ALLERGIC ASTHMA

THE DAWN OF QUANTITATIVE UNDERSTANDING AND RATIONAL THERAPY

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OUTLINE

Anyone who would glibly set out to analyze the current status of our knowledge of allergic asthma does not understand the complexity of the existing data, is biased at the outset, or no longer has any regard for his professional reputation (1). An attempt seems will be made dispite these risks. Our perception of the molecular and pathophysiologic basis of asthma is improving very rapidly. New rational strategies for the diagnosis and management of allergic asthma are likely to emerge from these insights in the near future.

Allergic asthma can be defined as a pulmonary disorder characterized by 1.) reversible airway obstruction, 2.) association of exacerbations with specific antigen exposures, and 3.) evidence of the presence of IgE to an antigen that triggers an exacerbation of asthma (Table I). Asthma affects 4% to 7% of the adults in this country and a substantially higher percent (approximatey 12%) of children (2-28). In 1981 asthma resulted in over 5 million office visits to physicians (8). Of these asthmatics, some 50% to 80% appear to be predominantly allergic asthmatics. Approximately 2,000 people die from asthma each year in this country. Populations composed of children with asthma tend to have high prevalence of allergic asthma, populations composed of adults with emphysema and asthma have very low prevalence of allergic asthma.

TABLE I

Allergic Asthma

* Reversible airway obstruction
* Evidence of relationship of antigen exposure to asthma:
Exacerbation during exposure
Seasonal, occasional, inhalation challenge exposures
Remission when exposure ceases
* Evidence of IgE to antigen:
Wheal and flare skin tests, RAST, CRIE

While asthma was recognized as a clinical entity in the earliest of medical literature, only in recent years has the association of

asthma with some forms of asthma been proven (2-6, 26). Clinical and basic studies of allergic asthma have generated an imposing body of literature with bewildering apparent complexity. As noted on the first page of this protocol, any attempt to quickly analyze the entire subject is likely to prove ineffective. Nevertheless several recent research breakthroughs deserve detailed presentation. Most of them are in a state of rapid development, however.

The purpose of this Grand Rounds is to present a view of five important areas of recent advancement in our knowledge: specific causes of allergic asthma; leukotriene mediators of asthma; abnormalities in cAMP metabolism that dispose to allergic asthma; biphasic asthma and acquisition of airway hyper-responsiveness; and immunotherapy for asthma (Table II). Future presentations at these rounds will focus on important individual aspects of allergic asthma, hopefully in much clearer light than is possible today.

TABLE II

Areas of Emphasis

* Causes of allergic asthma
Mites, molds, animals, chemicals, pollen, food
* Leukotrienes and asthma
* cAMP and asthma
* Airway inflammation and asthma
* Immunotherapy and asthma

ANTIGENS KNOWN TO CAUSE ALLERGIC ASTHMA

While many sources of antigen have been shown to be capable of inducing human allergic asthma, some antigens have received particular attention (29-94) and can provide valuable insights (Table III)

TABLE III

Sources of Antigens That Can Cause Asthma

* Mold spores
* Dermatophagoides mites
* Animal emanations
* Food
* Pollen
* Occupational antigens

Mold Spores. Antigens derived from mold spores are common causes of inhalant allergy (29-34). When mold sensitivity is widespread in a population and the number of mold spores in the air is very high, true epidemics of allergic asthma can occur (30-32). In New Orleans, fall epidemics have completely overwhelmed Charity Hospital. The enormous diversity of spore producing organisms and the large number of potential antigens each expresses makes the task of accurate diagnosis difficult.

The development of crossed radioimmunoelectrophoresis (CRIE, 34) has been of particular value in studies of mold antigens. In this technique complex mixtures of potential antigens, such as extracts of mold spores, are subjected to electrophorsis in gels. After separation according to charge they then are electrophoresed into agar containing rabbit antibody to the crude mixture. A multitude of precipitin arcs form. Thus each of the antigens is separated and visible. Next, human serum is placed over the gel. If IgE to any of these antigens is present it will bind to the appropriate precipitin line. After washing, gels are treated with radiolabeled antibody to human IgE. After washing, an autoradiogram can be used to show which if any antigens IgE has bound. This method permits specific antigen assessment without antigen purification. CRIE has permitted rapid progress in our understanding of the antigens involved in mold spore allergy. CRIE also is being applied to standardization of materials for diagnosis and treatment of mold spore allergy.

House Dust Allergy. Perennial allergic respiratory tract disease has long been associated with "house dust" (35-52, Table IV). In recent years, the immunologically relevant constituents have been proven to arise primarily from breakdown products of common household mites of the Dermatophagoides genus. These creatures consume desquamated human skin (approximately 1.5 gm/day/person). Studies of mite allergy have shown that environmental control measures can diminish or eradicate asthma in selected patients (51,52) and that immunotherapy can be beneficial in mite induced asthma (see below).

