Rostrums

Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003

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The nomenclature proposed in the October 2003 report of the Nomenclature Review Committee of the World Allergy Organization is an update of the European Academy of Allergology and Clinical Immunology Revised Nomenclature for Allergy Position Statement published in 2001. The nomenclature can be used independently of target organ or patient age group and is based on the mechanisms that initiate and mediate allergic reactions. It is assumed that as knowledge about basic causes and mechanisms improves, the nomenclature will need further review. (J Allergy Clin Immunol 2004;113:832-6.)

Key words: *Nomenclature, allergy, hypersensitivity, IgE, atopy, asthma, dermatitis, eczema, rhinitis, anaphylaxis*

Abbreviations used
EAACI: European Academy of Allergology and Clinical Immunology
NPS: Nomenclature Position Statement
WAO: World Allergy Organization

The terminology used to characterize allergic and allergy-like reactions is confusing. Without a common understanding and a strict use of terms to define allergic disease, neither science nor patient care can be optimal. In the late 1990s, the European Academy of Allergology and Clinical Immunology (EAACI) appointed a Task Force to standardize the nomenclature of allergy. Their report, published in 2001 as the official EAACI Position Statement ''A Revised Nomenclature for Allergy,''[1] has gained substantial international recognition. It is available today, in extenso or slightly condensed, in more than 10 languages. A glossary of the key words is available in 24 languages on the EAACI Web site.

The World Allergy Organization (WAO)—IAACI used the revised nomenclature in its Web site educational materials and in the WAO/World Health Organization joint project Prevention of Allergy and Asthma. Before promoting the new terminology globally, the WAO created a Nomenclature Review Committee to review the EAACI Nomenclature Position Statement (NPS) and to present a globally acceptable nomenclature for allergic diseases, with the ultimate goal of improving communication in the field of allergy. Special consideration was paid to the provisional terms introduced by the EAACI NPS for certain allergic skin disorders. For a more detailed description of the EAACI nomenclature, please refer to the EAACI Position Statement.[1] It is hoped that this revision will be accepted and used not only by physicians and other health care professionals in education, research, and patient care but also by patients and other lay persons interested in allergy.

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GENERAL TERMS

The revision of nomenclature proposed in the EAACI NPS is based on the mechanism initiating the reaction, which is usually inflammatory, and causing the symptoms and signs of the allergic disease. Because very similar inflammation and clinical presentation can be initiated by different mechanisms, it is of great importance for the researcher, physician, and patient to understand the initiating mechanism. Failure to do so can lead to incorrect conclusions, inappropriate advice on prevention, and ineffective treatment.

The term *hypersensitivity* should be used to describe *objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons*. *Sensitivity* is an acceptable alternative in special circumstances. As a consequence of this stringent definition, entities within the field of so-called environmental medicine, such as total drug sensitivity, multiple chemical sensitivity,[2] and multisymptomatic reactions such as those attributed to amalgam in tooth fillings[3] and electrical waves,[4] do not fulfill the criteria and thus should not be called hypersensitivity.

Allergy is *a hypersensitivity reaction initiated by specific immunologic mechanisms*. When other mechanisms can be proven, as in hypersensitivity to aspirin,[5] the term *nonallergic hypersensitivity* should be used.

Allergy can be antibody-mediated or cell-mediated. In most patients with allergic symptoms from mucosal membranes in the airways and gastrointestinal tract, the antibody belongs to the IgE isotype, and these patients may be said to have an IgE-mediated allergy. IgE in this context refers to IgE antibody to an allergen. There is no known allergy-related biological activity of nonantibody active IgE molecules; thus, allergy cannot be defined on the basis of an increased level of IgE, often referred to as total IgE, or presumed from the presence of IgE on a cell surface. It seems possible that in a more chronic stage of an originally IgE-initiated allergic inflammation, the inflammatory reaction causing the symptoms is dominated by allergen-specific lymphocytes. Because of the hyperreactivity induced by the allergic inflammation, the allergic symptoms can also be induced or aggravated by nonimmunological factors such as infection, irritants, exercise, and so forth. Moderate levels of IgG antibodies to an antigen or positive lymphocyte stimulation tests with moderate to high (>1 μg/mL) antigen concentrations are not necessarily a sign of allergic disease.

