulmonary mediator release is a direct effect of alpha-adrenergic or cholinergic agents on the mast cells or whether it reflects their actions on other cell types [57]. Nevertheless, in this context it may be added that pertussis or pharmacologically established beta-adrenergic blockade has been reported to cause peritoneal mast cell degranulation in rats and mice, whereas beta-adrenergic stimulation protects these cells against propranolol induced degranulation [114]. As judged by the PCA reaction in guinea pigs, propranolol has the same enhancing effect on immunologic mediator release [115].

15. THE ALLERGIC TISSUE INJURY, BETA ADRENERGIC SUBSENSITIVITY AND BRONCHIAL ASTHMA

Recent studies in patients with extrinsic asthma [116,117] and in animal models of experimental asthma [118,119,120] raised the possibility that the allergic tissue injury itself may result in the development of some forms of beta-adrenergic subsensitivity. In the studies of deVries et al. [116], and Koeter et al. [117], patients with complaints of episodic wheezing after exposure to allergens, specific IgE and skin tests, and an increased bronchial response to histamine inhalation were included. Symptoms of these seven patients were mild and well controlled without a history of respiratory tract infections or acute asthmatic attacks two months prior to the study. No patient was on beta-adrenergic or corticosteroid therapy.

These studies were designed with the assumption that there might be a relationship between the allergic tissue injury and the adrenergic system. Therefore, the latter was studied before and after an inhalational allergen challenge. Two parameters were measured: 1) *in vivo* propranolol threshold to assess bronchial beta-adrenergic reactivities and 2) *in vitro* lymphocytic cAMP production in response to beta-agonist stimulation. The propranolol threshold changed from 1.32 percent before challenge to 0.86 percent the day after. In the same patients the maximal cAMP response of lymphocytes changed from 339 percent above basal level before the challenge to 194 percent after the challenge.

Recently, the development of beta subsensitivity of airways smooth muscle was studied in greyhound dogs in order to determine its relationship to the hyperreactivity of the same airways to aerosols of *Ascaris suum* antigen [119,120]. Using thoracic trachealis smooth muscle, it was found that the airways hyperreactivity was statistically significantly inversely correlated with 1) beta-adrenoceptor density; 2) isoproterenol stimulated cAMP production; and 3) isoproterenol stimulated relaxation. These authors concluded that the beta-adrenergic subsensitivity of airway

smooth muscle that is associated with airways hyperreactivity in this canine asthma model is due to a deficiency of beta-adrenoreceptors, since all post receptor beta-adrenergic responses that were measured (cAMP, protein kinase, relaxation) tended to be depressed in animals with airways hyperreactivity.

These studies clearly indicate that the allergic tissue injury may be one of the contributory factors in the development of beta-adrenergic sub- sensitivity in some forms of human asthma, or alternatively the sole factor in some subsets of human asthma. They may not, however, support the interpretations of deVries [116] and Koeter et al. [117] that these findings suggest that 1) in the seven asthmatics they studied the beta-adrenergic subsensitivity was due to endogenous desensitization by catecholamines released in response to the allergic tissue injury; and 2) in all forms of asthma, this same mechanism is responsible for the manifestation of beta- adrenergic subsensitivity.

Several lines of evidence argue against the general applicability of these interpretations to human asthma and other manifestations of atopy. First of all endogenous catecholamines released from neuronal and adrenal medullary catechol stores would be expected to desensitize both alpha- and beta-adrenoceptors more or less evenly. In the foregoing studies alpha-adrenoceptor concentrations or their sensitivities were not measured, but in those studies where they were, this was not the case. Thus, pulmonary homogenates of sensitized guinea pigs that had been exposed chronically to antigen aerosol showed significant increase in alpha-adrenoceptors and a decrease in beta-adrenoceptors [118] reminiscent of the reciprocal adrenoceptor changes observed in a number of other human and animal studies described in the literature [121–125]. This alpha dominance is also reflected by the demonstration that alpha-adrenergic agonists produce bronchoconstriction in asthmatic patients but not in normal subjects [126,127]. Similarly, in vitro studies show alpha-receptor mediated constriction of bronchial smooth muscle from patients with increased airways resistance but not from normal controls [24,128]. In addition, increased alpha-adrenergic receptor mediated responses in vascular and pupillary smooth muscles have been reported in asthmatics [129].