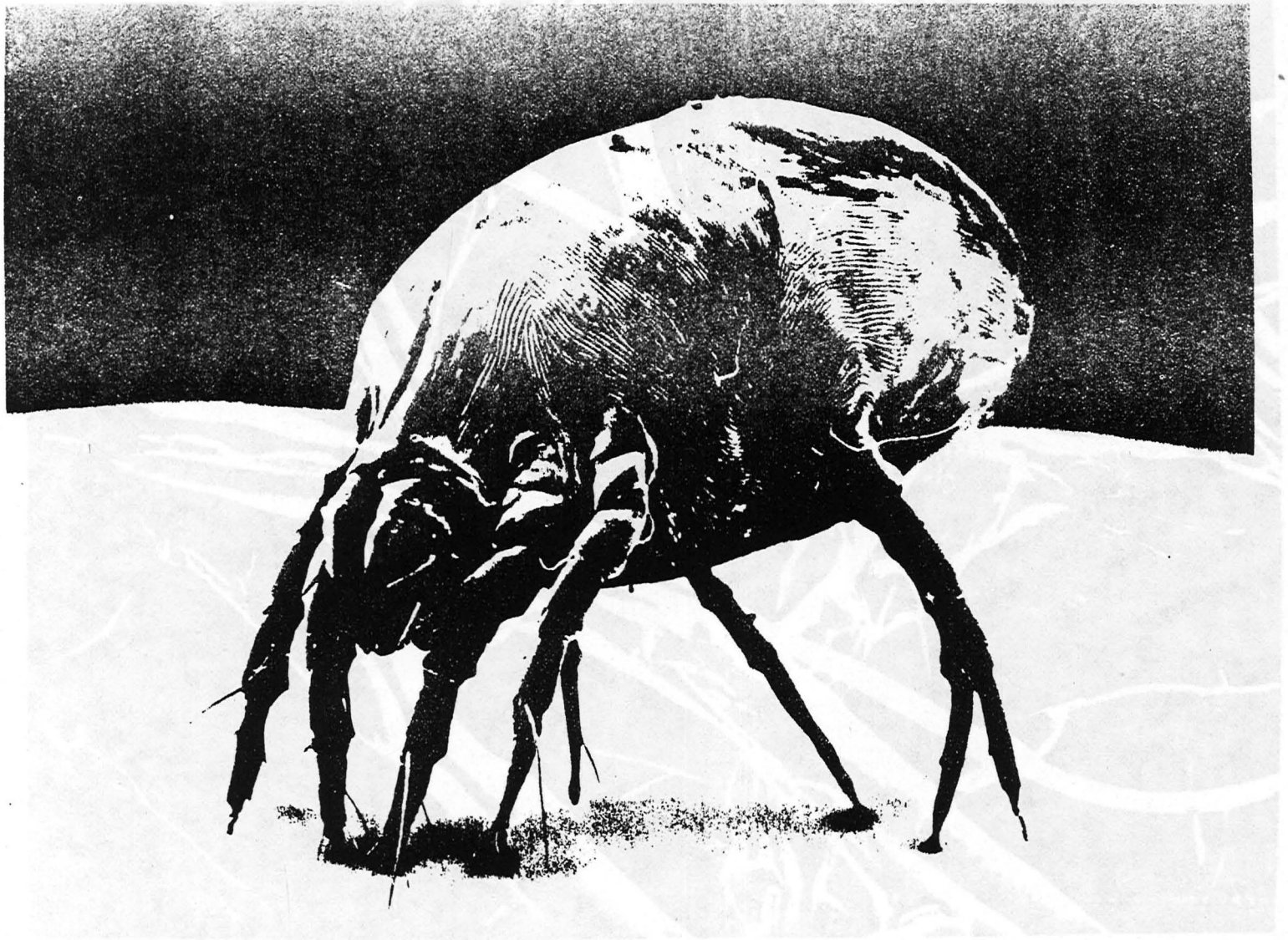
TABLE IV

House Dust Allergy

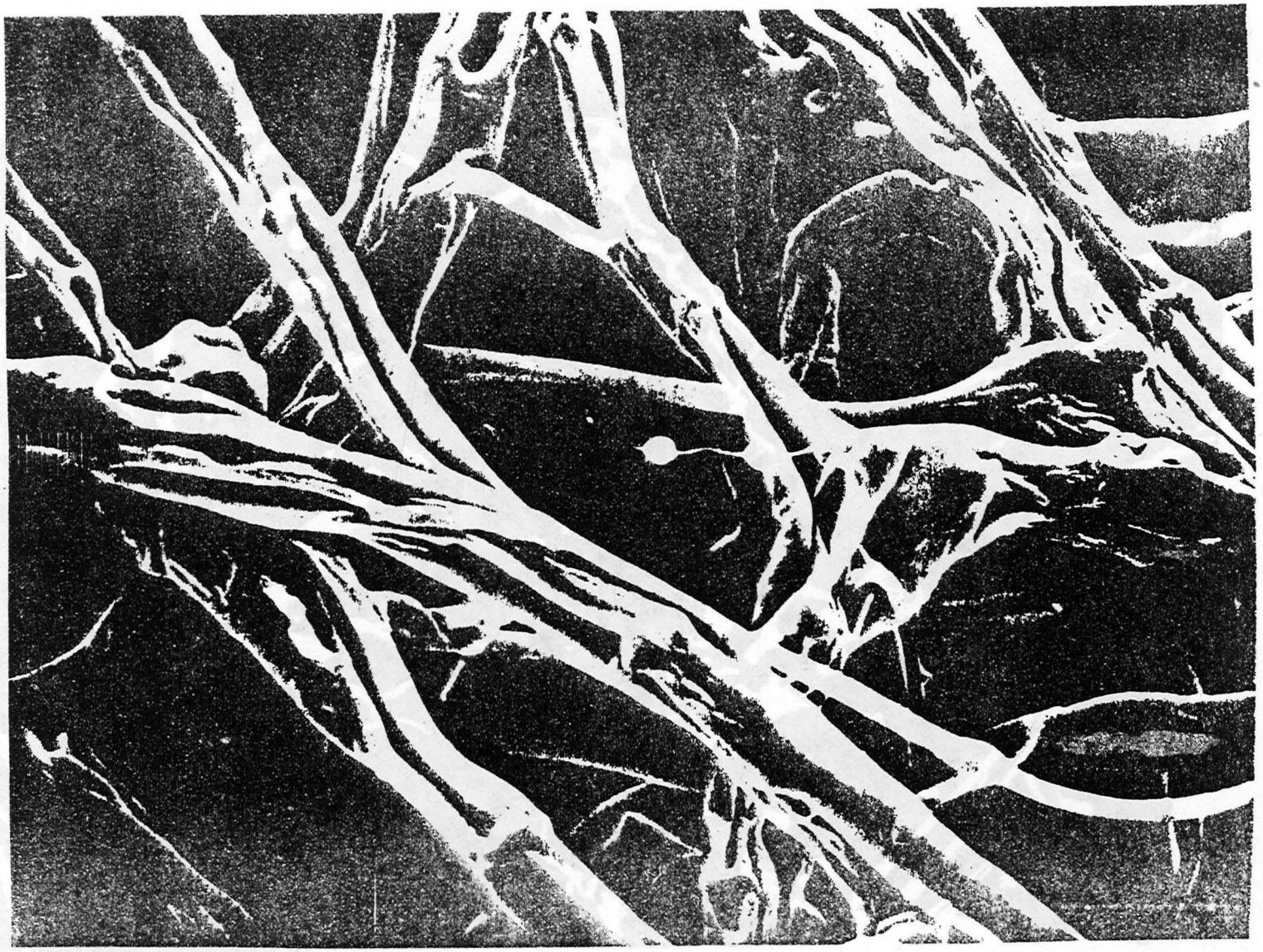
* Dermatophagoides pteronyssimus and Dermatophagoides farinae
* Mites consume desquamated epithelium
* Inhabit bedding, closets, rugs - particularly in bedrooms
* Emanations constitute the dominant antigenic material in house dust

The availability of extracts of D. pteronyssimus and D. farinae and more recently of partially purified antigens from these creatures has revolutionized our understanding of perennial allergy respiratory tract disease linked to "house dust". Better materials for diagnostic skin testing or RAST testing has permitted more accurate