In the conglomerate *non–IgE-mediated allergy,* the inflammation can be mediated by allergen-specific lymphocytes, as in allergic contact dermatitis, or by antibodies of the IgG isotype, as in anaphylaxis caused by immune complexes containing dextran[6] and the classical, but now rare, serum sickness, which gave rise to the term allergy.[7] Both IgE and IgG antibodies have been found to be of importance in allergic bronchopulmonary aspergillosis.[8] IgG antibodies to environmental antigens are commonly found without causing signs or symptoms.

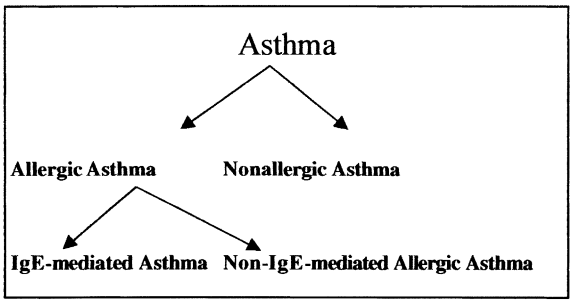

FIG 1. Allergic and nonallergic asthma. The subgroup non–IgE-mediated allergic asthma is probably very small.

However, after chronic inhalation of high concentrations of certain protein-containing material, eg, derived from thermophilic *Actinomycetes* and certain molds (farmer's lung)[9] and bird droppings (bird fancier's disease), airway symptoms of alveolitis or hypersensitivity pneumonitis[10] may occur. The term *allergic alveolitis* should be used for such diseases.

Atopy is *a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema*. The term atopy should be reserved to describe the genetic predisposition to become IgE-sensitized to allergens commonly occurring in the environment and to which everyone is exposed but to which the majority do not produce a prolonged IgE-antibody response. Thus, atopy is a clinical definition of an IgE-antibody high-responder. The term atopy can not be used until an IgE sensitization has been documented by IgE antibodies in serum or by a positive skin prick test. Allergic symptoms in a person of the atopic constitution may be referred to as *atopic*, as in atopic rhinitis. A positive skin test or the presence of IgE antibody to a less common allergen, especially if the exposure is not low-dose or does not occur via mucosal membranes, is not a diagnostic criterion for atopy. Typical examples are Hymenoptera sting allergy and most drug allergies. Such patients should be referred to as *skin test–positive* and *IgE-sensitized*, respectively.

An *allergen* is an antigen causing allergic disease. For detailed definitions of antigens, reference is made to the allergen Web site.[11] Allergen immunotherapy or vaccination,[12] which is an allergen-specific immune modulation, would be best referred to as *allergen-specific immunotherapy* (ASIT). Injection of a monoclonal antibody to IgE[13] could consequently be termed *anti-IgE immunotherapy* (ESIT).

ALLERGIC DISEASES

Asthma

Asthma[14] resulting from immunological reactions should be called *allergic asthma* (Fig 1). Most cases are initiated by IgE antibodies, and if there is a wish to

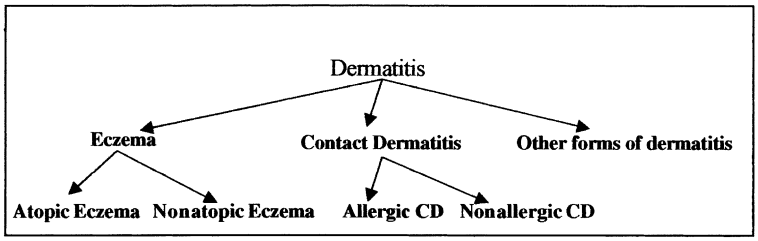

FIG 2. Under the umbrella *dermatitis, eczema* is now the agreed term to replace the transitional term atopic eczema/dermatitis syndrome (AEDS). Atopic eczema is eczema in a person of the atopic constitution.

highlight that fact, a proper term is *IgE-mediated allergic asthma*. The importance of other immunologic mechanisms in initiating the inflammation associated with allergic asthma needs further investigation. Eighty percent of childhood asthma[15,16] and >50% of adult asthma has been reported to be allergic. The mechanisms initiating *nonallergic asthma* are not well defined, although similar inflammatory changes occur in both forms of asthma. There are indications that the prevalence of allergic asthma is increasing[17] along with the general increase in allergic diseases.

