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Position paper

A revised nomenclature for allergy

An EAACI position statement from the EAACI nomenclature task force

This report has been prepared by an EAACI task force representing the five EAACI Sections and the EAACI Executive Committee composed of specialists that reflect the broad opinion on allergy expressed by various clinical and basic specialties dealing with allergy. The aim of this report is to propose a revised nomenclature for allergic and related reactions that can be used independently of target organ or patient age group. The nomenclature is based on the present knowledge of the mechanisms which initiate and mediate allergic reactions. However, the intention has not been to revise the nomenclature of nonallergic hypersensitivity.

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Introduction

Allergic reactions can express themselves in many different organs and in any age group. Allergic diseases have a significant effect on the emotional and social health of patients and their families. The high prevalence of allergic diseases and improved diagnostic procedures and treatments have had a great impact on the provision of medical care to allergic patients. Doctors in all community- or hospital-based specialties are faced with patients who have, or suspect they have, an allergic disorder underlying their medical presentations. To avoid being misunderstood by patients and colleagues,

physicians should adopt very clear designations of the allergic disorders and adhere to this nomenclature in their professional and public communications.

In the early 1920s, Coca & Cooke (20) introduced the term "atopy" to designate some phenomena of hypersensitiveness in man. They considered "atopy" to be all of the following:

1) hereditary
2) limited to a small group of patients
3) different from "anaphylaxis" in referring to a lack of protection, and from "allergy" meaning an altered reactivity
4) "qualitatively an abnormal response" occurring only in particular individuals (atopics)
5) clinically characterized by hay fever and bronchial asthma
6) associated with immediate-type (wheal-and-flare) skin reactions.

At this time, they were evidently unaware of the work that Prausnitz & Küstner (73) published in 1921 about the passive transfer of immediate hypersensitivity in man by serum. In their original definition of "atopy", Coca & Cooke included only allergic rhinitis and bronchial asthma. Wise & Sulzberger proposed the term "atopic dermatitis" to denote "confusing types of localised and generalised lichenification, generalised neurodermatitis or manifestation of atopy" (93).

Coca and Grove investigated atopy further (21), throwing light on certain important aspects but reaching some curious conclusions (70). They reported the presence of heat-labile "bodies", which they called "reagins" by virtue of their similarity in this respect to the heat-labile reagins (complement) of the Wassermann reaction. They concluded that it is "advisable for the present to avoid the term 'antibodies' ", because there was "no evidence that these bodies appeared as the result of immunological stimulation".

In the following decades, many population studies, particularly those by Schwartz (81) and by Schnyder (80), and follow-up studies of children first seen with infantile eczema (60, 83) demonstrated the classic atopic diseases and the close association of asthma, hay fever, perennial rhinitis, atopic dermatitis, and food allergies in such infants. It was later shown that serum IgE levels (42) are increased, on average, in "atopic dermatitis" (46, 64), and that this serum IgE increase is related to the increase of IgE specific against several environmental allergens (35, 96, 107). However, it was also observed that in moderate or mild forms, and even in a few cases of severe "atopic dermatitis" without coexistent asthma or rhinitis, the IgE values may lie in the normal range (79, 106).

The field of allergy has developed rapidly during the last 50 years. Knowledge about immunologic mechanisms and pharmacologic effects has improved our understanding (61). The classical nomenclature for allergic reactions introduced by Gell & Coombs in 1968 (25) (the familiar types I–IV hypersensitivities) has been useful. However, too much emphasis has been given to the supposedly distinct and mutually exclusive roles of antibodies and immunocompetent cells. This dichotomy is not consistent with our present knowledge of the dynamic immune response, as orchestrated by dendritic cells and T helper cells, and mediated by effector cells of several types, antibodies, chemokines, and cytokines. The last two groups have been mostly identified since Gell & Coombs produced their classification of allergic reactions. Therefore, a revised nomenclature is much needed.

In 1968, the WHO International Reference Center for Immunoglobulins decided that enough critical data were available to announce the presence of a fifth immunoglobulin isotype, IgE (12). The classical "reaginic activity" could be linked to IgE (41, 82). Whether other types of tissue-sensitizing activity present in animals, such as short-term sensitizing antibody (67), occur also in man is still not settled.

In the mid-1970s, classical, IgE-mediated allergic reactions to inhalant allergens were termed by Pepys "atopic allergy" (69). The term "atopic" is today used synonymously with "IgE-mediated" by most doctors and scientists involved in allergy. However, others, especially pediatricians and dermatologists, also consider "atopy" a constitutional trait. They find "atopy" to be a clinically useful term since IgE-mediated allergy is common in children and young adults, and often runs in families.

Typical allergic symptoms include asthma, rhinoconjunctivitis, gastrointestinal symptoms, and characteristic skin lesions, generally referred to as "atopic diseases" (for the new nomenclature of some of these diseases, see below). Typically, an atopic patient develops a spectrum of "atopic diseases" with age, sometimes referred to as "the atopic march". During the first years, gastrointestinal and eczematous skin symptoms, often caused by food allergens, predominate. Asthma and rhinitis to inhalant allergens develop later.