definition of mite allergic subjects. These newer reagents also have proven effective in specific desensitization of mite allergic patients.

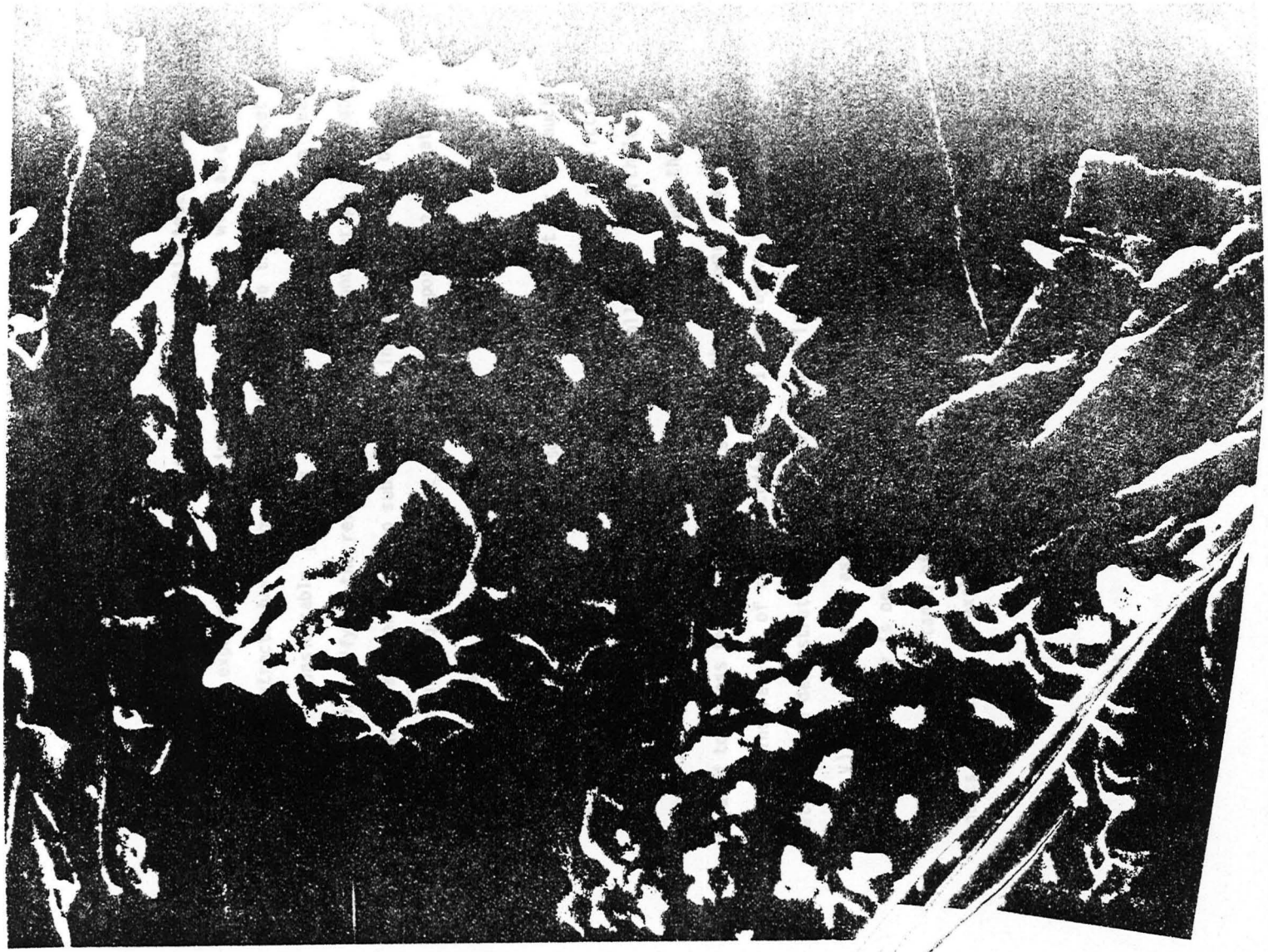
Animal Emanations. Allergic reactions to animal emanations are common causes of allergic rhinitis and asthma (53-68). Cats, dogs, furred laboratory animals, hamsters, gerbils, and farm animals can cause allergic disease in susceptible subjects. Positive skin tests to cat pelt extracts have been reported in 19% to 30% of unselected asthmatics. Some 70% of atopic patients with positive skin tests and significant exposure to cats have been reported to have asthma, in contrast to a 34%



