

## REVIEW

# Asthmatic responses to inhalation of anti-human IgE

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### Introduction

Allergen inhalation tests in allergic asthmatics usually elicit isolated early or early followed by late (dual) asthmatic responses. The early asthmatic response depends upon involvement of immunoglobulin E (IgE) antibodies but whether antibodies are required for the late asthmatic response in humans is less well defined.

Cutaneous reactions with both early and late responses have been studied in some detail in man. Reversed allergic reactions with anti-human IgE and Prausnitz-Kustner (PK) reactions in passively sensitized skin sites produced a similar pattern of early followed by late cutaneous allergic responses [1]. Removal of IgE from highly purified serum fractions prevented sensitization in PK tests for the occurrence of early and late cutaneous responses [2]. These studies show that, in the skin, IgE is involved in the late as well as the early allergic responses. The processes involved in the airway responses to allergen might be analogous to the cutaneous responses in their involvement of IgE. We utilized a reversed allergic reaction to examine this possibility.

### Materials and methods

#### *Study design*

Two adults with asthma were studied in 1972. Allergy prick tests were carried out with normal saline, sixteen common allergen extracts and normal sheep serum in both subjects and with sheep antiserum to human myeloma IgE in one subject (Table 1). Inhalation tests were performed with allergen extracts, anti IgE and, in one subject, with sheep serum.

#### *Subjects*

At the time of study symptoms of asthma were controlled without treatment,

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spirometry was normal and histamine airway responsiveness (measured by the method described by Cockcroft *et al.* [3]) was mildly increased (Table 1). There had been no recent natural exacerbation and no exposure to common allergens to which the subjects were allergic (with the exception of housedust in subject 2).

### Inhalation tests

These were carried out as described by Robertson *et al.* [4]. The baseline FEV<sub>1</sub> before each tests was within 15%. The response was measured by FEV<sub>1</sub> at 10, 20, 30, 45, and 60 min and then hourly for at least 8 hr.

### Test materials

A single batch of extracts of whole ragweed pollen and cat epidermis was obtained from Omega Laboratories, Toronto, Ontario, Canada. They were dissolved in phosphate-buffered saline and, after dialysis, the allergen preparations were sterilized by filtration, divided into several samples and stored at -20°C. Each sample was thawed only once prior to use.

Antiserum to human myeloma IgE was prepared in sheep as previously described [1]. This was adsorbed with an agarose-insolubilized immunoabsorbent of normal human serum. The antiserum produced a single line of precipitation in double-diffusion reactions with IgE myeloma protein but there was no visible precipitate in reactions with normal human serum. Radioimmunodiffusion tests, by a two-step method, with the sera of subjects sensitive to ragweed, demonstrated that the antiserum reacted with nonmyeloma IgE. In radio-immunoelectrophoresis tests with numerous sera from ragweed-allergic people, there was no evidence of reactivity with other immunoglobulin classes. The anti-human IgE was sterilized by passage through a millipore filter and stored at 4°C until used. Normal sheep serum was diluted 1:10 with phosphate buffered saline.

## Results

Inhalation tests with anti-IgE elicited an early followed by late asthmatic response in subject 1 and an isolated early asthmatic response in subject 2 (Figs 1 and 2). The specificity of the responses in subject 1 was indicated by the absence of responses to inhaled normal sheep serum. The pattern of asthmatic response to inhalation of anti-

**Table 1.** Subject characteristics

| Subject | Gender | Age<br>(years) | Common*<br>allergens | Normal sheep<br>serum | Skin tests             |      | Mean<br>baseline<br>FEV <sub>1</sub><br>[l] | PC <sub>20</sub><br>Histamine<br>(mg/ml) |
|---------|--------|----------------|----------------------|-----------------------|------------------------|------|---------------------------------------------|------------------------------------------|
|         |        |                |                      |                       | Anti-human<br>IgE (mm) |      |                                             |                                          |
|         |        |                |                      |                       | Early                  | Late |                                             |                                          |
| 1       | F      | 40             | 1                    | —                     | 4                      | 13   | 2.62                                        | 4                                        |
| 2       | M      | 49             | 7                    | —                     | ND                     | ND   | 2.34                                        | 2                                        |

\* Number with a weal > 2 mm. — = negative. ND = not done.

FEV<sub>1</sub> is forced expired volume in 1 sec.

PC<sub>20</sub> is provocation concentration of histamine acid phosphate to cause a fall in FEV<sub>1</sub> of 20% [3].

