ALLERGIC DISEASES IN ADULTS

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December 1, 1977

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The development of allergy as a separate medical specialty began some 75 years ago with the classic description of anaphylaxis by Portier and Richet (1). These investigators demonstrated that the injection of a small amount of toxin into dogs occasionally produced increased sensitivity to subsequent injections rather than protection as was anticipated from immunization. Shortly after the description of anaphylaxis, the phenomenon was linked to clinical disease states. Hay fever, which was initially described by Wyman in 1872 (2), was felt to be caused by "pollen toxin" until Wolff-Eisner advanced the concept that the disease was related to anaphylaxis (3). Similarly, Meltzer hypothesized that asthma might be explained as a type of anaphylaxis (4), and the disease was taken out of the hands of psychiatrists where it had been considered a form of neurosis and put under the care of allergists - an achievement of dubious merit.

The widely advocated principle of inducing protection against toxins by immunization found its way into allergy by virtue of the erroneous assumption that a toxin in pollens produced the disease. In the early 1900's, Leonard Noon and John Freeman introduced the concept of immunizing against allergic toxins, and "clinical improvement" indicated efficacy (5, 6). Robert Cooke described the presence of "blocking antibody" in the serum of patients receiving injection therapy to add further support to its usefulness (7). Other early work in the field of allergic diseases was carried out by Prausnitz (8) and Arthur Coca (9), founder of the Journal of Immunology. A lag in the scientific development of allergic disorders was largely corrected after the discovery in 1967 of an immunoglobulin class, IgE, primarily responsible for allergic phenomena (10). Over the past 10 years significant advances have been seen in the area of IgE-mediated hypersensitivity. This discussion will focus on advances in the immunologic basis of allergy and certain allergic diseases.

IgE STRUCTURE AND FUNCTION

The discovery of Immunoglobulin E and of its correlation with reaginic or allergic activity began a series of basic immunologic investigations to define the antibody's structure and function (11). These aspects of human IgE have been reviewed (12), and only certain characteristics will be discussed here.

TABLE I

CHARACTERISTICS OF IMMUNOGLOBULIN E

Homocytotropic	
Production:	Respiratory and gastrointestinal
Molecular weight:	190,000
Serum half-life:	2.7 days
Serum concentration:	80-200 ng/ml

The term homocytotropic antibody has been used in reference to IgE because of the molecule's ability to passively sensitize human and primate skin but not that of other species. This affinity characteristic, which is the basis of the Prausnitz-Küstner (P-K) test, will be examined further when target cells are discussed. The location of IgE-producing plasma cells was studied using immunofluorescent techniques. In man these cells are found predominantly in mucous membranes and regional lymph nodes of the respiratory and gastrointestinal tracts (13). This localization may be a phenomenon of sensitization by antigen, however, because subsequent animal studies have identified other areas of IgE plasma cells using different methods of immunization. The IgE molecule, having two light chains and two heavy chains and a molecular weight of about 190,000, is very similar in structure to other immunoglobulins. IgE, however, has the shortest survival rate, highest fractional catabolic rate, and lowest synthetic rate of any of the immunoglobulin classes. Normal serum concentrations are in the range of 80 ng/ml (14), and catabolic studies show a half-life of 2.7 days (15). There is a tendency of allergic individuals to have high serum IgE levels generally above 230 ng/ml (14-17). Approximately 20% of non-allergics will have levels above this value while a similar percentage of allergics will have lower levels. Elevated serum IgE levels are not specific for allergic disease and have been reported in dermatitis (18), parasitic infections (19), cystic fibrosis (20), thymic hypoplasia (20), severe liver disease (21), and syndromes of increased susceptibility to infection (22). IgE has been detected in secretions including nasal washings and sputa (23) and in tears (24) with the highest concentrations in allergic individuals. A mechanism for local production appears likely and must be considered in evaluating serum levels of specific antibody.

Total serum IgE levels may be determined by a variety of techniques designed specifically to detect small amounts of protein in serum. Radial immunodiffusion (RID) is known to be relatively insensitive, and the manufacturer (Meloy Co., Springfield, Va.) suggests a lower limit of sensitivity of about 900 IU (2,160 ng/ml). A further disadvantage of this test is the occurrence of occasional false positive results (25).

Other commonly used tests of serum IgE employ radioimmunoassays. Two competitive binding tests, the radioimmunosorbent test (RIST) and the double-antibody radioimmunoassay (RIA), and a noncompetitive test, the paper disc radio immunosorbent test (PRIST) are commercially available. These radioimmunoassays correlate well with each other and are capable of accurately measuring IgE down to serum concentrations of 24 ng/ml (25). Most Dallas area hospitals (Baylor, Medical City, Parkland, Presbyterian, St. Paul) use a radioimmunoassay method while the Veterans Administration Hospital uses the

RID method. Levels are reported in Units where one Unit equals 2 ng. Normal values vary with age, but adults having values above 100 Units (200 ng/ml) are considered to have elevated IgE levels.

TARGET CELLS FOR IgE

Using radiolabeled anti-IgE antibodies, Ishizaka, et al, demonstrated the presence of IgE on basophils but not other neutrophils (26) and on tissue mast cells (27). Electron microscopy using hybrid antibody techniques has also shown IgE molecules on the surface of basophils (28). To determine the region of the IgE molecule responsible for its unique property of binding to these target cells, various enzymatically cleaved fragments of an IgE myeloma have been used in an attempt to block passive sensitization of skin with antigen-specific IgE. These studies demonstrated that the Fc fragment alone was capable of blocking passive sensitization (29). Based on these findings, Hamburger attempted to block passive sensitization with a synthetic peptide alledgedly representing that region of the Fc fragment responsible for mast cell binding (30). Although the publication of the success of this putative receptor blocker was widely heralded as a break-through in allergy research, attempts by four different laboratories to reproduce the experiment were unsuccessful (31). Attempts to characterize the mast cell receptor for IgE are presently underway in a number of laboratories using rodent peritoneal mast cells and tumor cells (32, 33). Identification of this receptor may allow for satisfactory ways of therapeutically intervening in IgE attachment to mast cells.