Scanning Electron Micrograph of the House Dust Mite (X 300)



Scanning Electron Micrograph of Alternaria (X4000)



Scanning Electron Micrograph of Ragweed Pollen (X 6,000)

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incidence of asthma in atopic subjects with positive skin tests, but no significant cat exposure. Bronchial inhalation challenges with aerosals of cat pelt extracts have proven that asthma can be triggered by cat emanations. Considerable progress has been made by Dr. Ohman and colleagues in purifying the relevant antigens. Immunotherapy with cat pelt extracts has been shown to substantially increase the amount of cat antigen exposure required to cause an asthmatic response to inhalation challenge studies.

Food. Few areas of medical science are as beset by as much unfounded opinion, hucksterism, and outright fraud, and as little systematic objective study as the issue of food allergy. Nevertheless, double-blind, placebo-controlled procedures have been developed that can be used to assess the nature of allergic or other untoward reactions to foods. The results of recent studies (69-71) employing these rigorous methods have demonstrated several interesting principles (summarized in Table V). In regard to asthma, these studies have unequivocally proven that food allergy is one potential cause of asthma and rhinitis. The frequency and importance of food allergy induced asthma in children and adults remains to be explored.

TABLE V

Food Allergy

* Clinical allergic reactions to foods can be restricted to allergic rhinitis or asthma

* Positive blind challenges are nearly always associated with positive wheal and flare skin tests or RAST tests with the agent in question

* Positive skin test reactions to food extracts are predictive of positive blind challenges in approximately one-third of cases

* Positive blind challenges are accompanied by increased levels of plasma histamine

Pollen. The association of pollen with allergic asthma is thoroughly documented and does not require special emphasis (72). Recent studies have demonstrated that small fragments of pollen and pollen antigens in water vapor air are preminent sources of antigen during periods of plant pollination (73). Thus the dilemma of attributing allergic disease of airways 5 μ or less in caliber to antigens in pollen 20 μ or more in diameter seems to have been resolved.

Occupational asthma. Allergic asthma induced by antigen exposures in the workplace is an important occupational hazard in diverse settings (74-94). Perhaps most familiar to general physicians are reactions to animals among laboratory workers and veterinarians. A remarkable range of occupational exposures can lead to allergic asthma (Table VI). Careful inquiry into the occupation and hobbies of an asthmatic can reveal important clues to the factors contributing to asthma.

knowledge of the location of the patients' workplace and home can be helpful since they may live or work near but not in an important source of environmental antigens.

TABLE VI

Occupational Asthma

*	Antigens of organic origin -
	Animals, flour, mushrooms, B. subtilis enzymes, plant derived materials
*	Chemical dust haptens -
	Metal salts, penicillin
*	Chemical vapor haptens -
	TDI, phthalic anhydride, piperazine

MEDIATORS OF ALLERGIC ASTHMA

Immunologic activation of mast cells in the lung leads to the release of preformed and newly formed inflammatory mediators with a remarkable range of acute and longer lasting effects on the microenvironment (95-145; Table VII). Of these molecules, histamine, PGD_2, and leukotrienes C_4 and D_4 have been shown to be capable of inducing acute airway obstruction in humans after inhalation of the agents in aerosols. Chemotactic factors appear to contribute important forces in the later, sustained airway responses to antigens (see below).

TABLE VII

Mediators of Immediate Hypersensitivity*

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* Preformed mediators secreted from mast cell granules:

  Histamine
  Eosinophil chemotactic peptides
  Neutrophil chemotactic peptides
  Proteases
  Glycosidases

* Mediators formed at the time of mast cell activation:

  PGD_2
  Leukotriene B_4
  Leukotrienes C_4, D_4 and E_4

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* Molecules emerging from mast cells and basophils affect nearby cells and molecules to induce a complex series of cellular responses and secondary waves of mediators.

Leukotrienes may prove to play pivotal roles in asthma (Table VIII). recent studies indicate that cells that can be affected by leukotrienes express surface receptors for LTC_4 and separate receptors that can be activated by LTD_4 and LTE_4. Enormous efforts are being expended to develop clincially useful inhibitors of these receptors. Primitive, rather weak competitive inhibitors already have been developed. Leukotriene B_4, a very powerful neutrophil chemotactic factor, may play an important role in the cellular inflammatory aspects of chronic asthma.

