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Pseudoallergy or nonallergic hypersensitivity

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In an editorial in the November 1998 issue of *Allergy*, Lilja & Wickman (1) reviewed the current discussion on how to designate specific intolerance reactions that are not based on a sensitization of the immune system. Since the first description of ASA intolerance by Hirschberg in 1901 (2), then termed "idiosyncrasy", this type of reaction has repeatedly been described and is now known to occur to NSAIDs, local anesthetics, and contrast media as well as natural and artificial food ingredients.

In the past, various terms such as "idiosyncrasy", "intolerance", and "pseudoallergy" have been used, and, as stated in the editorial (1), the term "nonallergic hypersensitivity" has recently become common in Scandinavia. In our paper (3), we had originally used the term "pseudoallergy" in the title but changed it, at the specific request of the editor, to "nonallergic hypersensitivity". We are not entirely happy with the term "pseudoallergy", but we are convinced that it is the best of the terms used so far. This is based on the following reasons:

- 1) In medicine, the prefix "pseudo-" is often used to describe symptoms or syndromes mimicking another disorder. Examples are pseudotumor cerebri and pseudocyst. The same applies to the term "pseudoallergy", which denotes a condition mimicking an allergic reaction. Thus, from the clinician's point of view, it is impossible to determine whether the cause of urticaria following the ingestion of a certain food is allergic or pseudoallergic. An example of this is hives related to tomatoes, for which both IgE-dependent and non-IgE-dependent reactions have been described.
- 2) Medical terms need to be correctly understood by the great majority of specialists as well as by physicians practising in different fields. This applies to the term "pseudoallergy", which, in contrast to the term "nonallergic hypersensitivity",

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is widely used throughout the world literature, whereas the term “nonallergic hypersensitivity” was not found at all in a MEDLINE search of recent years.

- 3) To limit confusion, it is desirable to keep terminology simple and easy to understand by both physicians and patients. This holds for the term “pseudoallergy”, with the eliciting agents then being called “pseudoallergens”, a designation which, in correspondence to the terms “allergy” and “allergens”, very neatly implies the nature of the reaction. In this regard, the term “nonallergic” hypersensitivity offers nothing comparable. In fact, the term “eliciting factors of nonallergic hypersensitivity reactions” is surely

too complicated for everyday use in explanations to patients.

In conclusion, in view of all these arguments, we feel that at the moment the term “pseudoallergy” is the best choice we have. The only alternative we can see is to coin a new term which offers a real improvement in the nomenclature.

Comments from Editor-in-Chief: The EAACI has created a task force to present to the EAACI Executive Committee a proposal for a new nomenclature, which is to be published in *Allergy* as an EAACI Position Paper.

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Multiple vaccination effects on atopy

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Asthma, tuberculosis, cancer, myalgic encephalomyelitis, and Gulf War syndrome have all been linked recently to a shift in the immune profile favouring a T helper 2 (Th2) cell bias (1). In the UK, this situation has been associated with the multiple vaccinations given to troops before Gulf combat (2). This has led to the suggestion to manipulate the immune response in order to encourage the development of Th1 cells and thereby to counter the effects of these conditions, but this has led to concern that this will not be achieved without some form of immunologic penalty (1).

My concern, however, is the price we may be already paying for the immune deviation toward a Th2 profile.

The soldiers in question were immunized against anthrax, cholera, plague, tetanus, typhoid, and pertussis (whooping cough), all of which require potent Th2-inducing vaccines. This large antigen loading further favours a systemic shift toward a Th2 predominance and associated cytokine profile (1) and has raised questions regarding the safety of the procedure. A UK government report confirms that troops received a pertussis vaccine as an adjuvant for an anthrax vaccine, so that the latter was effective from 7 weeks instead of 32 weeks. The use of pertussis vaccine in this way was highly experimental, relying on the preliminary findings of Ministry of Defence-sponsored research, and was performed despite a warning by the National Institute for Biological Standards and Control, a UK regulatory control body (2).

This highlights a possible serious drawback of combined pertussis vaccine use and is of considerable concern since pertussis vaccination is known to be an etiologic factor in the development of childhood asthma (3). The incidence of asthma is on the increase and so is the use of multiple vaccination procedures. When pertussis is combined with diphtheria and tetanus (the DTP vaccination given in the UK to 8-week-old babies along with Hib and, in some cases, tuberculosis), the same immune deviation develops, a bias toward Th2 responsiveness. The pertussis vaccine may not be the culprit in the case of asthma, but may be a marker for

the effects of multiple vaccination, as it is not usually given in isolation.

Apprehension about this apparent shift in immune cell population is clear. In a Th2-dominant system, interleukins (IL) 4, 5, and 13 are upregulated, along with excessive synthesis of IgE via clonal expansion and secretion of IL-4 (4). Combine this with the resultant enhanced eosinophil activity, and all the ingredients are present for atopic conditions such as asthma, eczema, hay fever, and food intolerances to develop. By contrast, a bias toward Th1-regulated cytokine synthesis would inhibit type 1 hypersensitivity reactions via IFN- γ , which counterregulates IL-4 and thereby decreases IgE production. The balance between IFN- γ and IL-4 determines the level of IgE synthesis. This interrelationship is key since these cytokines are secreted by Th1 and Th2 cells, respectively, supporting the concept that immune balance is crucial if atopy is to be avoided (4). Multiple vaccinations shift this delicate balance, favouring the development of atopy and, perhaps, autoimmunity through vaccine-induced polyclonal activation leading to autoantibody production. An increase in the incidence of childhood atopic diseases may be expected as a result of concurrent vaccination strategies that induce a Th2-biased immune response. What should be discussed is whether the prize of a reduction of common infectious diseases through a policy of mass vaccination from birth is worth the price of a higher prevalence of atopy.

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Response to Dr Taylor-Robinson's letter on vaccination and atopy

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The Letter to the editor from Dr Taylor-Robinson in this issue of *Allergy* focuses on the connection between multiple vaccinations in early infancy, the Th2 deviation of the immune system, and the development of atopic diseases during childhood. Pertussis vaccine, especially when combined with vaccine against diphtheria and tetanus, is discussed as being associated with the development of atopy.

The findings in the literature on a connection between vaccination against pertussis in early infancy and the development of atopy are inconsistent. Kemp et al. (1) and Odent et al. (2) have shown an increased risk of atopy after vaccination in retrospective studies. A large prospective study in Swedish children found no increase in allergic symptoms nor in atopic diseases up to 2.5 years after vaccination with different pertussis vaccines combined with diphtheria and tetanus (3). Furthermore, there was an increased incidence of atopic diseases in children in Sweden in 1979–91, when there was no general vaccination against pertussis (4).

Although the suggestions of Dr Taylor-Robinson are of great interest, more epidemiologic studies are needed to elucidate the role of vaccinations in the development of atopy.

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