Atopy is inherited. For example, the risk of a child developing an IgE-mediated allergy is 40–60% if both parents are atopic. This risk used to be 5–10% if neither parent was atopic (49), but the percentage is increasing. In "highly atopic" children, IgE sensitization and atopic diseases develop early in life. Associations between several gene loci and asthma, high IgE levels, and other conditions have been reported (10, 52). However, so far, no specific genetic markers for atopy have been identified. The most likely explanation is that atopy is a polygenic disorder.

Some individuals that cannot be described as atopic escape sensitization to common allergens in childhood and adolescence, but develop IgE-mediated allergy later in life when exposed to high doses of allergen, often together with some adjuvant, such as tobacco smoke

(66). This situation is illustrated by many cases of occupational allergy (74), as to laboratory animals such as mice (90), enzymes such as α-amylase (11, 101), *Bacillus subtilis* protease (95), and houseplants such as *Ficus benjamina* (7, 78). There are some indications that, in addition to the IgE trait, atopy includes some kind of target organ sensitivity, as shown, for example, by the adverse effect of exercise in some patients, the finding of nonallergen-specific bronchial hyperreactivity in patients with allergic asthma, and the disturbed barrier function of atopic skin.

Without a genetic marker, the atopic individual cannot be identified before developing allergen-specific IgE sensitization. However, it is not widely appreciated by nonspecialists in allergic disease that the presence of IgE antibodies does not necessarily mean clinically active disease, although such antibodies represent a risk in the appropriate circumstances; for example, allergen exposure and a concomitant promoter such as infection or exercise. In addition, the presence of IgE antibodies may have a predictive value. Several groups have found that even without symptoms, the presence of IgE antibodies to hen's egg white in infants predicts the development of atopic symptoms before 7–10 years of age (31, 62).

In a typical case of atopy, the dose of inhalant allergen necessary to induce sensitization and symptoms is extremely low. Estimates based on pollen counts indicate an annual dose of a few micrograms (57), and sensitization to cat allergen Fel d 1 can occur (88) at levels around 25 ng/g of dust. Levels of animal allergens in the air of public buildings such as schools have been found to be in the ng/m^3 range, i.e., about the same level of exposure as to pollens.

IgE-mediated mechanisms are often involved in allergies to insect venom (58, 59), usually in the same frequency as in individuals that cannot be described as atopic, and to certain drugs (87). An IgE involvement, with markedly raised serum levels of IgE and the presence of specific IgE antibodies, has been detected in helminth infestations (36, 43, 77), and it is thought that the beneficial function of IgE is related to our defense against helminth parasites. However, more studies are needed to explain the entire possible range of beneficial functions of IgE.

The IgE antibody response may represent a remarkably large proportion of the IgE pool; in some cases of allergic rhinitis, as much as 50–60% of IgE in a serum sample can be recovered as antibody to the pollen allergen (44). However, in other cases, e.g., IgE-mediated "atopic" dermatitis, the polyclonal production is considerable, and the IgE antibody can represent as little as 2% or less of the total IgE production (99, 106).

According to the currently favored hypothesis of how the immune system is controlled, there is a balance between Th_1 and Th_2 helper cells. Th_1 cells promote immune protection against bacterial and viral infections, and Th_2 cells protect the body from helminth infestations and perhaps also maintain pregnancy (37). It should be remembered that cells and mediators of the immune system are also found in biopsies of inflammatory sites, as immunologic reactions are of course involved in mediating and initiating inflammatory as well as allergic responses. Inflammatory reactions, especially the Th_2-driven ones, are also involved in the immune defense, as against helminths, and eosinophilia can be stimulated by bacterial and viral infections. Various types of inflammatory reactions, especially eosinophilic inflammation, are of fundamental importance in allergic reactions. Thus, the presence in the tissue or circulation of increased numbers of eosinophils, IL-5, or even polyclonal IgE without significant antibody activity does not necessarily indicate an allergic reaction. On the other hand, the presence of IgE antibodies to classical allergens is always the sign of a potentially significant allergic reaction.

The same cytokines and interleukins of the Th_2 system are involved in both the beneficial and harmful effects. In addition, various substances can act as adjuvants and polyclonal IgE stimulants. One example is the enterotoxins of *Staphylococcus aureus*, sometimes referred to as "superantigens", that seem to be capable of stimulating eosinophilic inflammation and a polyclonal IgE response in "atopic dermatitis" (53) and also in typically nonallergic nasal polyps (8). Other examples are cigarette smoke (26), cytomegalovirus (CMV) infection (63), and graft versus host disease (GVHD) (76). Similarly, the microscopic and immunologic appearance of the bronchial mucosa is similar in the biopsies of both classical allergic asthma (previously also referred to as extrinsic or exogenous asthma) and nonallergic asthma (previously referred to as intrinsic or endogenous asthma) (16, 38). The same is true also of allergic and nonallergic rhinitis (6) and different kinds of eczema/dermatitis (5, 51, 79, 89).