TABLE VIII

Leukotrienes and Asthma

* LTC_4 Receptor
* LTD_4-LTE_4 Receptor
* Competitive Inhibitors
* Role in Asthma
* LTB_4 and Neutrophils

Neurotransmitters also may play a role in allergic asthma (Table IX). Particularly interesting in this regard is the recent demonstration that histamine can trigger reflex release of acetylcholine from the vagus nerve.

TABLE IX

Neurotransmitters and Asthma

* Cholinergic Factors
* Adrenergic Factors
* Purinergic Factors
* Peptides released at synapses
* Histamine and the Vagus Nerve

We have moved from an era in which we had little knowledge of the mechanisms of asthma to a time in which evidence has been developed to identify several mediators, cells, and neurotransmitters almost certainly playing roles in allergic asthma (Table X). Resolution of the roles of these factors is a prime goal of current research. More rational therapy is sure to follow once these issues are clarified.

TABLE X

Pathophysiology of Asthma

MEDIATORS	CELLS	NEUROTRANSMITTERS
Histamine	Mast Cells	Cholinergic
PGD_2	Basophils	Adrenergic
LTC_4	Eosinophils	Purinergic
LTD_4	Macrophages	Peptides
LTB_4	Endothelial	
PAF	Platelets	
Adenosine	Smooth Muscle	
	Secretory Cells	

GENETIC FACTORS THAT INFLUENCE SUSCEPTIBILITY TO ALLERGIC ASTHMA

Atopy. While ancient documents record clear recognition of the association of some patients' asthma with specific environmental exposures (27), insight into the basis of these responses was limited

until the early part of this century. By the 1920's investigators using wheal and flare skin test reactions and passive transfer (PK), to detect sensitivity to envirnomental substances had noted a striking frequency to positive responses among patients with three common illnesses - asthma, seasonal rhinitis, and what is now called atopic dermatitis (Table XI). Susceptibility to these three illnesses was clearly recognized as hereditary by this time. Coca coined the term "atopy" to describe this genetic force. This led Wise and Sulzberger to coin the term atopic dermatitis to describe the skin disease seen in association with asthma and rhinitis (159). If one parent has an atopic disease, approximately 50% of their children will develop an atopic disease. If both parents have atopic disease approximately, 75% of the children will as well.

TABLE XI

Atopic Diseases

* Allergic Asthma
* Allergic Rhinitis
* Atopic Dermatitis

The atopic genetic influence is expressed as a general susceptibility. Individual members of a kindred may express one or more atopic diseases, but there is no recognized additional propensity to develop exactly the same organ expression as others in the kindred. Specific IgE responses are very common in these kindreds, but the antigens

selected by each individual's immune system can be quite divergent. The hereditary force called the atopic tendency is a predisposition to develop one or more atopic diseases, not specific IgE responses or specific clinical expressions. As discussed in more detail below, the molecular basis for this tendency may be expression of abnormally high levels of cAMP phosphodiesterase enzymes (158).

Genetic influences on total and specific IgE. A second genetic factor influencing susceptibility to allergic asthma is the propensity of an individual to make antibody responses to antigens in which the IgE isotype is expressed at high levels for prolonged periods of time (Table XII; 146). Normal individuals express IgE to many antigens, but they usually do so only at low levels and only for a period of a few weeks after initial exposure. Atopic individuals are prone express much larger amounts of IgE and they fail to extinguish the response. Thus there appears to be defective suppression of IgE responses in atopic subjects (158).

TABLE XII

IgE Responses

* IgE responses are normal
* IgE responses usually are transient
* Atopic subjects express more IgE
* Atopic subjects express IgE longer
* Defective suppression of IgE responses

Specific immune response genes have been shown to exist in man that influence the decision by a person's immune system to mount an IgE response to a specific epitope (site on an antigen molecule). These immune response genes have been mapped to the HLA-D region of the short arm of the 6th human chromosome (Table XIII; 146). While this area of knowledge is just beginning to be explored, data in hand unequivocally indicate that specific human IgE responses are subject to the influence of inherited forces. The specific HLA-D region genes involved are a matter of uncertainty at this point. We can not yet accurately define how critical this influence is nor can we accurately predict specific IgE responses. Knowledge of familial propensity to develop atopic disease, total serum IgE, and Ir gene phenotype may soon permit accurate prediction of specific IgE responses. This in turn may permit accurate prediction of clinical atopic disease. An ability to predict IgE responses accurately may permit development of strategies to suppress the appearance of allergic diseases.

TABLE XIII

Immune Response Genes

* Human immune response genes exist
* IgE responses are influenced by Ir genes
* HLA-D region of 6th chromosome
* Predictive value

TABLE XIV

Factors That Influence Susceptibility to Allergic Asthma

* Familial atopic disease
* Propensity to express persistent IgE responses
* Immune response genes
* Intrinsic and acquired alterations in β-adrenergic responsiveness

ABNORMALITIES IN cAMP METABOLISM THAT CONTRIBUTE TO SUSCEPTIBILITY TO ALLERGIC ASTHMA

Role of cAMP in asthma. The intracellular second messenger cAMP appears to play an important series of roles in mediating or regulating immunologic and asthmatic reactions (Tables XV and XVI; 153-169). Acting through protein kinases, the levels of this molecule influence the release of the mediators of asthma, the responses of resident pulmonary cells, and infiltrating inflammatory cells.