Although the receptor has not been fully characterized, the affinity of IgE binding to human basophils has been examined (34). Basophils from a group of 7 non-allergic and 6 allergic individuals were assayed for the number of bound IgE molecules/basophil before and after passive sensitization of their cells with IgE myeloma protein. These data together with serum concentrations of IgE provided the necessary information to determine affinity constants for IgE to basophils.

TABLE II

	Subject	Serum IgE ng/ml	IgE molecules/basophil Before	After	$K \times 10^{-9}$
Normal	SS	168	20,000	41,500	1.07
	JH	154	25,000	62,000	0.71
	EG	142	27,000	85,000	0.66
	IK	178	17,000	36,500	1.01
	TK	230	15,170	31,800	0.87
	KI	178	5,300	36,000	0.17
	MO	394	15,000	30,000	0.51
Allergic	EE	1370	34,000	38,000	1.31
	LL	154	32,800	36,800	11.6
	KC	8160	23,000	30,000	0.08
	MS	1620	18,400	38,000	0.11
	JM	343	31,000	47,000	1.17
	LG	720	15,400	30,000	0.28

Three clinically relevant points are evident from these data: 1) Similar serum IgE concentrations may be found in allergic and non-allergic individuals, 2) Basophil receptor sites are not completely saturated indicating reversibility, and 3) There is a high affinity of the IgE for its receptor. Serum IgE concentrations, therefore, do not distinquish allergic from non-allergic individuals and are not diagnostic. The reversibility of binding and high affinity explain the prolonged duration of passive sensitization by IgE which lasts weeks in contrast to free serum IgE whose half-life is days. The high IgE-basophil affinity accounts for the prominent immunopathologic response to antigen despite a very low serum level (35).

MEDIATORS OF THE ALLERGIC REACTION

Before examining the cellular events involved in immediate hypersensitivity, a brief review of participating mediators is appropriate. In 1941 Katz and Cohen demonstrated that histamine was released from whole blood of an allergic patient after the addition of antigen (36). Histamine has been the most extensively studied of the mediators of immediate hypersensitivity, and its mechanisms of action have recently been reviewed (37). Histamine is known to increase vascular permeability and airway resistance (38) and has recently been shown to be eosinophilotactic at certain concentrations (39). Histamine released from basophils and mast cells can feed back to an H_2 receptor on the cell surface and elevate cyclic AMP, thereby inhibiting further release of histamine (40).

TABLE III

MEDIATORS OF IMMEDIATE HYPERSENSITIVITY

Mediator	Action
Histamine	Contracts smooth muscles (1-10 min.) Increases vascular permeability
SRS-A	Contracts smooth muscles (up to hours)
ECF-A	Attracts and hold eosinophils
PAF	Releases histamine and serotonin from platelets
NCF	Attracts neutrophils
Arginine esterase	Forms kinins from kininogens
Prostaglandins	Bronchodilates (E) Bronchoconstricts ($F2\alpha$)

A second mediator of immediate hypersensitivity which produces smooth muscle contraction of slower onset and greater duration than histamine was described in 1940 (41). This activity was

later shown to persist despite the presence of antihistamines, and it was named slow reacting substance of anaphylaxis or SRS-A (42). SRS-A has not been entirely characterized, but it is a small (M.W. 400) acidic molecule which can contract certain smooth muscles and increase vascular permeability (43). Intravenous administration of SRS-A in guinea pigs has resulted in a decrease in lung compliance without a change in total pulmonary resistance (44). This finding may suggest its site of action is on more peripheral airways. The actions of SRS-A are inhibited by arylsulfatase which is found both in eosinophils and in lung tissue (45, 46). This inhibition is another mechanism for autoregulation and limitation of the allergic reaction.

Eosinophils, which have long been associated with immediate hypersensitivity, are attracted both through the action of histamine and a third important mediator: eosinophil chemotactic factor of anaphylaxis. This latter substance, abbreviated ECF-A, was discovered in 1971 and has been characterized and synthesized (47, 48). ECF-A represents two tetrapeptides differing only in their N-terminal amino acid. Both tetrapeptides are chemotactic for eosinophils and prevent subsequent migration due to a second chemotactic stimulus (49). The demonstrated release of ECF from polymorphonuclear leukocytes during phagocytosis indicates that its role is not exclusively related to immediate hypersensitivity (50).

The final primary mediator of IgE-induced basophil activation is platelet activating factor (51). Platelet activating factor (PAF) causes agglutination of platelets and serotonin release. PAF is inactivated by eosinophil phospholipase D, and this reaction may represent another autoregulatory system in immediate hypersensitivity (52). The role of this substance in the pathophysiology of immediate type hypersensitivity reaction is not well delineated, but its role in immune complex disease has been studied (53).

All four of the primary mediators are released from basophils as demonstrated by studies of cells from a patient having a basophilic leukemia (54). Histamine and ECF-A are found preformed in basophil granules and mast cells prior to activation of the cell while SRS-A and PAF cannot be identified before activation and are likely formed just prior to degranulation of the cell (55, 56).

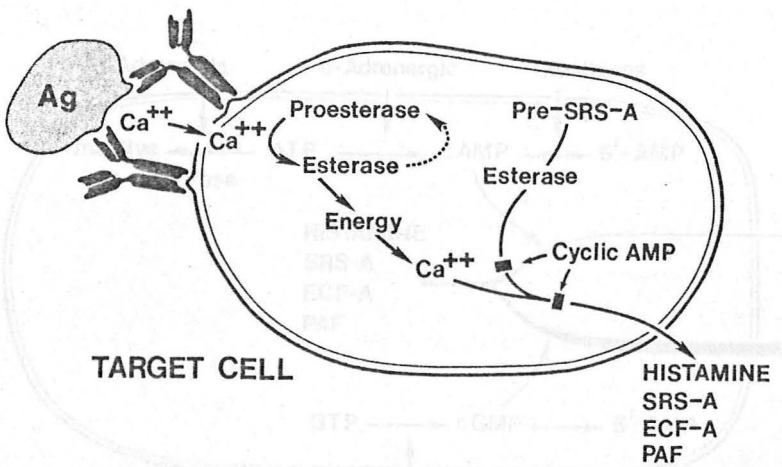
Other mediators may also be involved in IgE-mediated reactions and will be briefly discussed. Prostaglandins have been demonstrated in the incubates of sensitized human lung fragments exposed to allergen (57), and increased PGF_2 formation has been documented after isolated sensitized human bronchi were exposed to antigen (58). Although this finding suggests participation of prostaglandins in immediate hypersensitivity their role, if any, is not clear.