In the following paragraphs, we propose that "hypersensitivity" be used as an umbrella term (see below), and that the term "allergy" be reserved for clinical reactions in which an immunologic mechanism is proven or strongly implicated. The term "atopy", discussed above, has also been revised. We propose that the term "atopy" be used to describe a familial or personal tendency to develop allergen-specific IgE on exposure to environmental allergens, and to suffer typical allergic symptoms.

1 Hypersensitivity

There has been a tendency during the last couple of decades to use the word "allergy" to describe not only allergy as defined below but all kinds of unexpected reactions in the skin and mucosal surfaces. These include

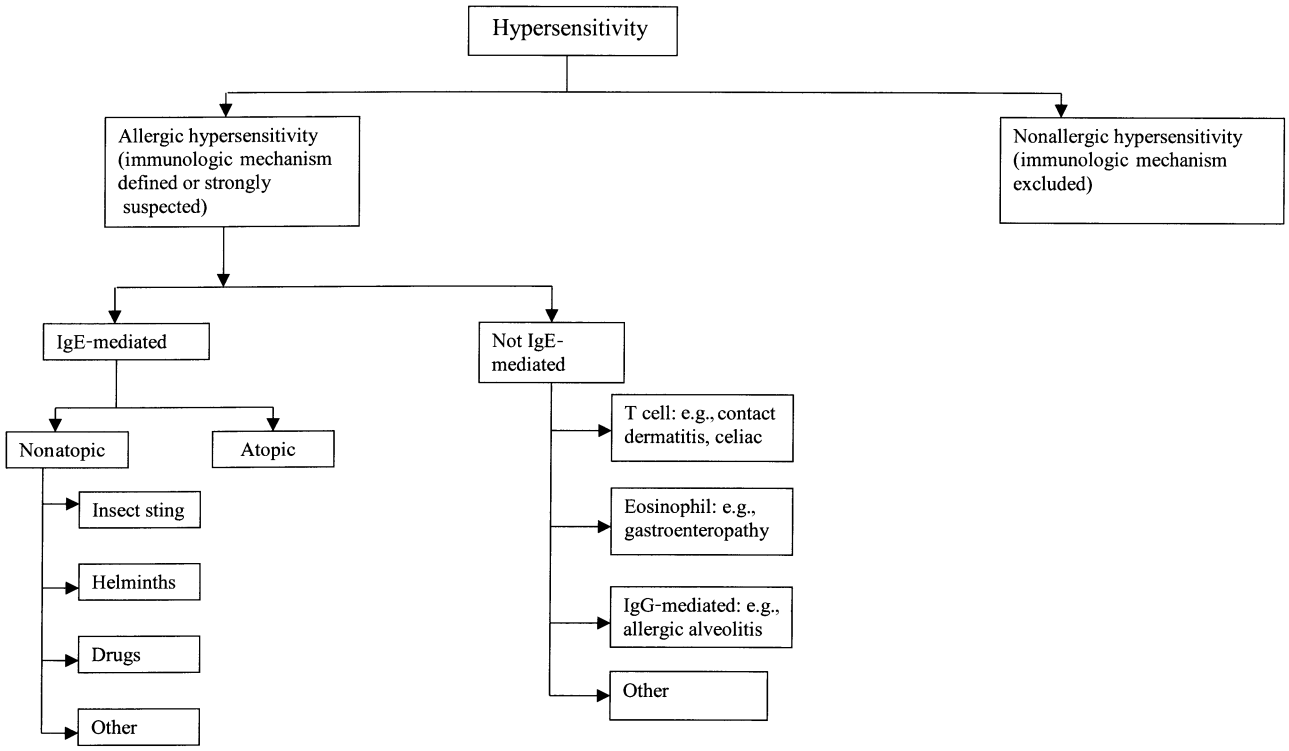

Figure 1.

all kinds of controversial adverse reactions to food and food additives (17, 65), side-effects to drugs, psychological reactions blamed on environmental factors ("allergy to electricity") (54), behavioral disorders, and others.

We propose that the term *hypersensitivity* be used as the "umbrella" term to cover such reactions (Fig. 1), and that its definition should be as follows:

Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects.

This definition does not accommodate classical responses to infection, autoimmunity, or toxic reactions. It is important that the hypersensitivity reaction be reproducible in the sense that there is reasonable evidence from history, examination, or investigation of a link between the symptoms and the environmental factors to which the patients attribute their symptoms. In this context, "reproducible" does not mean, for example, that a food provocation test of a patient in the doctor's office must be positive at any time. The old term "idiosyncrasy" is no longer needed. Furthermore, hypersensitivity must be distinguished from hyperreactivity, which is an exaggerated normal response to a stimulus.

As a consequence of this stringent definition of hypersensitivity, many entities within the field of "environmental medicine", such as "total drug sensitivity" and "multiple chemical sensitivity" (27), as well as reactions attributed to amalgam in tooth fillings (55) and electromagnetic waves, should not be called hypersensitivity.

We propose to use the term *nonallergic hypersensitivity* when immunologic mechanisms cannot be proven, as in hypersensitivity to aspirin (84). The term "pseudoallergy", introduced many years ago (22) and still occasionally used in some European countries, should be abandoned.

The term "nonallergic hypersensitivity" embraces many different disorders. However, it is not within the remit of this group to classify these entities.