The recent Grand Rounds by Dr. Lefkowitz reviewing β-adrenergic receptor activation of adenylate cyclase, and by Dr. William Pettinger reviewing α_2-adrenergic receptor inhibition of adenylate cyclase as

TABLE XV

Cyclic Adenosine 3',5' Monophosphate

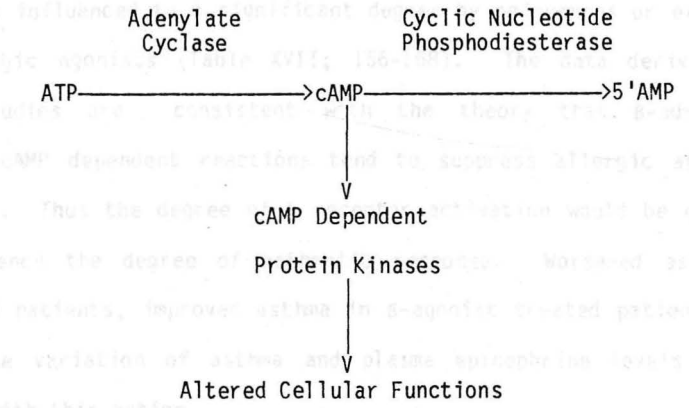

TABLE XVI

Effects of Increased cAMP Levels

* Suppression of mast cell mediator release
* Relaxation of bronchial smooth muscle
* Inhibition of airway mucous production
* Suppression of lymphocyte activation
* Induction of cAMP-PDE
  Histamine (H_2), $PGE_{1 \text{ or } 2}$,
  β-adrenergic agonists

well as reviews by Dr. Alfred G. Gilman and others (154-155) have provided a thorough recapitulation of our recent understanding of cAMP generation.

Several lines of evidence have indicated that the expression of asthma is influenced to a significant degree by endogenous or exogenous β-adrenergic agonists (Table XVII; 156-168). The data derived from these studies are consistent with the theory that β-adrenergic receptor-cAMP dependent reactions tend to suppress allergic asthmatic reactions. Thus the degree of β receptor activation would be expected to influence the degree of asthmatic response. Worsened asthma in β-blocked patients, improved asthma in β-agonist treated patients, and coordinate variation of asthma and plasma epinephrine levels are in keeping with this notion.

Viewed from this perspective any factors that block β-receptor activation (autoantibodies to β-receptors, competitive inhibitors), factors that reduce the number of cell surface β-receptors, factors that uncouple β-receptors from adenylate cyclase, or factors that increase the rate of cAMP hydrolysis would tend to enhance or even permit the expression of asthma. As reviewed below allergic asthmatics appear to have several such factors present, some congenital and some acquired (Table XVII).

TABLE XVII

Relationship of β-Adrenergic Receptors to Asthma

* Pharmacologic activation of β_2-receptors improves asthma
* Pharmacologic blockade of β-receptors worsens asthma
* Antigen-induced mast cell mediator release and asthma are suppressed by β_2-receptor activation, while both are enhanced by β-blockade
* Circadian variations in asthma are correlated with variations in plasma epinephrine

Genetic abnormalities in cAMP metabolism in allergic asthmatics. Recent studies by Dr. Hanifin and coworkers have provided important insight into what might well prove to be the molecular basis of the general atopic tendency. Several groups have noted that peripheral blood mononuclear cells from patients with allergic asthma, allergic rhinitis, and atopic dermatitis have low levels of cAMP compared to control cells and that these cells produce lower levels of cAMP after β-receptor activation. This defect, has been traced to an abnormally high level of cAMP phosphodiesterase (PDE) activity. Cells from atopic subjects appear to lack some PDE activities found in normal cells, but the overall low apparent Km PDE activity is markedly increased. The PDE abnormality is present in cord blood cells of children born to parents with atopic diseases. Thus abnormally high PDE activity appears to be a nearly uniform characteristic of atopic patients, apparently genetically

determined, and would be expected to blunt the effect of β-adrenergic receptor activation.

Diminished cAMP responsiveness arising from an acquired increase in PDE activity. Persistent cellular stimulation by histamine isoproterenol or PGE, (all agents that increase production of cAMP) results in increased levels of cAMP-PDE activity (158). This results in a blunted cAMP response to subsequent adenylate cyclase activation. Thus the persistent presence of histamine or histamine stimulated prostaglandins in the pulmonary tissues of asthmatics would be expected to induce increased PDE activity in patients who already express excessive PDE activity.

Alterations in cAMP metabolism induced by antigen challenge of allergic asthmatics. Recent data indicate that an acute inhalation of antigen by an allergic asthmatic can lead to a decrease in β-adrenergic receptor number and also directly diminished adenylate cyclase activity (168). Thus active allergic disease can induce a decrease in β-receptor number and in the ability of adenylate cyclase to be activated by a panel of hormones or direct activators. Recognition of this process may help explain the reduced numbers of β-receptors demonstrable on the peripheral blood cells of active asthmatics and variations in the degree of blunting of cAMP responses to β-agonist stimulation of cells from such patients.

Tachyphylaxis of β-receptors resulting from β-agonist therapy. While considerable variability has been observed, chronic therapy with oral or inhaled β-adrenergic agonists can cause a significant degree of tachyphylaxis (1). Diminished β-receptor numbers and diminished cAMP generating responsiveness of the remaining receptors have been reported. Several aspects of this area are controversial but an excellent balanced review is available (1).