The other major candidates as mediators of allergic reactions are bradykinin or other kinins which increase vascular permeability and contract certain smooth muscles (59). Immune activation of basophils results in the release of an arginine esterase having kallikrein activity i. e., the ability to split kininogens to kinins (60). The similarity in kinetics of release to those of histamine led to the postulate that this esterase might link allergic reactions to kinin formation. In addition, a neutrophil chemotactic factor (NCF) has been found in the serum of allergic individuals after inhalation challenge with antigen (61). The exact role of this mediator in allergic reactions remains to be described, but all of these secondary mediators are presently being studied to clarify their role and provide more specific pharmacological intervention.

ACTIVATION, GENERATION, AND RELEASE OF MEDIATORS

Although mediator release follows the cross-linking of two IgE molecules on the surface of a basophil (62), there is no correlation between the concentration of cell-bound IgE and amount of anti-IgE required for histamine release (35). This finding would indicate that intrinsic cellular factors are important in mediator release and coincides with the interesting observation that individuals shown to be hypersensitive to certain foods by double-blind testing have high spontaneous release of histamine (63). Some cellular events in mediator release should be reviewed to better understand these intrinsic differences as well as the rational approach to pharmacologic treatment of allergic reactions.

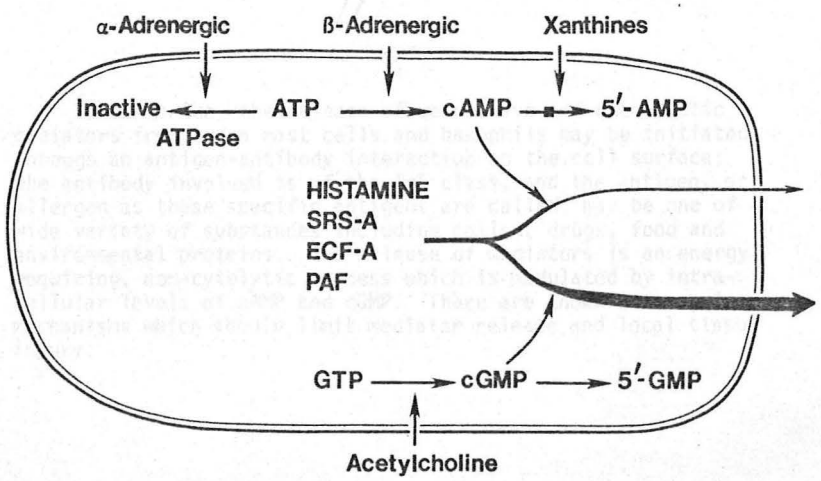
FIGURE I



An early event in the initiation of the release process is the calcium-ion dependent activation of a serine esterase (64). There follow an energy-requiring step (inhibitable by 2-deoxyglucose) and an intracellular calcium-ion dependent step (65). The release of mediators appears by electron microscopy to be sequential exocytosis, which leaves the cell intact and able to regenerate mediators (66).

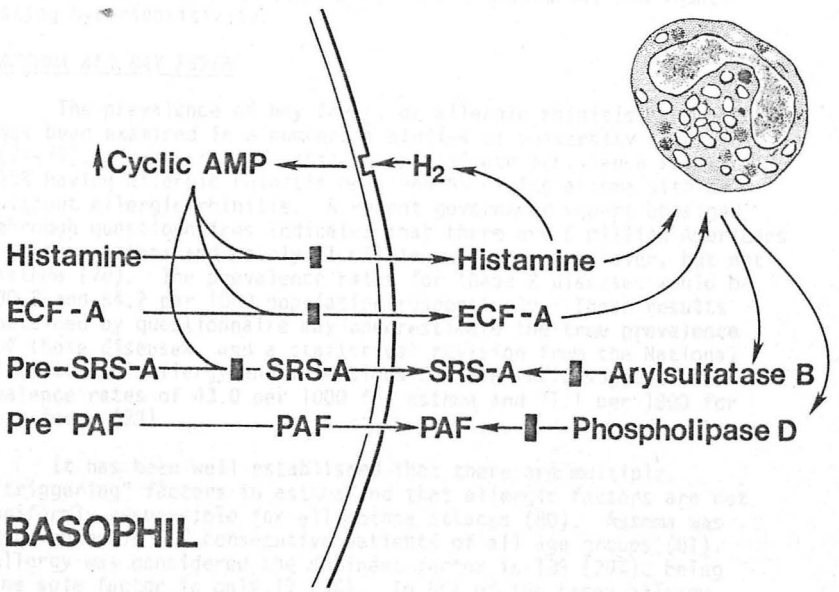
The modulation of mediator release by intracellular cyclic nucleotides has been well described in a series of investigations from Austen's laboratory. Studies using sensitized human lung and nasal polyp fragments have shown an augmentation of mediator release associated with a fall in tissue levels of cyclic AMP and, conversely, an inhibition of release accompanying elevated levels (67, 68). These alterations in mediator release were accomplished through the use of various adrenergic and phosphodiesterase inhibiting drugs, and the magnitude of change in mediator release paralleled the concentration of the pharmacologic agents. More direct studies confirming this relationship have now been done using purified rat mast cells (69). As has been true of other systems, there appears to be an opposing effect of cyclic GMP on those functions effected by cyclic AMP. Cholinergic agents such as acetylcholine enhance mediator release with no change in cAMP levels, and 8-bromo cyclic GMP has a comparable augmenting effect on mediator release (70). Thus, increases in cAMP inhibit release and increases in cGMP enhance release. The mechanism of action of these cyclic nucleotides has been postulated as influencing microtubular function (71) which is essential for histamine release (72). The β-adrenergic drugs through activation of adenyl cyclase and the theophylline preparations through inhibition of phosphodiesterase serve to elevate intracellular cAMP and may be important in reducing mediator release.