2 Atopy

We propose that the definition of atopy should be as follows:

Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis.

We propose that the terms atopy and atopic be reserved to describe this clinical trait and predisposition, and not be used to describe diseases. The first manifestations of atopy in a child are often "allergic" symptoms, such as diarrhea, wheezing, and skin rashes, and only later can the responsible IgE antibody be

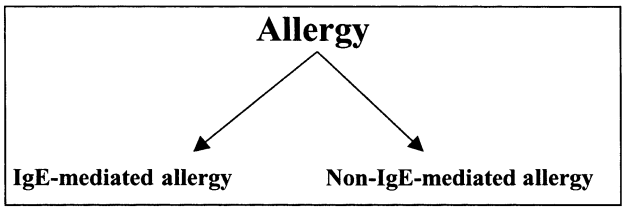

Figure 2.

detected. The term atopy should be used with caution until IgE sensitization can be documented. Allergic symptoms in a typical atopic individual may be referred to as atopic, as in atopic asthma. However, in general, IgE-mediated asthma should not be called "atopic asthma", and the same applies to the other clinical manifestations. Nor can a positive skin prick test or the presence of IgE antibody per se be a criterion for atopy. Such patients should be referred to as "skin prick test positive" and "IgE sensitized", respectively.

3.1 Allergy

Allergy is a hypersensitivity reaction initiated by immunologic mechanisms.

Allergy can be antibody- or cell-mediated. In most patients, the antibody typically responsible for an allergic reaction belongs to the IgE isotype and these patients may be said to suffer from *IgE-mediated allergy* (Fig. 2). It must be noted that not all IgE-associated allergic reactions occur in atopic subjects; see the disease classifications below.

In *non-IgE-mediated allergy*, the antibody may belong to the IgG isotype, as in anaphylaxis due to immune complexes containing dextran (32) and the classical, now rare, serum sickness previously referred to as a type III reaction (25), whereas both IgE and IgG antibodies are found in allergic bronchopulmonary aspergillosis (ABPA) (68).

Inhalation of large amounts of protein, as in mold, grain dust, etc., stimulates the immune system to produce antibodies mainly of the IgG, IgA, and IgM isotype. The serum concentration is often high enough to allow detection of the antibody, historically termed "precipitin", as a precipitate in gel when allowed to react with the corresponding antigen. There is a relation between degree of exposure and antibody concentration. Similarly, the presence in serum of IgA, IgM, and especially IgG antibodies, as a result of exposure but without any obvious pathogenic role, has also been reported to food antigens, such as those of cow's milk and hen's egg (39). In the same way, antigen-specific lymphocytes can often be found by using the antigen-specific lymphocyte stimulation test (50, 71).

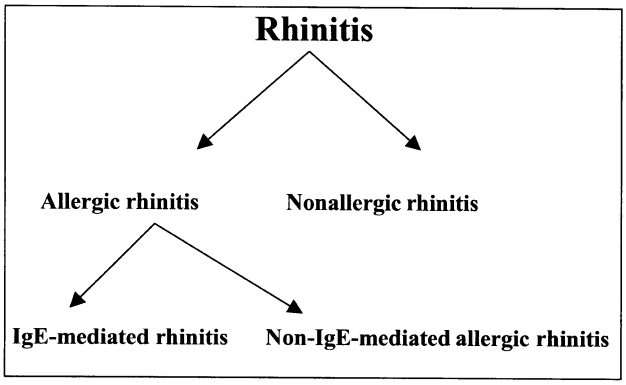

Figure 3.

Some individuals with high IgG antibody levels as a result of chronic inhalation of large amounts of certain protein-containing material, such as *Actinomyces* and molds (farmer's lung) and bird droppings (pigeon breeder's disease), may exhibit symptoms from the airways, often referred to as "alveolitis", upon exposure. We propose that the term *allergic alveolitis* be used for such diseases.

Allergy can also be cell-mediated, as in allergic contact dermatitis, in which immunologically sensitized lymphocytes play a major role. Similar immunologic mechanisms seem to be important in celiac disease (29) and in non-IgE-associated "atopic dermatitis/eczema" (see below). Therefore, we propose that non-IgE-mediated allergic reactions be subdivided into those in which the reaction is initiated predominantly by mechanisms associated with allergen-specific antibodies other than IgE, and those in which a cellular response is predominant.

3.2 Allergens

Antigens stimulating hypersensitivity mediated by an immunologic mechanism (defined above as "allergy") are referred to as *allergens*. Most allergens reacting with IgE and IgG antibodies are proteins, often with carbohydrate side chains (1, 56), but in certain circumstances pure carbohydrates have been considered to be allergens (2, 24). In rare instances, a low-molecular-weight chemical, such as isocyanates and anhydrides acting as haptens, is still referred to as an allergen for IgE antibodies (47). Certain drugs are recognized by T cells in a MHC-restricted way. In the case of allergic contact dermatitis, the classical allergens are low-molecular-weight chemicals, such as chromium, nickel, and formaldehyde, which act as haptens and react with T cells.