Rhinitis

Hypersensitivity symptoms from the nose, eg, itching, sneezing, increased secretion, and blockage, when immunologically mediated, should be called *allergic rhinitis*. Because the great majority of cases are IgE-antibody−mediated, a proper term would be *IgE-mediated allergic rhinitis*. If the symptoms are seasonal, eg, pollen-induced allergic rhinitis, *seasonal allergic rhinitis* is an appropriate term. A novel classification of allergic rhinitis according to duration and severity of symptoms was suggested by the World Health Organization initiative Allergic Rhinitis and Its Impact on Asthma (ARIA).[18] Thus, *intermittent* and *persistent* describe duration, and *mild* and *moderate-severe* define effect of symptoms on sleep, work, and other activities. A great variety of forms of rhinitis is covered by the term *nonallergic rhinitis*.

Conjunctivitis

IgE-mediated allergic conjunctivitis commonly accompanies allergic rhinitis, so this disorder is appropriately termed *allergic rhinoconjunctivitis*. Besides IgE-mediated conjunctivitis, contact allergic conjunctivitis involving T_H1 mechanisms occurs.[19] *Nonallergic conjunctivitis* also often accompanies nonallergic rhinitis. The relationship between allergic and nonallergic conjunctivitis and atopic keratoconjunctivitis and vernal keratoconjunctivitis,[20] requires further studies.

Dermatitis

The umbrella term for a local inflammation of the skin should be *dermatitis* (Fig 2).

Eczema. The term *eczema* is proposed to replace the provisional term atopic eczema/dermatitis syndrome (AEDS).[1] Since the work of the EAACI Nomenclature Task Force started, there has been increased acceptance of the basis for a term describing an aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect.[21-23] This genetically determined target organ sensitivity[24] constitutes the basis for eczema, as is true for asthma and rhinitis. In children and young adults of the atopic constitution, the underlying inflammation is dominated by an IgE-antibody−associated reaction, which would allow use of the term *atopic eczema*. In some countries, the corresponding term would be *atopic dermatitis*, which is not fully consistent with the new nomenclature. As long as the immunological mechanism of eczema is unclear,[25] the disease should be referred to as eczema. It should be remembered that the classification of atopy, and thus atopic eczema, is based on IgE sensitization and thus cannot be reached without an IgE-antibody determination or skin test. In chronic cases, the inflammation seems to be less influenced by IgE antibody, and the dominating cells in biopsies are lymphocytes. The mechanisms initiating the skin disorder in *nonatopic eczema* require further study.

Eczema without any signs of an atopic constitution is common in preschool children.[26] Recent studies reported a prevalence of 45% to 64%,[27,28] but even in adults, figures as high as 40% have been reported.[29] Non-atopic children with eczema have been reported to have less risk to develop asthma as adolescents than atopic children with eczema.[30,31] However, nonatopic eczema in children may evolve into atopic eczema. The differentiation of atopic eczema from eczema in general seems to be of significant prognostic importance.

Contact dermatitis. Close contact with low-molecular-weight chemicals or irritants may provoke a local inflammatory reaction in the skin. When the reaction is mediated by immunological mechanisms, predominantly T_H1 lymphocytes, it should be called *allergic contact dermatitis*. Typical allergens, acting as haptens, are nickel, chromium ions, fragrances, preservatives, and urushiol, from the poison ivy plant. Exposure can occur through oral uptake, so-called *systemic allergic contact dermatitis*. If there is no immune mechanism involved, the proper term is *nonallergic contact dermatitis*, but terms like *irritant/toxic contact dermatitis* could be used to describe the disease.