FIGURE II



At least 3 autoregulatory mechanisms are operative in the mediator phase of the allergic reaction. First, histamine feeds back to a basophil H_2 receptor causing an elevation of intracellular cAMP and inhibition of further mediator release (40). Histamine and ECF-A serve to attract eosinophils which provide two inhibitory effects. Eosinophil arylsulfatase B inactivates SRS-A (45), and phospholipase D inactivates PAF (53).

FIGURE III



To summarize, the release of vasoactive and chemotactic mediators from human mast cells and basophils may be initiated through an antigen-antibody interaction on the cell surface. The antibody involved is of the IgE class, and the antigen, or allergen as these specific antigens are called, may be one of a wide variety of substances including pollen, drugs, food and environmental proteins. The release of mediators is an energy requiring, non-cytolytic process which is modulated by intracellular levels of cAMP and cGMP. There are known autoregulatory mechanisms which should limit mediator release and local tissue injury.

ALLERGIC DISEASE

A uniform definition of allergy is necessary before discussing these specific disease states. Farr suggested that "allergy" refers to a broad group of untoward physiologic responses which are mediated by immunologic mechanisms (73). Present usage in this country largely restricts the term to diseases related to IgE-mediated reactions although the literature from other countries includes all adverse immunologic diseases such as systemic lupus, autoimmune hemolytic anemia, and so forth. This discussion will limit the term to IgE-mediated reactions and include asthma, hay fever, urticaria, and insect sting hypersensitivity.

ASTHMA AND HAY FEVER

The prevalence of hay fever, or allergic rhinitis, and asthma has been examined in a number of studies of university students (74-77). These studies indicate approximate prevalence rates of 15% having allergic rhinitis only and 5% having asthma with or without allergic rhinitis. A recent government report obtained through questionnaires indicates that there are 6 million Americans who have asthma and nearly 11 million who have hay fever, but not asthma (78). The prevalence rates for these 2 diseases would be 30.2 and 54.2 per 1000 population respectively. These results obtained by questionnaire may underestimate the true prevalence of these diseases, and a statistical revision from the National Institute of Allergy and Infectious Disease would suggest prevalence rates of 43.0 per 1000 for asthma and 71.1 per 1000 for hay fever (79).

It has been well established that there are multiple "triggering" factors in asthma and that allergic factors are not uniformly responsible for all asthma attacks (80). Asthma was documented in 487 consecutive patients of all age groups (81). Allergy was considered the dominant factor in 139 (29%), being the sole factor in only 17 (3%). In 56% of the cases allergy was felt to play some role while in the remaining 44% it was of no significance. Although a complete description of methodology is lacking, the authors state that in addition to history and physical examination, skin testing and inhalation tests were performed when deemed necessary. Substantiation of these figures in terms of mechanisms provoking asthma attacks can be found in a study of 234 asthmatic patients whose mean age was 41 years (82). In this latter study, both skin tests and corroborative seasonal history were required to document allergic asthma. Allergy was found to be the predominant factor in 58 cases (25%) of which only 12 (5%) were solely precipitated by allergy. In 45% allergy was considered to play some role while in 55% it was not related to asthma attacks.

TABLE V

ALLERGY AS A PROVOKING FACTOR IN ASTHMA

Author	Total no. of patients	Sole factor	Predominant factor	Contributing factor
Williams (1958)	487	17 (3%)	139 (29%)	130 (27%)
Stevenson (1975)	234	12 (5%)	58 (25%)	47 (20%)

As with asthma, rhinitis may be caused by factors other than allergies. The primary disease mimicking allergic rhinitis is vasomotor rhinitis. Symptoms of vasomotor rhinitis include nasal congestion and rhinorrhea as seen in allergic rhinitis, but there is generally less associated pruritis and conjunctivitis (83). Symptoms of vasomotor rhinitis may occur after alcohol ingestion and temperature change, or they may be precipitated by factors such as perfumes, tobacco smoke, fumes, and other non-specific irritants. Good data are not available as to the prevalence of vasomotor rhinitis, and it is often misdiagnosed by both patients and physicians as "allergy".

TABLE VI

CHARACTERISTICS OF ALLERGIC AND VASOMOTOR RHINITIS

	Allergic	Vasomotor
Seasonal variation	Usually	No
Rhinorrhea	Watery	Mucoid
Collateral allergy	Common	Coincidental
Family history of allergy	Common	Coincidental
Nasal smear for eosinophil	Usually positive	Rarely positive

Additional forms of rhinitis which might be confused with allergic rhinitis include (a) drug induced rhinitis such as is seen with Rauwolfia derivatives and estrogens, (b) infectious rhinitis, (c) rhinitis associated with pregnancy or with hypothyroidism, (d) atrophic rhinitis, (e) rhinitis medicamentosa, and (f) nasal polyposis. Most of these latter forms of rhinitis would be evident from history and examination although they may be found in an allergic individual and, thus, be initially considered IgE-mediated.

Diagnosis

Since both allergic and non-allergic mechanisms may produce very similar clinical pictures of both asthma and rhinitis, what criteria help determine which patients have allergies? The history is probably the most important single aspect of correctly diagnosing allergy. The age of the patient as well as the age of

onset of symptoms may be helpful. Allergic asthma is the more common in the age group from 15-30 years old while younger (<5 yr.) and older patients have predominantly non-allergic asthma (82, 84). Information as to the prevalence of various forms of rhinitis at different ages is not available. The age of onset of allergic rhinitis has been analyzed in a population study at Tecumseh, Michigan between 1962-1965 (85). The percentage distribution of 455 cases of allergic rhinitis in males and 482 in females is shown:

Percentage Distribution of Allergic Rhinitis by Age at Onset

Age Group (yr)	Male (%)	Female (%)
0-9	36.6	33.5
10-19	28.3	31.1
20-29	14.4	17.7
30-39	11.2	11.4
40-49	6.5	4.3
50+	3.0	2.0

In this population approximately 80% of individuals having allergic rhinitis developed symptoms before 30 years old. Studies determining the age of onset of asthma indicate that non-allergic asthma, previously called intrinsic, generally begins before age 5 or after age 35 whereas IgE-mediated asthma begins in the intervening years (86).