Furthermore, beta-adrenergic subsensitivity in asthma can be shown to occur in the absence of allergic symptoms or beta-adrenergic medication, and under circumstances in which prior or concurrent beta adrenergic medication can be only one contributing factor to defective beta-adrenergic function. This is also reflected by the presence of beta-adrenergic subsensitivity in atopic dermatitis in which beta-adrenergic medication is not used as a therapeutic modality. Nevertheless, endogenous release of catecholamines in response to the allergic tissue injury may contribute to the development of beta-adrenergic subsensitivity through *homologous* desensitization of the beta-adrenergic receptors. At the same time the endogenous release of other pharmacologic mediators (i.e., histamine) in response to the allergic tissue injury may contribute to the beta-adrenergic subsensitivity through *heterologous* desensitization [36]. The differences between these two mechanisms are explained below.

16.   THE ALLERGIC TISSUE INJURY, BETA ADRENERGIC SUBSENSITIVITY, AND ATOPIC DERMATITIS

Differences between homologous and heterologous desensitization resulting in beta-adrenergic subsensitivity could be most conveniently explained through the model of Delean and associates [130] originally used for the interpretation of adrenoceptor-adenylate cyclase interactions and based to a large extent on ligand binding experiments. This model envisions three principal

components of the system in the plasma membrane, i.e., the receptor (R), a nucleotide-binding regulatory protein (N), and adenylate cyclase (C). The binding of an agonist (A) to the receptor is believed to bring about a change that either promotes or stabilizes the formation of a ternary complex, ARN. The formation of the complex promotes the dislodging of a tightly bound guanosine diphosphate (GDP) molecule from N and its replacement with guanosine triphosphate (GTP), which enables N to activate C, thus stimulating the formation of cAMP. The GTP is subsequently hydrolyzed to GDP by guanosine triphosphatase (GTPase) associated with N, and this leads to inactivation of the cyclase. All three components of the system are then capable of being reactivated by renewed interactions of R with agonist molecules. The formation of the ternary complex ARN is of crucial importance to the functional coupling of the receptor to the cyclase in this hypothetical model. Antagonists occupy the receptor but do not promote or stabilize the formation of the ternary complex and thus do not activate the catalytic moiety of adenylate cyclase. Biochemical experiments indicate that the free form of the receptor (R) has a low affinity for agonists, while the complex of the receptor plus the nucleotide protein (RN) has a high affinity for agonists. Changes in receptor binding properties showing a lack of high affinity of R for agonists are thus believed to indicate that the crucial ARN complex is not formed. Not surprisingly, there is no activation of the cyclase under these circumstances. This phenomenon resulting in the inability of agonist-stimulated beta-receptors to activate adenylate cyclase is referred to as *uncoupling*. As discussed below, uncoupling is one of the mechanisms by which agonist—induced desensitization of beta-adrenergic receptors take place [131].

The loss of a tissue's responsiveness to an agonist caused by repeated exposure to the agonist has been described using a variety of terms including desensitization, tolerance, refractoriness, and tachyphylaxis. Su and colleagues [132] have divided these phenomena into two major categories, heterologous and homologous desensitization. Heterologous desensitization refers to the desensitization that occurs after exposure of cells to a biologically active agent that produces tissue refractoriness to itself and to a variety of other pharmacologically different agonists. By contrast, homologous or agonist—specific desensitization is a loss of responsiveness to only the particular agonist that induced the desensitization (or to a specific group of pharmacologically related agonists, all acting at the same tissue receptor site, e.g., the catecholamines).

The mechanisms by which desensitization is produced are complex and variable depending on the tissue. Isoproterenol-induced desensitization of turkey erythrocytes appears to fall into the category of heterologous desensitization because loss of sensitivity to fluoride ion and 5'guanylylimidodi- phosphate (Gpp(NH)p)* (a less hydrolyzable analog that can substitute for GTP) is also produced in this situation. There is no decrease in receptor number in the isoproterenol-desensitized turkey erythrocyte, but rather an apparent uncoupling of the beta-adrenergic receptor from adenylate cyclase takes place due to impairment of the ability of occupied receptors to form a stable high-affinity ARN complex [133]. Similar refractoriness can be produced by exposure of the cells to 8-bromo-adenosine 3',5'-cyclic monophosphate, a cAMP analog, suggesting that the desensitization to isoproterenol is caused by the agonist-stimulated levels of cAMP within cells. Stadel and co-workers [133] suggested that cAMP-dependent phosphorylation of the nucleotide regulatory protein (N) may be the mechanism of desensitization in this system, and thus no alteration in the receptor per se but rather uncoupling of the receptor from adenylate cyclase due to modification of the nucleotide regulatory protein takes place in this example of heterologous desensitization.