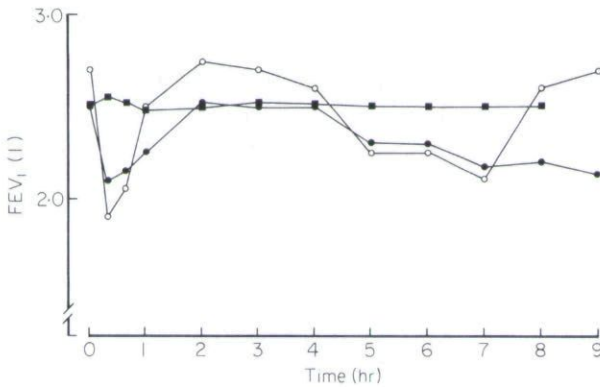


Fig. 1. Dual asthmatic responses in subject 1 after inhalation of ragweed antigen (1:1000) (○ ---- ○), anti-human IgE (1:10) (● ---- ●) and normal sheep serum (■ ---- ■).

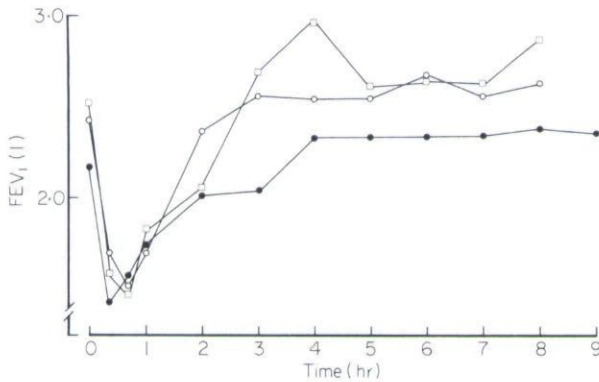


Fig. 2. Early asthmatic responses in subject 2 after inhalation of ragweed 1:10 (○ ---- ○) and cat 1:10 (□ ---- □) antigens and anti-human IgE 1:10 (● ---- ●).

IgE was similar to that which followed inhalation of allergens by the same subject, and to the pattern of cutaneous response to anti-IgE in subject 1.

### Discussion

The observation that inhalation of anti-human IgE can cause, through a reversed allergic reaction, both an early and late asthmatic response similar to that after allergen inhalation points to a role for IgE in both airway responses. One possible alternative conclusion is that the subject had pre-existing antibodies to the heterologous IgG antibody which participated in the reaction and contributed to the late response. However, there was no cutaneous reaction from intracutaneous injection, and no asthmatic response after inhalation, of normal sheep serum, but there was a dual cutaneous response to anti-human IgE in the subject so tested, which paralleled the airway response. Thus, the airway responses were likely due to the interaction of anti-human IgE with the IgE of the subject.

The dependence upon IgE of allergen-induced late as well as early asthmatic responses in animals is now well established [5]. Evidence in man has been necessarily

less direct. The importance of early IgE-related events is suggested by inhibition of both the early and late asthmatic responses by sodium cromoglycate taken before the allergen challenge [6]. The predominance of eosinophils in bronchoalveolar lavage fluid in association with the late asthmatic response is consistent with this hypothesis [7]. The present observations with inhaled anti-IgE is further indication of the relevance of the IgE-dependent reaction.

The apparent involvement of IgE in early and late asthmatic responses suggests the following hypothesis. Mast cell degranulation and release or activation of chemical mediators in response to combination of antigen with mast cell-associated IgE leads to the early asthmatic response [8]. The release or activation of chemical mediators together with influx of inflammatory cells in response to chemotactic factors generates the airway inflammation, which results in the late asthmatic response [8,9]. The occurrence of a late response may depend, at least in part, on a tendency for a continuing release or activation of mast cell or basophil mediators. The observed correspondence between anti-IgE and allergen-induced patterns of response suggests involvement of a host factor independent of the characteristics of the immunologic responses to allergen.

We performed the studies in these subjects with considerable caution to avoid any adverse effects from the inhalation of heterologous protein. No adverse effect was seen in our two subjects or in the subjects whose cutaneous responses had previously been studied by Dolovich *et al.* [1]. Nevertheless, it could be argued that a detrimental effect, separable from an acute reaction, could result from sensitization and a reaction to subsequent exposure to sheep products. Thus, it should be noted that these studies were performed in 1972 when ethical restraints were not quite as rigorous as now, and the inhalations with anti-IgE were discontinued when the principle seemed to be demonstrated that a late response as well as an early response could be stimulated.

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