Autoantibodies to β-receptors as a source of diminished β-adrenergic responsiveness. In preliminary studies IgG antibodies capable of blocking ligand binding to β-receptors have been reported to be present in the blood of approximately 5% of adult asthmatics. The validity and importance of this observation are not established at this time.

Iatrogenic β-adrenergic receptor blockade. The widespread use of β-blocking agents in the treatment of angina, hypertension, migraine, thyrotoxicosis, and several other conditions has led to an acute appreciation of the probable importance of endogenous epinephrine as a countervailing force in asthma. Asthma, allergic rhinitis, allergic urticaria, and anaphylaxis frequently are made worse by β-blocking agents. Fatal exacerbations may occur in asthmatics placed on such medication.

Diminished cAMP levels in asthmatics - a recapitulation. Taken as a whole it is apparent that cAMP metabolism plays an important if not

pivotal role in determining the clinical expression of asthma. Diverse intrinsic and acquired forces lead to diminished levels of cAMP in the tissues of allergic asthmatics and to diminished β-adrenergic responsiveness. This abnormality in the intracellular melieu seems to dispose the asthmatic to the characteristic exaggerated airway responses to antigen, mediators, irritants and a variety of nonspecific influences (1,159).

BIPHASIC ASTHMATIC RESPONSES AND AIRWAY HYPERSENSITIVITY

Exposure of allergic subjects to antigen by aerosol in the nose or lungs or by injection into the skin results in an immediate alteration in the tissues grossly manifested as nasal obstruction and signs of allergic rhinitis, acute airway obstruction, or a wheal and flare response respectively. Recent studies in these three systems have demonstrated that a second phase of inflammation often ensues beginning approximately 4 hours after antigen stimulation, reaching a peak after 8-12 hours, and then receding over the next 24 hours (170-176). Recent studies also indicate that both the early and the late phases of the pulmonary response to antigen are associated with the release of histamine and mast cell associated neutrophil chemotacatic factors (171). Thus biphasic mast cell mediator release seems to be a normal response to acute antigen exposure. These observations help explain the chronicity of some allergic processes.

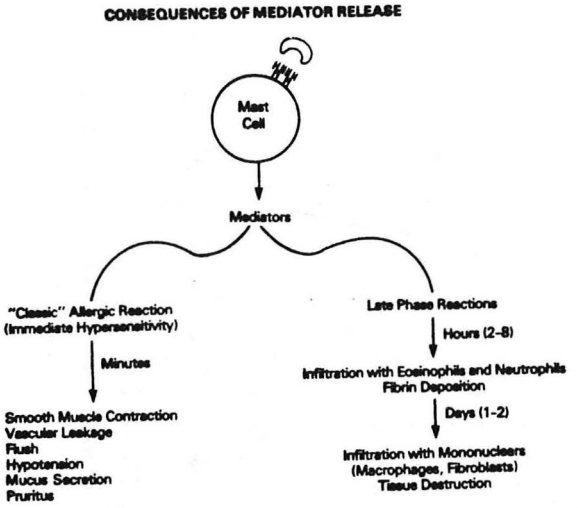

FIG. 2. Consequences of mast cell-mediator release can be divided temporally into immediate and late-phase reactions. Late-phase reactions develop over a period of hours and are characterized histologically by an early influx of polymorphonuclear leukocytes and fibrin deposition followed later by infiltration of mononuclear cells. (Reprinted with permission from Oertel HL, Kaliner M: The biologic activity of mast cell granules. III. Purification of inflammatory factors of anaphylaxis (IF-A) responsible for causing late-phase reactions. J Immunol 127:1398, 1981)

From reference 170

Particularly interesting are the studies of Hargreave and of Cockcroft and their coworkers who have demonstrated that patients who experience a second phase asthmatic response to antigen acquire markedly increased airway hypersensitivity to nonspecific stimuli such as methacholine, histamine, exercise, and cold air inhalation. This hypersensitivity can last 2 to over 8 weeks. The realization that a

single acute allergic reaction can make the airways hyperreactive for prolonged periods of time help explain why multiple nonimmunologic factors usually can exacerbate allergic asthma (177-218).

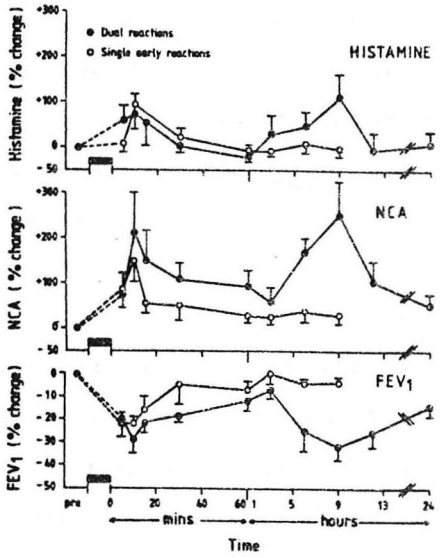

FIG. 1. Histamine and NCA in early- and late-phase reactions. The mean ± SEM of the percentage changes for histamine and NCA in relation to changes in FEV_1 in 10 patients with dual reactions *(closed circles)* and seven patients with single early reactions *(open circles)*. The period of challenge is represented by the *solid bar*. The data at 12 and 24 hr are from four patients. There was no significant difference between the increases in histamine and NCA for the two groups during the early reaction. The maximal increases for histamine and NCA during the late reaction (6 to 9 hr) were significantly higher for the dual responders when these increases were compared with the corresponding values for the single early responders (histamine $p < 0.05$, NCA $p < 0.01$), Mann Whitney U test.