Homologous desensitization of beta-receptors has been observed in a number of different types of cells including frog erythrocytes and astrocytoma cells and is produced by agonists but is blocked by antagonists [134]. Experiments on astrocytoma cells have shown that beta-

adrenoceptor desensitization produced by isoproterenol involves at least two steps. The earliest change to occur is uncoupling of the receptor from the cyclase, followed by the second step, which involves a loss of 80 to 95 percent of the assayable beta-receptors on the cell surface [135]. More recent studies on catecholamine-desensitized frog erythrocytes have shown that the down-regulated (unavailable) beta-receptors are sequestered in cytosolic vesicles apart from the guanine regulatory protein and catalytic moiety of the adenylate cyclase which remain in the plasma membrane [136].

The sequestered receptors appear not to be rapidly degraded and, therefore, may be recycled later during recovery of the tissue from desensitization [136,137]. Human neutrophils have been found to undergo desensitization involving both an uncoupling, which is highly analogous to that demonstrated in frog erythrocytes, and also a 40 percent reduction in number of receptors [138].

Drawing on the information available at the present time, one might formulate the following view: heterologous desensitization of beta-adrenoceptors involves uncoupling due to impairment of the ability of receptors to form the high-affinity ARN complex and consequently to activate adenylate cyclase; this impairment is produced by the agonist-stimulated accumulation of cAMP within cells. By contrast, homologous regulation is a multistep process involving early uncoupling of the receptor from the cyclase followed by later internalization of the uncoupled receptors in vesicles.

With this understanding we can return to the foregoing section on the reactivities of the mediator—storing cells to antigenic and pharmacologic influences and their relations to cyclic nucleotides. As stated earlier, in addition to beta adrenergic agents, allergic release of histamine or of many, if not most of other pharmacologic mediators of immediate hypersensitivities, is also inhibited by prostaglandins of the E series, prostacycline, adenosine, and histamine (i.e., by substances that interact with cell membrane receptors that activate adenylate cyclase). Normal physiologic inhibition of allergic mediator release by these agents is kept in check by their feedback effect on their respective receptors through the mechanisms of homologous and heterologous desensitization. In atopic disease, however, where there are multiple abnormalities in the receptor-adenylate cyclase- and cyclic AMP systems, this physiologic balance between inhibition versus enhancement of mediator release would be expected to lead to an exaggerated release reaction to the allergic tissue injury.

Indeed, enhanced "releasability" of histamine from basophils and mast cells has been shown to occur in atopic dermatitis. "Releasability" is defined in this context as the capacity of mediator secreting cells to release preformed or newly synthesized mediators [139–141]. Among the pharmacologic mediators, histamine is the best-studied substance, and the best-established mechanism is the IgE-mediated release reaction. The first study to show enhanced anti-IgE induced histamine releasability from basophils was performed by Lebel et al. [142], which was confirmed by Ring and his associates [130]. During the last few years numerous, more extensive investigations have been carried out that further confirmed the *de facto* existence of altered releasability in atopic dermatitis [71,144–146]. Similarly, increased releasability of histamine was also found to occur in bronchial asthma [147,148].

In a way, in vitro IgE-secretion by peripheral lymphocytes might also be viewed as a form of *"releasability"* too. Therefore, it is important to mention that several authors have provided evidence of increased spontaneous in vitro IgE-secretion in patients with atopic dermatitis

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* 5'Guanylylimidodiphosphate is an analog of GTP that contains an imidodiphosphate rather than a pyrophosphate linkage.