Nomenclature of allergic diseases

Classifications of the common allergic diseases are presented below. We have used a similar scheme to

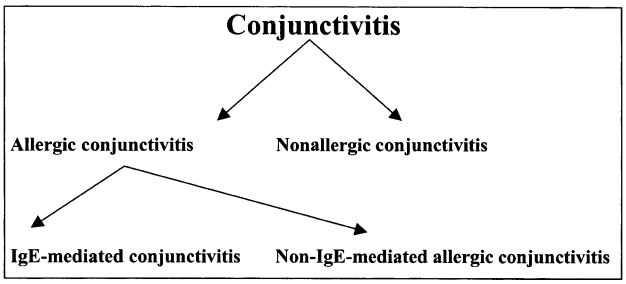

Figure 4.

present each disease to encourage uniform description of these related diseases, often found together in a particular individual.

4 Rhinitis

The symptoms resulting from an immunologically mediated hypersensitivity reaction in the nose should be called *allergic rhinitis* (Fig. 3). If we wish to highlight the role of IgE, the term *IgE-mediated rhinitis* or *IgE-mediated allergic rhinitis* should be used. It is not clear whether non-IgE-mediated forms of allergic rhinitis can be defined further (97). It might be useful to distinguish between subgroups of IgE-mediated rhinitis depending on the duration of the symptoms. The WHO document "Allergic Rhinitis and its Impact on Asthma" (ARIA) recommends that the old terms "seasonal" and "perennial", which are not useful where climatic seasons are perennial, should be replaced by the terms *intermittent* allergic rhinitis and *persistent* allergic rhinitis, respectively. However, in describing symptoms during the pollen season in a case of pollen-induced allergic rhinitis, the old term "seasonal allergic rhinitis" is valid.

All other forms of rhinitis should be subsumed under *nonallergic rhinitis*, which is sometimes referred to as "hyperreflectory rhinopathy", including such entities as aspirin hypersensitivity, infectious reactions, side-effects of systemic drugs, and abuse of topical decongestants. It is not the aim of the present task force to consider the details of the nomenclature for such disorders outside the field of allergy (Fig. 3).

5 Conjunctivitis

Conjunctivitis often accompanies rhinitis. It is therefore logical to use a nomenclature for conjunctivitis that is structured in the same way as for rhinitis. *IgE-mediated conjunctivitis* (Fig. 4), a subgroup of *allergic conjunctivitis*, may be divided into intermittent and persistent allergic conjunctivitis as in the subdivision of allergic rhinitis. Whenever necessary, the term allergic conjunctivitis may be combined with allergic rhinitis, as in *allergic rhinoconjunctivitis*. Conjunctival contact allergy

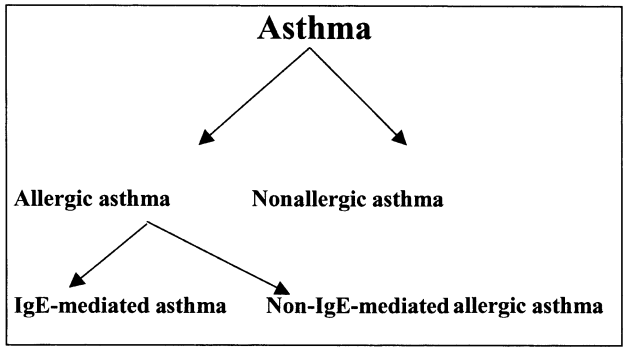

Figure 5.

to eye-drops has been reported (40). It is not clear at the moment whether other non-IgE-mediated forms of allergic conjunctivitis can be defined.

Persistent allergic conjunctivitis is divided into subgroups that have distinct morphologic appearances (4). Both "vernal keratoconjunctivitis" and "atopic keratoconjunctivitis" are in part explained by IgE-mediated reactions and may be classified as subgroups of IgE-mediated conjunctivitis (Fig. 4).

"Atopic keratoconjunctivitis" is the ocular manifestation of "atopic dermatitis", and the term "atopic" is used here in a similar way as in "atopic dermatitis". All other forms of conjunctivitis should be listed under *nonallergic conjunctivitis* and named according to the recommendations of specialists in the field.

6 Asthma

Allergic mechanisms are of importance in about 80% of childhood asthma (3, 28) and in about 40–50% of the adult form (48). We propose to use the term *allergic asthma* (Fig. 5) as the basic term for asthma mediated by immunologic mechanisms. When there are indications of IgE-mediated mechanisms, the term should be *IgE-mediated asthma*. IgE antibodies can initiate both an immediate and a late asthmatic reaction. However, as in other allergic disorders, T-cell-associated reactions seem to be of importance in the late and delayed reactions. Today, it is not still clear whether other forms of allergic asthma can be defined. Other nonimmunologic types of asthma should be called *nonallergic asthma*. The old terms, "extrinsic", "intrinsic", "exogenous", and "endogenous" should no longer be used to distinguish between the allergic and nonallergic subgroups of asthma.

