

A.E.J. Dubois
G.R. de Monchy
J.P. Schouten
S. Durham
D.B.K. Golden
S. Rak
S.T. Weiss

Authors' affiliations:

A.E.J. Dubois, G.R. de Monchy, Department of Allergology, University Hospital Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands
J.P. Schouten, Department of Epidemiology, University Hospital Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands
S. Durham, Imperial College School of Medicine, At the National Heart and Lung Institute, Dovehouse Street, London S3W 6LY, UK
D.B.K. Golden, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA
S. Rak, Allergy Centre, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden
S.T. Weiss, Department of Respiratory and Environmental Epidemiology, Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA

Date:

Accepted for publication 4 March 1999

To cite this article:

Dubois A.E.J., de Monchy G.R., Schouten J.P., Durham S., Golden D.B.K., Rak S., Weiss S.T. Letter to the editor. *Allergy* 1999; **54**, 760-762.

Copyright © Munksgaard 1999

ISSN 0105-4538

We would like to respond to the invitation of Lilja & Wickman in their interesting editorial dealing with basic concepts relating to the field of allergology (1). That the time has come to re-examine terms used in this field is shown by the different meanings given to the term "hypersensitivity". In much of the Anglo-Saxon literature, the term covers all the immunologic effector responses categorized by Gell and Coombs and is thus synonymous with the term "allergy". Since this redundancy of terms is confusing, it might indeed be wise to adopt the Scandinavian definition of the term "hypersensitivity" as signifying any quantitatively and/or qualitatively distinct adverse reaction elicited by a foreign substance which is not encountered in the general population. As the mechanisms of such reactions become known, they may be then classified as either a form of allergy or a form of nonallergic hypersensitivity. The latter category would include true food intolerances (such as lactose intolerance) as well as pharmacogenetic (or "idiosyncratic") reactions to drugs. Pseudoallergy could thus be classified as a form of nonallergic hypersensitivity where a foreign substance exerts a direct effect on a part of the immune system which may be involved in effector responses to true allergens, resulting in clinical phenomena indistinguishable from allergic disease. Such conditions must, in turn, be distinguished from disorders such as intrinsic asthma and idiopathic urticaria, which exhibit numerous clinical similarities to their allergic counterparts, but in which foreign substances are not thought to play an etiologic role.

With regard to the term "allergy" itself, we agree with Lilja & Wickham that most authorities have used this concept to denote clinical reactivity. Allergic patients have symptoms and are not merely sensitized. It is also clear that allergy is not simply "IgE disease". This latter view has gained acceptance in recent years with the appreciation of the fact that inflammatory phenomena, even in the classical

atopic diseases, cannot be explained by IgE alone. The definition of allergy must thus be a broad one, while excluding potentially deleterious effects accompanying otherwise beneficial immune responses to foreign substances. Thus, allergy could be defined as a uniformly adverse immunologic reaction directed against a foreign substance occurring in a portion of naturally exposed individuals. The "portion" of individuals referred to here is usually a minority, although some authorities believe that atopy-associated allergic diseases may exceed 50% prevalence if current trends continue (2).

Lilja & Wickham continue with the question, "What exactly is 'atopy'?" As they point out, the definition of Pepys does not require the presence of clinical symptoms. In addition, he referred to production of reaginic (IgE) antibodies in response to "ordinary exposure to common allergens of the subject's environment". Both of these aspects deserve consideration in the light of current knowledge.

Natural exposure to allergens associated with atopy may induce the production of IgE antibodies, but not all allergens inducing IgE production are associated with atopy. An example of a nonatopic allergen which may induce specific IgE production is toluene diisocyanate. Individuals sensitized to this substance are not more frequently sensitized to common environmental "reference" allergens, such as house-dust mite, than individuals from the general population (3). Thus, there is no particular epidemiological association between sensitization to toluene diisocyanate and sensitization to allergen of house-dust mite. In this way, allergens inducing the production of specific IgE antibodies may be divided into those belonging to the atopic "cluster" and those which do not. A limitation of this kind of analysis is that conclusions pertain to the allergen exposure circumstances encountered in the population being studied (which will usually, but not always, be "natural" exposure) and that exposure must be sufficient to allow for a representative prevalence of sensitization to occur in predisposed individuals. An atopic allergen is thus an allergen which may cause epidemiologically significant cosensitization with known "reference" atopic allergens. In most parts of many Western countries, such a reference allergen is exemplified by house-dust mite. Thus far, most atopic allergens have turned out to be (glyco)proteins, whereas nonatopic allergens capable of IgE induction are substances such as low-molecular-weight sensitizers and drugs.