Seasonal variation in symptoms is another important historical point in these allergic diseases. Exposure to pollen is by nature seasonal and related to geographical location (87). Familiarity with pollenating plants known to cause allergy and their season of pollenation is helpful.

TABLE IV

POLLEN SEASON OF COMMON TEXAS PLANTS

PLANT NAME	POLLEN SEASON
Elm trees	Feb.-Apr.
Oak trees	Mar.-Apr.
Grasses	Feb.-Aug.
Ragweed	Aug.-Nov.
Cedar trees	Dec.-Feb.

Other airborne allergens such as molds may have seasonal peaks (88) while still others such as animal dander may be perennial. Attempts to correlate occurrence of symptoms with either a specific season or with certain exposure is helpful.

The family history is of importance in the diagnosis of allergic diseases, and recent studies have indicated two types of genetic control. Basal IgE levels appear to be regulated as autosomal recessive traits (17) while immune response (Ir) genes likely control specific immune reactivity (89, 90). Early clinical studies showed that in 504 cases of allergy 48.4 percent had a positive antecedent family history while in 76 non-allergic individuals only 14.5 percent had a positive antecedent history (91). The increased risk of the occurrence of allergy in first degree relatives (sibs, parents, and children) has been analyzed from questionnaire studies of a large twin registry and was found to be 1.5 - 2.0 times greater than normal (92).

A large population study demonstrated a significant association between responsiveness to a low molecular weight ragweed antigen, Ra5, and the possession of the HLA specificities B7 and the B7 cross-reacting group (90). This latter type of genetic control of immune responsiveness may be of greatest importance in allergic individuals having low serum IgE concentrations. A positive family history is therefore helpful in consideration of allergic disease.

In contrast to the history, the physical examination is usually unrewarding in differentiating allergic from non-allergic causes of asthma or rhinitis. Few forms of rhinitis will have characteristic mucosal changes, and the physical exam cannot differentiate allergic rhinitis from vasomotor rhinitis.

Laboratory tests contribute to the diagnosis with the most readily obtained test being a peripheral smear for eosinophils. Conditions other than allergy are associated with eosinophilia, and the test is therefore non-specific (93). The presence of nasal eosinophils is of value in distinguishing allergic rhinitis from vasomotor rhinitis, but sputum eosinophils are found in all types of asthma (94). Elevated serum IgE levels are generally seen in allergic individuals (14, 16) although this finding is not diagnostic (20). An interesting report of specific IgE in nasal secretions but not in serum would indicate confined production of IgE at the target organ (95). If this finding is confirmed by others, the value of serum IgE levels may be less meaningful in certain cases. At the present time serum IgE levels are helpful in 2 situations. In those patients having histories which are suggestive but not convincing for IgE-mediated disease, a high level would make it reasonable to continue the evaluation for specific allergies. In the second situation, patients who think or have been told that they have allergies but whose histories are inconsistent with IgE-mediated disease may be reassured that their symptoms are not allergic if IgE levels are normal.

Other laboratory tests used in diagnosing allergic diseases are less commonly used by the non-allergist, but a familiarity with the tests will allow more objective assessment as well as better care of the patient (96). Skin tests are commonly used by allergists to diagnose specific allergies. The purpose of skin testing is to identify specific antigens which may contribute to a patient's symptomatology.

The immunologic basis for skin testing has been presented. Antigen specific IgE attaches to skin fixed mast cells, where encounter with the appropriate antigen injected into the skin causes immune release of mediators and subsequent wheal and flare formation. This reaction is seen 15-20 minutes after the antigen is introduced and is sensitive to antibody concentrations in the order of 0.25 ng/ml (97). There are two basic types of skin tests: one in which antigen is placed on the skin and the skin is then scratched and the other in which antigen is injected interdermally.

There are certain basic requirements which should be considered in doing this type of testing in which the interpretation is subjective. A negative control of diluent should be used to insure against false positive reactions to preservatives or dermographia (98-100). Similarly, a positive control of histamine (0.1 mg/ml) should be used to avoid poor skin reactivity or false negative reactions caused by antihistamines. The use of these controls allows for objective positive and negative reactions with which to compare antigen reactions (101). There are other significant possible errors in interpretation of skin tests. The extracts used in skin testing have not to date been well characterized or standardized (102), and log differences in potency have been documented in commercial extracts (103).

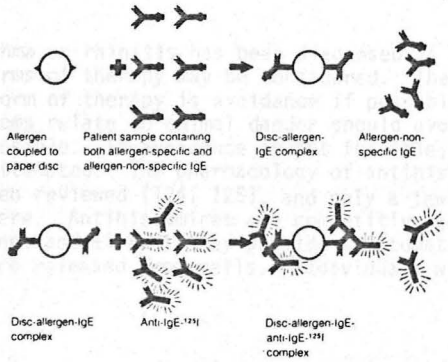
Furthermore, patients with no symptoms or evidence of allergies have been shown to respond to antigen in sufficiently high concentrations. Lindblad and Farr showed up to 50% reactivity in a population of 100 asymptomatic non-allergic subjects to specific antigens in high concentrations of 100 mg N/ml (104). Other authors using less well defined criteria have found similar positive reactions in asymptomatic individuals (105, 106). In other words, reactions may be called "positive" and certain symptoms attributed to "allergy" if inappropriately high antigen concentrations are employed. This practice has led to valid criticism of physicians and laboratories who abuse skin testing but does not alter the reliability of the procedure when properly used (107).

If appropriately administered in concentrations that do not produce non-specific results, skin tests can accurately determine immunologic responsiveness to specific antigen (104). In a study of 87 hay fever patients, skin test results of increasing concentration up to 10 µg N/ml were compared to histamine release results (108). The latter test is an *in vitro* method of objectively assessing the sensitivity of a patient's basophils to release histamine when challenged with a specific antigen (109). The results of skin testing were quantitatively comparable with the *in vitro* technique in sensitive patients and also correlated with symptom scores in these patients.