7 Skin diseases

Unlike the respiratory tract, where the symptomatology of allergic diseases is rather uniform, a variety of different diseases with distinctly different pathogenic mechanisms is manifested in the skin. Here we will consider only the most common allergic skin diseases,

namely, urticaria, angioedema, allergic contact eczema/dermatitis, atopic eczema/dermatitis, and exanthematous drug eruptions. Allergic diseases manifesting as purpura or vasculitis, as well as allergic granulomatous skin reactions, will not be discussed.

Since urticaria and angioedema often represent the first symptoms within the spectrum of "anaphylaxis", they will be discussed there.

The terms eczema and dermatitis are used interchangeably in the literature, although some authors prefer to call the more acute cases dermatitis, whereas the term eczema is applied to the more chronic forms. We have not distinguished between eczema and dermatitis in the present discussion.

In the current literature, eczema/dermatitis is subdivided into contact eczema/dermatitis (irritant or allergic), atopic eczema/dermatitis, nummular eczema/dermatitis, and seborrheic eczema/dermatitis. The pathogenesis of nummular and seborrheic eczema/dermatitis is largely unknown. These and other nonallergic skin disorders will not be further discussed.

7.1 The atopic eczema/dermatitis syndrome (AEDS)

Reaching a consensus on the definitions of the dermatologic aspects of allergy has been the most difficult issue for the nomenclature task force. The current term for eczematous hypersensitivity reactions in the skin, analogous to rhinitis in the nose and asthma in the lung, is "atopic eczema/dermatitis". The term "atopic dermatitis" consists of two words to allow definition of one distinct form of eczema/dermatitis (see above). In this designation, the modifier "atopic" has a different meaning (92, 105) than atopy as defined above. However, as Rajka has stated (75), "This... is an unfortunate choice of term, even when it is considered in the light of the definition [of "atopy"]... by Coca in 1953 (19). The flaw lies in the conclusion from recent experience that the disease can no longer be considered a typical atopic disease." However, it is even more confusing that one of the four major classical criteria (30) for the diagnosis of "atopic eczema/dermatitis" is atopy, as defined above. Thus, it is possible to select patients with "atopic eczema/dermatitis" in whom there is no evidence of IgE-associated mechanisms (79, 105). This internal contradiction and inconsistency must be addressed in the near future, however entrenched and familiar the current terminology may be. To describe "atopic eczema/dermatitis" as "extrinsic"/"intrinsic" in analogy with the superseded characterization of asthma would not be in accordance with the revised nomenclature that we propose. In addition, antigen-specific T-cell responses (91) and autoallergic phenomena have been described in the IgE-associated subgroup of the disease (86). Such a case would then incorrectly be classified as "extrinsic", a term which is not appropriate for an autoimmune disorder (Fig. 6).

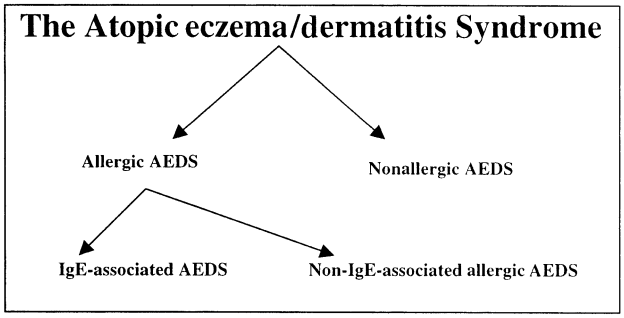

Figure 6.

It has been suggested that early signs and symptoms of the skin can be seen in individuals predisposed to "atopic diseases" long before the disease itself becomes manifest (the so-called stigmata or symptoms of minor criteria) (30, 102). Thus, in current dermatology, "atopy" is a clinical diagnosis, and a patient can be called "atopic" without knowledge of skin prick tests or the presence of IgE antibodies in his serum.

Since the aim of this task force is to harmonize the allergy-relevant definitions in the various fields, we need a new term for "atopic eczema/dermatitis". In some countries (France, Germany, Switzerland, and Austria), the term "neurodermatitis", or "neurodermitis", has been used, mainly by lay people. Other synonyms, such as "diathetic prurigo" (15), "prurigo Besnier" (13), "endogenous eczema", "exudative eczematoid", "asthma-eczema" and many others, are not suitable for international use. A compromise would be to use the term "constitutional eczema" proposed by Wüthrich (98), since it reflects the familial occurrence and the presence of the characteristic signs and symptoms independent of IgE. However, during a transition period, it may be useful to highlight the well-accepted view that "atopic dermatitis" is not one, single disease but rather an aggregation of several diseases with certain clinical characteristics in common (94).

We propose to use the term *atopic eczema/dermatitis syndrome* to describe what is currently referred to as "atopic eczema/dermatitis".

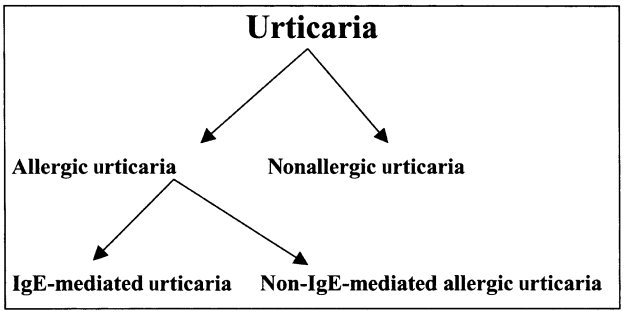

Figure 7.