A subgroup of contact dermatitis, protein contact dermatitis, is probably an IgE-associated reaction caused by absorption of proteins through damaged skin.[32] It may

be referred to as *allergic protein contact dermatitis*, or to highlight the role of IgE, *IgE-associated allergic protein contact dermatitis*. The relationship to eczema requires further study.

Other forms of dermatitis. This term covers entities such as nummular dermatitis and photosensitive dermatitis but also disorders referred to as eczema, eg, dyshidrotic eczema and seborrheic eczema. Although it is not within the task of the WAO Nomenclature Review Committee to discuss terminology or pathophysiologic mechanisms of these disorders, it would be logical to refer to all of them as dermatitis.

Urticaria

When the reaction is mediated by immunological mechanisms, the term should be *allergic urticaria,* which commonly is IgE-mediated but can also be immune complex-associated. These different mechanisms can be highlighted, eg, *immune complex associated allergic urticaria*. Urticaria can also develop locally after topical contact with the allergen, as occurs on the hands of a person with latex allergy wearing latex gloves[33,34] or in a person with dog allergy licked by a dog. Such urticaria, which can be IgE-mediated, should be referred to as *allergic contact urticaria*. In some cases of chronic urticaria, autoantibodies may be involved,[35] and thus the entity should be regarded as a variety of allergic urticaria.

Food hypersensitivity

The appropriate term is *food allergy* when immunologic mechanisms have been demonstrated. Food-specific IgG antibodies in serum are not of clinical importance but merely indicate previous exposure to the food. If IgE is involved in the reaction, the term *IgE-mediated food allergy* is appropriate. All other reactions should be referred to as *nonallergic food hypersensitivity*.[36,37]

Drug hypersensitivity

When immunologic mechanisms have been demonstrated, either antibody or cell-mediated, the reactions should be referred to as *drug allergy*. Adding the adjectives *immediate* or *delayed* both describes the onset of symptoms and indicates the probable responsible immunological mechanism, ie, IgE or lymphocyte cell-mediated,[38] respectively. *IgE-mediated drug allergy* represents a smaller fraction of drug hypersensitivities compared with *nonallergic drug hypersensitivity*. The immunologic mechanism is often difficult to identify because the allergen may be a low-molecular-weight breakdown product acting as a hapten. A positive intradermal skin test, a weak ($<$3-mm) skin prick test, or a basophil challenge test at a very high drug concentration (eg, $\geq$1 mg/mL) is not sufficient to identify a true immunopathologic mechanism. Similarly, the detection of IgG antibodies or a positive lymphocyte stimulation test merely indicates previous exposure unless the antigen stimulation dose is very low ($<$1 μg/mL).

Insect sting or bite hypersensitivity

Insect venom and saliva hypersensitivity mediated by an immunologic mechanism should be referred to as venom or saliva allergy, as in *bee venom allergy*. To highlight the role of IgE antibody, the term *IgE-mediated bee venom allergy* should be used. The large quantity of venom allergen in a sting is comparable with years of inhaled pollen allergen. This high-dose sensitization probably explains why there is almost the same prevalence of atopy among patients with IgE sensitization to venoms as in the normal population.[39]

Anaphylaxis

The term *anaphylaxis* is used differently by physicians throughout the world.[40] It is proposed that *anaphylaxis* is the umbrella term for an acute reaction defined as follows: *anaphylaxis* is *a severe, life-threatening generalized or systemic hypersensitivity reaction*. The term *allergic anaphylaxis* should be used when the reaction is mediated by an immunologic mechanism, eg, IgE, IgG, and immune complex complement-related. An anaphylactic reaction mediated by IgE antibodies, such as peanut-induced food anaphylaxis, may be referred to as *IgE-mediated allergic anaphylaxis*. Anaphylaxis from whatever nonimmunologic cause should be referred to as *nonallergic anaphylaxis*.

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