Properly administered skin tests have also been shown to correlate well with other diagnostic measures in allergic rhinitis and asthma (108, 110). Thus, skin tests, if properly performed using good quality reagents and if correlated with the history, can be a valuable tool in diagnosing allergic disease. Incorrectly interpreted skin tests may lead to unnecessary concern of allergy in patients and to the expenditure of money and time in treating symptoms which are not actually IgE-mediated.

In addition to skin testing, other methods are available to detect specific IgE antibodies. The RAST (radioallergosorbent test) is an in vitro means of measuring antigen specific serum IgE levels (111). The basic principle of the RAST is diagrammed in Figure IV. The allergen of interest is coupled to solid phase carriers. These carriers are then incubated with the patient's serum allowing allergen specific IgE antibodies an opportunity to bind to allergen on the carrier. The carriers are then washed removing any non-specific antibodies. Radioactive labeled antibodies to human IgE are added to the washed complex after which the tubes are again incubated. The non-bound radiolabeled antibody is then washed away, and the tubes counted to determine amount of specific IgE antibody in the patient's serum. Measurements of antigen specific IgE using RAST correlate well with skin tests and antigen challenge tests (108, 110). This test has several advantages: It requires only serum, it can be used for patients having dermographism or other skin disorders, and it can determine sensitivity to antigen that would be hazardous to use in skin testing. The primary disadvantages are cost and limited availability of antigens at present. Because it requires the use of radiolabeled antibody and is subject to variations in techniques, the test should be done by experienced technicians who standardize the procedure and perform it regularly. At this time serum for RAST should be processed by Pharmacia Diagnostics* who developed the test. The immediate applicability of this test is for allergen standardization although it may be used more for diagnostic purposes as purified antigens become available and less expensive (112).

FIGURE IV



*Pharmacia Laboratories, Inc., 800 Centennial Avenue, Piscataway, New Jersey 08854

Other techniques such as titration testing, provocation testing, and leukocyte cytotoxicity are of questionable scientific value but will be discussed for completeness. Titration testing as introduced by Phillips (113) and popularized by Rinkel (114-117) is based on the concept that an "optimal" treatment dose of antigen is related to the size of wheal formed when the patient is tested. If an initial test is negative, sequential 5-fold increments in concentration are tested until a concentration is reached (1:00 weight/volume) which has been shown to cause non-specific reactions in asymptomatic people (104). The rationale for using this "Rinkel" system to determine optimal or maximal dose of antigens for subsequent therapy is not founded on known immunologic principles. The support of its effectiveness is based on descriptive case reports rather than controlled studies (118).

Intracutaneous or sublingual provocation testing are similarly of questionable scientific merit. These tests are based on the elicitation of symptoms (headache, nasal symptoms, chest tightness, ear reactions, gastrointestinal reactions, fatigue, chilling, drowsiness, skin eruption or itching) after intracutaneous injection or sublingual administration of the antigen in question. These procedures have never been subjected to a well controlled study, and evaluation remains anecdotal (119, 120).

The leukocyte cytotoxicity test is applied mainly to "food allergy". It is performed by mixing the patient's leukocytes and serum on a slide with dried antigen. Cells are observed up to 2 hours for changes in physical characteristics (121). The mechanism of action has not been determined, and the test is performed without knowledge of physiological conditions. Two recent controlled studies have evaluated leukocyte cytotoxicity testing. Although results were reproducible, there was a false positive rate of 70% in allergic individuals (122). Furthermore, there was a high false negative rate in patients who reproducibly experienced symptoms after double-blind food challenge (123).

Treatment

If asthma or rhinitis has been diagnosed as allergic, certain specific forms of therapy may be considered. The most logical and effective form of therapy is avoidance if possible. Individuals whose symptoms relate to animal dander should avoid these animals whenever possible. If avoidance is not feasible, medical therapy should be attempted. The pharmacology of antihistamines has recently been reviewed (124, 125), and only a few points will be mentioned here. Antihistamines are competitive antagonists for histamine, and at best they provide symptomatic relief after mediators are released from cells. Individuals will respond

differently to the various classes of antihistamines, and a thorough trial should be undertaken before they are deemed ineffective. Antihistamines may also be used effectively in asthmatics with appropriate caution and adequate hydration, and there are reports of bronchodilation with antihistamines (126).

TABLE V

ANTIHISTAMINES

Class	Generic Name	Trade Name
Ethanolamine	Diphenhydramine	Benedryl
Ethylenediamine	Tripelennamine	Pyrabenzamine
Alkylamine	Chlorpheniramine	Chlor-Trimeton
Piperazine	Hydroxyzine	Atarax
Phenothiazine	Promethazine	Phenegran
Miscellaneous	Cyproheptadine	Periactin

Antihistamines do not inhibit mediator release and are, therefore, only effective in inhibiting the action of histamine. A newer drug, cromolyn sodium, may avoid the effect of all mediators by blocking their release (127). Cromolyn has been shown in double-blind trials to be effective in both allergic asthma (128, 129) and allergic rhinitis (130, 131). It has been used with minimal side effects and appears to be a logical choice in allergic asthma in addition to conventional therapy with theophylline and adrenergic agents. Cromolyn has not yet been approved in this country for use in allergic rhinitis or allergic conjunctivitis for which it may also be of benefit (132).

Another inhaled medication recently made available for asthma but not yet approved for rhinitis, is beclomethasone. This drug is highly effective topically and does not suppress adrenal function when used in asthma or hay fever (133, 134). The use of beclomethasone in asthma was recently described at these Grand Rounds (135), and only allergic rhinitis will now be considered.

