

Editor's note

Allergy used to be something that every other patient was complaining about and most physicians had an opinion about. However, this opinion was usually their own and the speciality allergology was rather confusing, being more of an art than something based on scientific knowledge. This situation started to change in the early 1960s, thanks to a few open-minded clinical researchers such as Jack Pepys. He, like few others, had a gift for combining clinical experience with laboratory science. To give one example, he made the connection between the combination of clinical symptoms and signs of farmer's lung with the occurrence of precipitating antibodies to thermophile fungi. He was also an outstanding teacher. I have vivid memories from my first international congress in Florence in the late 1960's, when Jack Pepys told us about the importance of precipitating antibodies to proteins from birds, and, of how when lifting the cover of a small bird cage, he enun-

ciated in his clear English, like a linguistic artist: "This is a budgerigar." I can still recall the way he pronounced the name of this Australian parrot.

In my opinion, one of his greatest achievements was to define atopy, in the mid-1970s. This term has become more and more useful as time has gone by. It is therefore a great pleasure for me to include in this issue of *Allergy* an Editorial by Jack Pepys on the definition of atopy.

By the way, you may not believe it, but Jack Pepys celebrated his 80th birthday in May. Jack, may I extend from the entire European allergology community, on both sides of the Channel, our warmest congratulations on your birthday. We wish you many happy and productive years to come.

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Editorial

"Atopy": a study in definition

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The central focus of analysis and recognition of the concept of "atopy", to be discussed further, is the nature and role of IgE antibodies. Major advances have been made since the discovery of IgE by Ishizaka et al. (8) and the remarkable boost to its investigation by the finding, by Johansson (9), that the myeloma protein, IgND, is identical with IgE. The unravelling at the genetic and molecular level of the "human IgE network" is dealt with only briefly

here. The increased understanding of some aspects of IgE in terms of its apparently novel bent shape, the molecular nature of the high- and low-affinity receptors, and the role of complement in its induction holds much promise (20). In respect of the last, the role of the C3 component of complement in IgE antibody response *in vivo* in mice was reported some years ago (16).

The practical recognition of atopy, as defined here,

and to which the basic advances are contributing, is discussed here in pragmatic terms, other aspects having been reviewed elsewhere (11–14). The events leading up to the introduction of the term started with the report by Cooke & van der Veer in 1916 (6), in the first volume of the *Journal of Immunology*, on immediate whealing reactions to common allergens in patients suffering from common allergic diseases. Because of the frequent multiplicity of reactions, they concluded “very strongly that such individuals as a group possess a very peculiar capacity to become sensitive in a natural way to certain proteins to which their environment and habits of life frequently expose them”. They regarded this as analogous to anaphylaxis.

The term “atopy” was introduced by Coca & Cooke in 1923 (4) to describe these findings. They proposed a compound and complex definition, including immediate sensitivity, in particular, in hay fever and asthma. They stated that the sensitivity was not passively transferable and was not analogous to anaphylaxis in experimental animals. They seem to have been unaware of the discovery by Prausnitz & Küstner in 1921 (17) of the passive transfer of immediate sensitivity. Coca & Grove investigated atopy further (5), throwing light on certain important aspects but with some curious conclusions. They reported the presence of heat-labile “bodies”, which they called “reagins”, by virtue of their similarity in this respect to the heat-labile reagens (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”. The term “atopy” was adopted with enthusiasm to start with, only to have an “up-and-down” career thereafter. In 1968, Sherman (18) declared that “its use had gradually decreased until after 20 years it was virtually abandoned, except for the designation of adult infantile eczema as atopic dermatitis”. Indeed, in 1947, Cooke (7), who was indirectly involved in its introduction in a symposium jointly with Coca, suggested that “it should be dropped from use to avoid further confusion”. Because of the complexity of its definition, it suffered from much prejudice and bias. Cooke used the phrase “immediate wheal-reacting allergy” instead.

A potentially useful term such as “atopy” can survive these hazards although general agreement on a more precise definition is needed. Problems of definition in medicine are common. The complexity of compound definitions in disorders of multifactorial causation and polygenic inheritance makes attempts at comprehensive definition unsatisfactory. Ideally, definitive terms should be based on a single field of study. This then provides a primary defining char-

acteristic for general adoption and agreement, to which secondary, tertiary, etc. characteristics can be added. It requires standardization of all aspects for comparable use by different observers. As far as “atopy” is concerned, a proposed appropriate definition reads, “that form of immunological reactivity of the subject in which reaginic antibody, now identifiable as IgE antibody, is readily produced in response to ordinary exposure to common allergens of the subjects’ environment” (12). This does not imply the presence of symptoms and is a description of the immunologic reactivity of the subject. It is now known that 30–40% of apparently healthy persons belong in such an atopic group, as shown by immediate whealing reactions to skin tests with common, environmentally relevant allergens. Serologic tests for specific IgE antibodies can serve a similar purpose (2).

Critical attention must be directed to the methods and interpretation of the skin tests. The author prefers the “modified skin prick test” (15) with small-gauge hypodermic needles. This test should, except for dermographism, elicit completely negative reactions at control tests; therefore, it is not necessary to have a convention, such as wheal size in itself or in relation to positive controls, to assess reactions as positive. Criteria for wheal size in relation to positivity have been thoroughly examined by Nelson et al. (10), who used five and six (1) different skin test methods and showed that positive whealing reactions have to be larger than 2–5.5 mm. The general emphasis on wheal sizes as above for positivity is based on the assumption of possible clinical relevance and may offer advantages. But, what we are dealing with here is immunologic reactivity, so that even very small wheals, 1–2 mm in diameter, with a flare and possibly itching, and capable of reproducibility, can be taken as positive evidence. In support of this, even in clinical terms, is the presence of specific IgE antibodies in subjects causing wheals of less than 3 mm diameter (19). Clinical support is also provided by the report of Bryant et al. (3) that while more than 90% of patients with positive skin prick test reactions greater than 3 mm had positive bronchial provocation test reactions, so did more than 50% of those with smaller wheals. Some workers classifying atopy by skin prick tests also require more than one positive reaction to common allergens, a questionable procedure.

It is possible to assess atopic status by the number of positive prick test reactions. In an analysis of 1000 consecutive asthmatic patients, they were grouped according to whether they reacted to 0, 1, 2, 3 or more of a battery of allergens (11). These groups were then compared with each other for the presence in their families and first-degree relatives of asthma, hay fever and eczema. It was found that

there were no significant differences when compared against their families as units. However, comparisons of atopic status of the *propositi* with the total number of first-degree relatives in each group, showed highly significant, directly related differences (0.0001) between the presence of these disorders, directly related between each atopic status group successively. A further analysis was made in which comparisons were made based on the ages of onset, in decades, of symptoms in the *propositi*. This showed significant direct correlations between successive atopic groups as far as hay fever and eczema was concerned but for asthma this was present only in the group whose asthma started between 10–19 years of age. The latter is consistent with generally accepted opinion that there is an organ disease-specific genetic factor in asthma, though it does not exclude it in the other diseases. Such findings may be a pointer to more directed genetic studies than the usual grouping of subjects together, whatever their atopic status.

Whatever the views on the above definition and discussion of "atopy", there is need for standardisation in all respects and for recording of all sizes of reaction in skin tests and of serological tests, irrespective of opinions on clinical relevance, thus making it possible to compare the findings of different workers.

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