[149–151]. A significant positive correlation between serum IgE and *in vitro* IgE secretion has also been demonstrated [144]. In this connection, it should be noted that although much is known about IgE regulation in rodents [150], the mechanisms involved in the regulation of IgE-synthesis in man are not well established. It is generally assumed that isotype specific suppressor and helper T-cells play an important role, but the relevant subpopulation (perhaps FcE-receptor bearing lymphocytes, [152]), is not known at present. Furthermore, the exact pathogenetic role of IgE—reactions is atopic dermatitis is still controversial [153,154].

17. AUTOIMMIUNITY AS A DEVELOPMENTAL MECHANISM OF BETA-ADRENERGIC SUBSENSITIVITY

The concept that an autoantibody interacting with a cell membrane receptor of a hormone or neurotransmitter could cause functional derangements and subsequent disease is now becoming widely accepted, and the number of diseases that may be mediated by antireceptor antibodies is rapidly growing [155,156].

The leading examples of such diseases include myasthenia gravis, involving autoantibodies directed at nicotinic acetylcholine receptors at the neuromuscular end-plates [157–159], Graves' disease involving autoantibodies to the thyrotropin receptor [160,161] and the severe insulin resistance in Type B insulin-resistant diabetes that has been ascribed to autoantibodies to the insulin receptor [162–164]. Thus, the foregoing diseases may be viewed as receptor diseases, and some subsets of asthma and other atopic diseases may ultimately be recognized as legitimate members of this group. Indeed, it has been described that autoantibodies to beta adrenoceptors can be identified in the plasma of some subjects with atopic allergy [165–167]. Although these antibodies appear to be heterogeneous, they share the ability to affect binding of ^{125}I protein A to calf lung membranes, to inhibit stereospecific beta-adrenergic radioligand binding to calf lung $beta_2$ adrenoceptors, and to precipitate solubilized calf lung beta-adrenergic receptors in an indirect immunoprecipitation assay. Furthermore, the presence of autoantibodies to $beta_2$-adrenoceptors in these subjects correlates well with a reduced $beta_2$ and an increased alpha-adrenergic responsiveness.

It may be added that from the currently available material even the three of the 19 apparently normal subjects with circulating antibodies were significantly less responsive to beta-adrenergic stimulation than the remainder of the normal controls [168].

The precise frequency and distribution of these autoantibodies in various subsets of patients with asthma and other atopic disease are currently under investigation in several American and European laboratories, as is the molecular mechanism by which they produce beta-adrenergic subsensitivities. For a general account of the molecular mechanisms that are involved in the development of autoimmunities in general, the reader is referred to an analysis by Szentivanyi and Szentivanyi [100]. In the orientation of this chapter, however, we shall only mention the role of virus infections as a developmental-mechanism of autoimmunity produced by anti- receptor antibodies specifically directed to beta adrenoceptors. Thus, virus infections can elicit autoantibody formation by two mechanisms. First, the viral antigens and autoantigens may become associated to form immunogenic units. Viral antigens stimulating host T-lymphocytes could then function as helper determinants, thereby stimulating B-lymphocyte responses to auto-antigens. Second, some viruses such as the Epstein-Barr virus (EBV) stimulate proliferation of the B-lymphocyte cell line with autoantibody production. There are two ways in which viral and host antigens can form immunogenic units. Host antigens can be incorporated in the envelopes

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of some viruses, and viral antigens can appear on the surfaces of infected host cells [100]. The viral antigens also may form complexes with and modify histocompatibility antigens or other membrane constituents such as the contractile protein, actin. The modified viral antigens could stimulate T-cell helper effect and elicit autoantibody formation [100].

In humans, infection with viruses such as influenza, measles, varicella, and herpes simplex has often resulted in autoimmune manifestations such as platelet and red cell autoantibodies. The development of cold autoagglutinins after *Mycoplasma pneumoniae* infection probably occurs by a T-cell bypass mechanism. Following infectious mononucleosis, many patients' sera often react against several autoantigens. These include autoantibodies against nuclei, lymphocytes, erythrocytes, and smooth muscle. In addition, cross-reactive heterophile antibodies may be noted following infectious mononucleosis and other infections. The autoantibody is produced by a mechanism similar to that observed in altered self-component with virus or bacteria.

There has been much speculation about the possible involvement of an oncornavirus in the pathogenesis of human systemic lupus erythematosus [169].

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