Allergic AEDS (Fig. 6) would be dominated by the IgE-associated subgroup, i.e., those cases of the present "atopic dermatitis" in which the clinical selection is based on Hanifin & Rajka's criterion, "family history of or simultaneous occurrence of symptoms of atopy" (75). Since this is the only immunologically well-defined subgroup, one should always, when appropriate, use the term *IgE-associated AEDS*. Because less is known about the precise role of IgE antibodies initiating the disease than in other allergic diseases, the word "associated" is provisional. Another subgroup seems to include cell-mediated forms (33). It is characterized by positive atopy patch tests to aero- and food allergens or allergen-specific T cells in the peripheral blood or in skin biopsies, but in the absence of IgE sensitization. The term allergic, *T-cell-associated AEDS* might be appropriate. The term *nonallergic AEDS* should replace the term "intrinsic/cryptogenic variants". In the future, all these subgroups may be better defined, as by immunologic characteristics, in a way similar to the classification of bullous skin disorders on microscopic findings.

7.2 Urticaria

"Acute urticaria" may have a very rapid onset and disappearance and is linked to considerable pruritus. We propose the term *allergic urticaria* to denote urticaria mediated by immunologic mechanisms. When the disease is related to IgE-mediated reactions, the term *IgE-mediated urticaria* should be used (Fig. 7). "Chronic urticaria" should be referred to as *nonallergic urticaria* until proven to be mediated by immunologic mechanisms. Sometimes IgE-mediated urticaria can develop locally after topical contact with the allergen, as on the hands of a latex-allergic individual wearing latex gloves (72, 85) or in a dog-allergic individual licked by a dog. Then the term should be *allergic contact urticaria*, either *IgE-mediated* or *non-IgE-mediated*, and the corresponding, nonimmunologic form should be termed *nonallergic contact urticaria*.

7.3 Contact eczema/dermatitis

The term *contact eczema/dermatitis* describes hypersensitivity reactions in the skin occurring under special circumstances after close contact with low-molecular-weight chemicals or irritants. When these reactions are mediated by immunologic mechanisms, predominantly cellular (Th_1) related, the term should be *allergic contact eczema/dermatitis*. When there is no immune mechanism involved, *irritant/toxic contact eczema/dermatitis* is the best term.

A subgroup of contact eczema/dermatitis, *protein contact eczema/dermatitis*, is probably an IgE-associated reaction due to resorption of proteins through damaged skin. It may be referred to as *allergic protein contact eczema/dermatitis* or *IgE-associated protein contact eczema/dermatitis*. It is usually an occupational disorder, as when caused by exposure to bovine serum proteins in butchers, or to flour in bakery workers when linked to severe AEDS of the hands (34, 103).

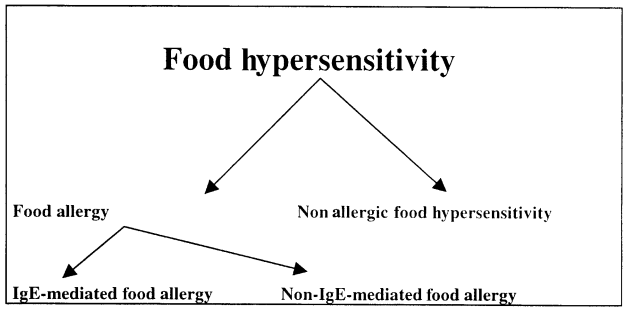

Figure 8.

8 Reactions to food, drugs, and venoms

There are situations in which organ-based classification is not adequate. Certain allergen sources give rise to hypersensitivity reactions that are more difficult to classify by the proposed system. The main reason might be a different multisystem response pattern when an individual is exposed to very high allergen/antigen dosages (milligram to gram) via mucosal membranes, as by food and drugs, or by injection (microgram to milligram), as by Hymenoptera venoms and drugs. Moreover, individuals with a less obvious tendency to mount an IgE antibody response will do this after a large, often repeated high dose of allergen stimulation. The clinical reaction covers a wide range of symptoms, often starting locally and sometimes developing into a general reaction, i.e., anaphylactic shock.

Subjects with rhinitis and asthma due to pollen allergy may have symptoms on oral exposure to often unstable food allergens, which may show structural similarities to pollen allergens. There are several examples of this "oral allergy syndrome" (23, 45, 65), such as reaction to birch pollen and apple or hazelnuts (23, 104) and to mugwort pollen and celeriac or celery

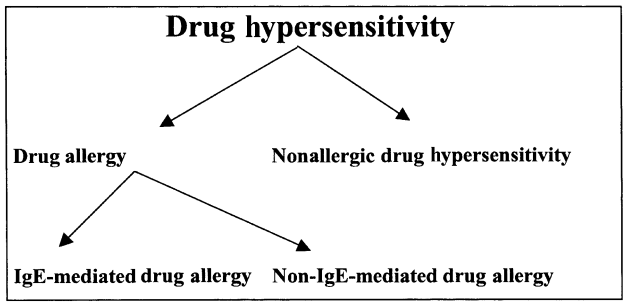

Figure 9.