The second issue is the nature of the relationship between atopy and clinical disease. When the term "atopy" was introduced by Coca and Cooke, asthma, hay fever, and later also infantile eczema – diseases with a "common hereditary

cause" – were considered atopic ailments. Atopy was thus the "common hereditary cause", and, if a genotypic definition of "atopy" was technically possible, there would probably be little discussion as to the meaning of this term. The question thus becomes: what are the phenotypes of atopy? The answer to this question must first be qualified by pointing out that phenotypic definitions are often imperfect because individuals may change their phenotypic status, a fact that is certainly relevant to atopy. Secondly, although having an "atopic disease" (i.e., asthma, rhinoconjunctivitis, or eczema) would seem to qualify as a phenotype of atopy, there is no satisfactory epidemiological evidence showing that the atopic forms of these disorders (where sensitization to atopic allergens may be demonstrated) are epidemiologically, and thus possibly genetically, related to their nonallergic counterparts in which no sensitization of any kind is found. This does not preclude that nonsensitized atopic phenotypes could be epidemiologically identified in the future. Finally, while the rationale for a disease-based definition of atopy is understandable and valid, it is probably more useful to think of atopy as an increased risk of disease rather than as simply having disease. While this would be in line with the hereditary concept of Coca and Cooke, as well as the idea that clinical symptoms need not be present in all atopic individuals, as expressed by Pepys, it does anchor atopy in relation to clinical diseases. Significantly, studies in recent years have clearly demonstrated that sensitization to atopic allergens in itself increases the risk of the development of atopic diseases (4, 5). Thus, phenotypically defining atopy simply as sensitization to atopic allergens also embodies the notion of increased risk of the development of atopic diseases.

The relationship of atopy and various forms of allergy may be represented by Fig. 1.

The circle on the left represents atopy and includes individuals with IgE sensitization to common inhalant allergens such as that from house-dust mite as well as other allergens in the "atopic cluster". Individuals in the

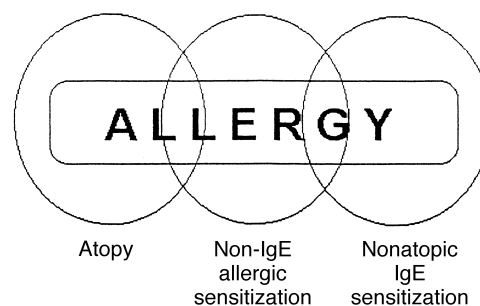


Figure 1.

corresponding part of the rectangle also have clinical symptoms such as anaphylaxis or allergic disorders of the airways or skin. The middle circle represents other (non-IgE) forms of allergic sensitization, such as that characterized by the presence of non-IgE cytotoxic antibodies, precipitating antibodies, antibodies capable of complement fixation, or specifically sensitized effector T cells. Individuals in the corresponding part of the rectangle have clinical symptoms, such as those encountered in allergic alveolitis or contact dermatitis. The circle on the right represents individuals with IgE sensitization to allergens not belonging to the atopic cluster such as toluene diisocyanate or penicillin. The corresponding part of the rectangle represents individuals with clinical symptoms such as asthma or anaphylaxis.

Two overlap areas are shown. The overlap of the middle and right circles represents concomitant IgE and non-IgE sensitization to nonatopic allergens, as may be encountered in individuals with serum sickness caused by penicillin administration. The overlap of the left and middle circles represents sensitization states involving both IgE production and other antibody or effector T-cell production specific for atopic allergens. The corresponding area of the rectangle includes individuals with diseases such as allergic bronchopulmonary aspergillosis or serum sickness reactions to immunotherapy with atopic allergen extracts. As our understanding of the effector mechanisms of allergic disorders related to atopy increases, this category is likely to increase at the expense of the "purely" IgE-mediated disorders.

References

1. Lilja G, Wickman M. Allergy – atopy – hypersensitivity – a matter of definition. *Allergy* 1998;**53**:1011–1012.
2. Martinez FD. Is the potential for developing allergies (almost) universal? Presentation at the Annual Meeting of AAAA & I. Washington, DC: 1998.
3. Karol MH, Tollerud DJ, Campbell TP, et al. Predictive value of airway hyperresponsiveness and circulating IgE for identifying types of response to toluene diisocyanate inhalation challenge. *Am J Respir Crit Care Med* 1994;**149** (3 pt 1):611–615.
4. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house dust mite allergen (Der p 1) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;**323**:502–507.
5. Kuehr J, Frisher T, Meinert R, et al. Sensitization to mite allergens is a risk factor for early and late onset of asthma and for persistence of asthmatic signs in children. *J Allergy Clin Immunol* 1995;**95**:665–662.