In a double-blind crossover study of 29 patients having hay fever by history and skin test, intranasal beclomethasone (50 µg/nostril qid) was compared to placebo (136). Efficacy of treatment was based on daily symptom scores, use of concomitant medication, and subjective preference of the patients for the two week trial for each preparation. Virtually no effect was noted in eye symptoms or the use of eye drops with the active drug, but both mean symptom scores (1.6 vs. 4.2) and antihistamine use (26 tablets vs. 214 tablets) were lower in the active drug periods compared to placebo periods. Twenty-five of the 29 patients chose the active drug as being more effective whereas 2 preferred placebo. Other double-blind trials, including some measuring nasal airways resistance (137, 138),

have indicated efficacy of the drug in allergic rhinitis. Doses lower than 400/µg/day are less effective in controlling nasal symptoms (139), and follow up of 16 patients using up to 400 µg of the drug daily for one year showed no atrophy or histologic chances in nasal epithelium (138).

A final form of therapy for allergic asthma and hay fever is the specific injection therapy first introduced over 50 years ago. This form of therapy, variously called desensitization, immunotherapy, hyposensitization or "allergy shots", was first used at a time when controlled clinical trials were not prerequisites. Attempts to determine effectiveness using controlled trials have taken place largely within the past two decades. A number of problems occur in such studies including the means of assessing benefit, form of placebo, and natural variability of the disease itself (140). These problems are seldom entirely overcome and criticisms of study design and particularly measurements of efficacy of treatment can be raised in all trials of immunotherapy for asthma (141-144). Even if one considers that immunotherapy is efficacious in the treatment of allergic asthma, one must recall that only about 50% of asthmatics have any allergic component to their disease (82). In most of these patients, asthma is triggered by other mechanisms as well as allergy, and other forms of therapy such as theophylline would be required anyway. Injection therapy may work in asthma, but it should not be considered before medical therapy is attempted. In allergic rhinitis the situation is somewhat different than in asthma, as there have been well designed controlled studies documenting effectiveness of therapy (145, 146). The pros and cons of injection therapy have been reviewed (147), and a complete discussion is beyond the scope of this paper.

At the present time certain guidelines regarding specific immunotherapy can be drawn. Only patients having an immunologic basis for their symptoms would be expected to benefit beyond the established placebo effect (141). Immunotherapy for rhinitis has been shown to be effective if properly administered to carefully selected patients. Such therapy is not without potential hazards, and other forms of medical treatment should probably be attempted first unless contraindications exist. As new and perhaps more effective forms of immunotherapy become available, this form of therapy may play a greater role in treatment of allergic disease (148, 149). Until that time, however, assessment of the patient with asthma or rhinitis should be completed, and immunotherapy should be reserved for those patients clearly shown to have an allergic basis for symptoms resistant to other therapy.

The immunologic effects of immunotherapy have been investigated to determine its mode of action. The first change seen is an increase of serum IgG antibodies directed against the antigen being used in therapy (150, 151). These IgG antibodies are felt to act

as blocking antibodies, since they combine with the offending antigen before it can reach cell-fixed IgE molecules. Clinical improvement has been shown to correlate with levels of IgG blocking antibodies (152). With prolonged therapy, a drop in antigen specific IgE levels can be demonstrated (153), and leukocyte sensitivity for histamine release to the antigen is decreased (154, 155). These latter changes may explain the long-term beneficial effects of immunotherapy given at intervals as great as 6 weeks (156).

In summary, allergic asthma and allergic rhinitis may be treated with the same drugs as used for asthma or rhinitis of other etiologies. If specific therapy is aimed at the allergic component, potential dangers, time, cost, and inconvenience of immunotherapy must be weighed against potential benefits in symptom relief for the patient.

URTICARIA

Urticaria is a common disorder for which medical attention may not be sought, and hospitalization is seldom necessary. It is therefore difficult to determine precise incidence and prevalence rates, but a survey of 1,424 college students revealed that 15.7 percent had had at least one episode of urticaria (157). Of 1,000 consecutive patients attending the Palo Alto Medical Clinics, 11.8 percent had had urticaria (158). In 1972, the prevalence of urticaria in 36,475 people surveyed in Sweden was approximately 0.11% in males and 0.14% in females (159). The age group with the greatest incidence of acute urticaria was found to be 21-33 years, and the average age of onset of chronic urticaria was 35 years (157).

Urticaria, like asthma and hay fever, was considered to be a neurosis until the 1930's when an allergic mechanism was described for some cases (160). Unfortunately, the opinion that urticaria is usually allergic in origin has persisted to some extent to the present day. The multiple causes of urticaria and standard diagnostic steps have been reviewed (161-164), and only certain points relating to urticaria and allergy need be made. Of 554 cases of urticaria seen over a 12 year period, 17 (3.1%) were felt to be allergic in etiology (165). Furthermore, it was shown that in chronic urticaria there was not an increased prevalence of histories of allergy when compared to the normal population. One must therefore consider urticaria to be a disease which may involve the same mediators as allergic reactions, but its underlying pathogenesis is not allergic in most cases.

Diagnosis

The diagnosis of urticaria is based on history or the physical finding of cutaneous elevations which may be smooth or irregular in outline and are generally pruritic. A careful history should be taken to determine the etiology of urticaria, and special attention should be paid to foods, medicines, and contactants such as soaps and perfumes.

Laboratory tests to determine an allergic etiology are generally unrevealing. Patients with chronic urticaria generally have normal IgE levels (18), and random skin testing in patients whose history does not clearly suggest an allergic etiology is futile (166). Skin testing for foods is unreliable in itself, but may be used to help design an avoidance diet as a therapeutic test.

Many foods, including nuts, peanuts, fish, and shellfish cause acute IgE-mediated urticaria (167) while others, such as tomatoes and strawberries, act as direct histamine releasers (168). The patient is usually aware of acute urticaria associated with specific foods, and skin tests are not indicated. Dyes and preservatives, such as tartrazine (FD&C Yellow #5) and benzoic acid derivatives are commonly being used in foods. These additives can cause urticaria and their wide distribution in foods makes the association and diagnosis difficult. The mechanism of this urticaria is unclear and skin tests are not useful. Although an allergist or dermatologist may help in elucidating inciting factors in urticaria, one should not anticipate that skin testing will be generally helpful. Skin test results should never be considered diagnostic without corroborative history or trial of antigen avoidance.