From reference 171

Bronchoalveolar lavage studies in asthmatics have confirmed the presence of large numbers of eosinophils and neutrophils in the airways of asthmatics. Several lines of evidence, reviewed recently by Dr. Kaliner (170), suggest that the initial response to antigen is primarily the direct result of mast cell mediators while the later phase seems to depend upon mast cell mediators and the cells lured to the site by mast cell chemotatic factors. Dr. Goetzl has presented evidence that LTB_4 can induce marked hypersensitivity in the footpads of experimental animals and that this hypersensitivity does not occur in the absence of infiltrating neutrophils (215).

Taken as a whole, these studies indictate that allergic responses to antigen cause immediate and then sustained pulmonary inflammation. They also indicate that marked and prolonged hypersensitivity of the airway can ensue after a single antigen exposure.

THERAPY FOR ALLERGIC ASTHMA

Allergic asthmatic patients can benefit from identification of the specific causes of their asthma in several ways. Some causes of asthma can be avoided (e.g. animals, occupational antigens and to a degree mites) resulting in amelioration or actual cure. Demonstration of specific causes can guide therapy by predicting periods of exacerbation from unavoidable exposures such as pollen, thereby permitting more aggressive pharmacologic management before the exacerbation becomes significant. Some patients are relieved to have evidence of specific

causes of their asthma - a legacy of the rather vicious and unfounded attitude of some nonasthmatic physicians and members of the general public that asthma is a self-inflicted psychiatric disorder.

TABLE XVIII

Effects of Immunotherapy

* Antigen specific IgG (blocking antibody)
* Diminished basophil reactivity to antigen
* Diminished mast cell reactivity to antigen
* Antigen specific suppressor T lymphocytes
* Diminished antigen specific IgE Seasonal rises Absolute decrease
* Diminished late phase responses to antigen in lung, nose, and skin

Studies of several kinds are converging to indicate another potential benefit of proving the presence of specific inhalant allergen triggers of asthma - possible benefit from specific high dose immunotherapy (219-233). Double-blind, placebo-controlled trials of immunotherapy for allergic rhinitis have demonstrated significant benefit in some 75% to 85% of properly selected and properly treated patients (see for example refs. 219-222). Studies of the mechanisms of desensitization demonstrated a variety of in vitro alterations including diminished cellular responsiveness to antigen, appearance of antigen-specific suppressor cells, and diminished antigen specific IgE

responses (222-225). These parameters correlated with clinical improvement, but not well enough to judge their relative importance.

Clinical studies of the impact of immunotherapy on asthma have been of varied quality. Some have employed poor design (e.g. no blinded therapy), poor therapy (e.g. homeopathic amounts of antigens), or have used imprecise end points (e.g. "better"). Several blinded studies have been performed with reasonable attention to the rules for proper clinical studies (226-233). The results of these studies consistently indicate that immunotherapy can be effective for asthma. The National Institute of Allergy and Infectious Diseases has initiated a multicenter trial of immunotherapy for asthma to help define the patients who would benefit, the antigens that are effective, the frequency of improvement, and the degree of improvement.

Perhaps the most important development in this area is the recognition that immunotherapy can diminish or abolish the second phase of the response to antigen challenge (231). Clinical improvement in asthma appears to correlate with the degree of inhibition of the late asthmatic response to antigen. Unpublished studies in progress at the Mayo Clinic and at Johns Hopkins are said to indicate that immunotherapy can suppress the late cutaneous and late nasal responses to antigen challenge and that the degree of suppression seems to correlate wtih the degree of clinical improvement in allergic rhinitis. Thus an objective parameter for assessing the impact of immunotherapy may be in hand. These observations also are in keeping with the notion that the late

phase responses to antigen challenge are more relevant models of chronic allergic diseases than the immediate responses.

Needless to say studies are in progress to determine whether or not the presence or degree of a late response predicts effectiveness of immunotherapy. Assessment of the progressive impact of immunotherapy on late responses in individual patients might provide an objective basis for continuing, increasing or stopping immunotherapy. This could prove especially useful when several factors contribute to asthma.

Immunotherapy has been proven effective for allergic rhinitis and probably can be effective for allergic asthma. Studies over the next few years should provide major new insights into who would benefit, how much, and why.

TABLE XIX

Immunotherapy for IgE-Mediated Diseases
of the Respiratory Tract

* Diminished cellular responsiveness to antigens
Basophils Mast cells
* Antigen specific suppressor cells
* Abolition of seasonal increases in specific IgE
* Decline in specific IgE
* Proven efficacy in allergic rhinitis
* Efficacy for dust-induced asthma in children
* Abolition of the late phase reactions

SUMMARY

Major new insights into allergic asthma have accrued in the recent past. The causes of allergic asthma are being defined with increasing precision. Methods for diagnosis of allergic asthma are improving. Our perception of the factors that dispose to asthma and the mediators of asthma is becoming quantitative. Knowledge of the mechanisms of immunotherapy and the clinical value of specific antigen immunotherapy are improving. For investigators this is a very exciting time indeed. For clinicans these developments represent the dawn of an era of major advances in the diagnosis management of allergic asthma.

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Epidemiology of Allergic Asthma

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