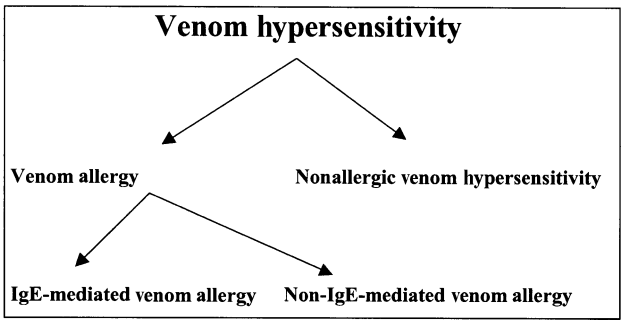

Figure 10.

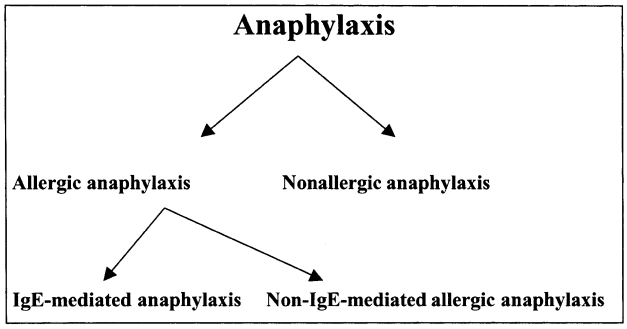

Figure 11.

(9, 100). Therefore, these food allergies can present with symptoms in other organ systems that do not justify a diagnosis of anaphylaxis (see below).

8.1 Food allergy

We propose that an adverse reaction to food should be called *food hypersensitivity* (Fig. 8). When immunologic mechanisms have been demonstrated, the appropriate term is *food allergy*, and, if the role of IgE is highlighted, the term is *IgE-mediated food allergy*. All other reactions, previously sometimes referred to as "food intolerance", should be referred to as *nonallergic food hypersensitivity* (17, 65). Severe, generalized allergic reactions to food can be classified as anaphylaxis (see below).

8.2 Drug allergy

The side-effects of drugs of the type discussed here should be referred to as *drug hypersensitivity* (Fig. 9). When immunologic mechanisms have been shown, either antibody or cell mediated, the reactions should be referred to as *drug allergy*. By adding the adjective *immediate/late* or *delayed*, we can both describe the onset of symptoms and indicate the probable mediating mechanisms, IgE and lymphocytes (71), respectively. If we wish to highlight the role of IgE antibody in a reaction, it may be called *IgE-mediated drug allergy*. All other reactions should be referred to as *nonallergic drug hypersensitivity*. Such reactions may have identifiable associations, such as G6PD deficiency, or unknown mechanisms. A positive intradermal skin test or a weak (<3 mm) skin prick test is not an objective or sufficient measure of an immunologic reaction – for example, compare direct mediator release by certain neuropeptides and basic secretagogues such as compound 48/80 (18) – and should not be accepted as the only evidence for a possible immunologic mechanism.

8.3 Insect sting allergy

As with drugs, individuals stung, for example, by a Hymenoptera insect are exposed to large quantities (58), i.e., several micrograms of major allergens per sting, an amount similar to the annual dose of inhaled pollen allergen. This is probably the reason for almost the same prevalence of atopy among patients with IgE sensitization to venom as in the normal population (14). We propose that any *venom hypersensitivity* reaction (Fig. 10) mediated by immunologic mechanisms be called allergy, as in bee *venom allergy*. To highlight the role of IgE antibody, we may use a term such as *IgE-mediated* bee *venom allergy*. A term such as *nonallergic* bee *venom hypersensitivity* should be used to denote other reactions.

9 Anaphylaxis

The term "anaphylaxis" is applied in various regions and by various physicians to different clinical entities and immunologic mechanisms. Some doctors confine application of the term "anaphylaxis" to reactions in which critical hypotension is evident – "anaphylactic shock" – with an IgE-mediated mechanism. Others extend its application beyond anaphylactic shock to include severe, life-threatening attacks of bronchospasm. Still other clinicians use it to describe any generalized or systemic allergic reactions, even if hypotension and severe bronchospasm are absent. We propose the following broad definition:

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction.

The reaction usually develops gradually, most often starting with itching of the gums/throat, the palms, or the soles, and local urticaria; developing to a multiple organ reaction often dominated by severe asthma; and culminating in hypotension and shock. Hypotension and severe bronchospasm do not have to be present for a reaction to be classified as anaphylaxis.

The term *allergic anaphylaxis* (Fig. 11) should be used when an immunologic mechanism can be shown to be important, as in an IgG immune complex, complement-related, or immune cell-mediated mechanism, or

when the role of IgE is unclear. An anaphylactic reaction mediated by IgE antibodies, such as peanut-induced food anaphylaxis or bee venom-induced anaphylaxis, may be called *IgE-mediated anaphylaxis*. All other situations, which are much less common, should be referred to as *nonallergic anaphylaxis*. The term "anaphylactoid" should not be used.

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