Treatment

Fortunately, most cases of urticaria improve, and symptomatic relief from antihistamines is the only therapy required. As is true in hay fever, some antihistamine classes may be more effective than others. Sympathomimetics have occasionally been used, and corticosteroids should be reserved for intractable chronic urticaria. A few poorly documented cases of urticaria due to inhalants such as pollens and molds have been reported (169, 170). These rare instances may respond to immunotherapy, but there is no proof of efficacy, and at this time immunotherapy cannot be recommended for any urticaria.

INSECT STING ALLERGY

Reactions to insect stings vary in severity depending in part on the immunologic status of the individual. Of the estimated millions of people envenomized by arthropods each year in this country, approximately 25,000 have severe reactions, and approximately 30 die (171). Deaths from Hymenoptera, i. e. bees, wasps, yellow jackets, hornets, and ants have been surveyed through death certificates over the ten year period from 1950 to 1959 (172). A total of 229 such fatalities occurred with 203 (89%) reported in individuals over 30 years old. The fact that the highest number of deaths [29] was reported from Texas is due in part to the size of the state, but it also reflects the higher proportion of venomous arthropods in the southern United States. Over the past 20 years two imported species of fire ants have spread throughout the Gulf Coast area into extreme south Florida and south central Texas (173). The presence of these insects may increase the number of fatalities in this part of the country since they cause generalized and anaphylactic reactions (174).

Allergy cannot be implicated in all reactions to insect stings even though the symptoms following a normal sting may be similar to an "allergic reaction". A typical reaction to a winged Hymenoptera sting in a non-allergic individual consists of initial pain and the subsequent appearance of a wheal and erythematous flare at the site of the sting. The swelling may progress and be associated with pruritis, but signs and symptoms generally resolve within 4-6 hours. In contrast, the reaction to a fire ant sting progresses beyond the wheal to a vesicle and then pustule, and it takes 3-8 days to resolve.

Larger local reactions than these "normal" reactions are associated with insect allergy in about 50% of cases (175). Unusual insect sting reactions, including manifestations of neurological disease (176-178), renal disease (179, 180), or myocardial disease (181, 182), may result from immune mechanisms, but the association is not uniform (183). Systemic reactions consisting of diffuse erythema and pruritis; urticaria or angio-edema; respiratory difficulty with wheezing or laryngeal edema; abdominal pain with nausea, vomiting or diarrhea; and anaphylaxis are all associated with IgE-mediated hypersensitivity (184).

Diagnosis

The diagnosis of insect sting allergy may be made in one of three ways: 1) history of a systemic reaction, 2) finding specific IgE antibodies, or 3) intentional insect sting challenge. The last method is used only under controlled observation in experimental study of efficacy of therapy and will not be discussed further.

Past histories of patients allergic to insects are only positive for other allergic diseases in about half of the cases and are therefore not valuable in diagnosis (185). A history of any systemic reaction or anaphylaxis following an insect sting should be accepted as diagnostic, and the patient should be treated accordingly.

Until recently it was only possible to diagnose Hymenoptera sensitivity by history. Uncontrolled and retrospective studies led to the belief that "whole body extract", comprised of protein constituents of the entire insect body, could be employed in the diagnosis of insect allergy (186, 187). Controlled studies, however, showed that these whole body extracts did not distinguish sensitive individuals from normals and gave up to 18% false negative reactions (188, 189). In contrast to methods using whole body extract, the determination of IgE antibodies directed against venom or venom constituents is highly specific in discriminating between sensitive and normal individuals (190). Skin testing (189, 190), RAST determination (175), and histamine release (184) using venom as the antigen correlate well with each other and with a history of insect sensitivity. The major antigenic components of venoms are presently being studied and provide hope for more accurate and safe means of diagnosis (191, 192).

Treatment

Having made the diagnosis of insect sting hypersensitivity, the physician should educate the patient as to potential dangers, measures of insect avoidance, and treatment. Otherwise, patients who have had severe reactions may alter their life styles significantly or live in constant fear of a recurrent episode. As with other allergic disorders, avoidance of the antigen is the optimal treatment. Patients should be given recommendations as to how they may go about their normal activities and minimize the likelihood of being stung (193).

Since the majority of fatal reactions occur within the first hour after a sting, the patient should be given instructions on treatment of possible anaphylaxis (172). Two methods are commonly employed: 1) self-administered adrenalin injections as found in insect sting kits or 2) aerosolized epinephrine from an oral inhaler (Medihaler-Epi). The patient should be familiar with local medical facilities and medical aid units, and he should seek medical evaluation following a sting. A medical alert bracelet should probably be worn by any patient known to be allergic to insect stings.

Those patients diagnosed as having insect sting allergy are generally treated with immunotherapy-type regimens consisting of

frequent injections of increasing concentrations of whole body extract. The rationale for this method of treatment is based on anecdotal evaluation of cases treated with whole body extract (194, 195). Only recently have studies been carried out to examine the immunologic parameters felt to be of importance in immunotherapy (196). Such studies suggest that whole body extracts are immunologically ineffective. Furthermore, cases of treatment failures using whole body extract have been reported (197, 198), and in one case subsequent treatment using venom for immunotherapy proved effective in preventing anaphylaxis (199). A single-blind well controlled study using insect sting prior to and after therapy has shown venom immunotherapy to be protective and whole body extract to be no different than placebo (200). In view of these data, it is not reasonable at this time to recommend whole body extract treatment because of the potential risk of injection therapy and the false-security which may accompany this "treatment". When the proper antigens become widely available, immunotherapy holds great promise as a preventitive form of treatment in this potentially fatal condition.

Insect sting allergy is, therefore, best diagnosed by history and treated by proper education of the patient in avoidance and initial therapy. As the relevant antigens become generally available, both diagnosis and treatment should be considerably improved.

Significant advances have been made in the understanding of allergic diseases in the past decade. As the immunologic mechanisms of allergy are better understood, improved specific therapy can be expected. At the present time sufficient data are available to allow the physician to rationally advise a patient as to the need for allergy evaluation, the proper type of investigations to pursue, and the therapeutic program most likely to be beneficial.

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