Mediator Release during Allergen-induced Bronchoconstriction in Asthmatic Subjects*

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In order to achieve a better understanding of asthma in man, more detailed information on the immunopathologic mechanisms responsible for clinical asthma is required. Much is known about the immediate pathologic mechanisms responsible for clinical asthma is only slowly emerging. Specific allergens; however, the exact role of such mediators in clinical asthma is only slowly emerging. Chiesa et al have demonstrated in dogs release of histamine from the lungs of allergic dogs when challenged with aerosols of Ascaris antigen.

In human asthma, while Bhat et al have demonstrated histamine in peripheral venous samples of blood following allergen challenge in asthmatic subjects, many other investigators have been unable to demonstrate rises in peripheral venous histamine following allergen challenge. This inability to detect elevation of histamine may be due to peripheral metabolism of histamine by enzymes contained in circulating leukocytes prior to sampling from a peripheral vein. Therefore, we collected blood shortly after it left the lung from the radial artery and also simultaneously sampled from a catheter in the pulmonary artery, thus obtaining blood just prior to it entering the lung.

Similarly, the role of complement in clinical asthma is not well understood. A small number of studies both in vitro and in vitro suggest that complement activation may participate in the immediate asthmatic response, but this role is not well established. This study was designed to determine the incidence of histamine release and complement activation following bronchial provocation with specific allergens, and this site of release of histamine.

**Material and Methods**

Five patients with immediate asthmatic responses and one patient with dual immediate and delayed asthmatic responses were challenged using a standard technique with specific allergens to which bronchial reactivity had been determined at least one week previously. Blood samples obtained simultaneously from the radial artery and the pulmonary artery were drawn both before and serially after challenge. Plasma histamine was measured by radioenzymatic assay. Samples were assayed in duplicate. The assay was sensitive enough to detect histamine concentrations down to 1 ng per ml. Duplicate samples varied by less than .2 ng per ml. Complement activity was assessed by CH50 and the measurement of complement split products of C3, C4 and factor B was performed by counterimmunoelectrophoresis.4

**Results**

Plasma histamine was elevated in four of the six patients within minutes of challenge. Figure 1 shows a typical patient with systemic arterial plasma histamine peaking at 12 ng per ml two minutes after challenge.

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With cat dander allergen 1:50, the histamine remained elevated approximately ten minutes after challenge. It should also be noted that the systemic arterial plasma histamine was greater than the mixed venous plasma histamine suggesting lung release followed by peripheral metabolism of the amine. In three of the four patients, a similar picture of a greater rise in systemic arterial plasma histamine than mixed venous was seen, and in the fourth patient, similar levels were obtained in both mixed venous and systemic arterial plasma. The time course of the changes in arterial plasma histamine are shown in Figure 2. In addition, significant falls in both systemic arterial and mixed venous complement activity occurred shortly after challenge of one patient (Fig 1) and these were associated with the appearance of split products C3 and C4. CH ≈ fell more than 10 percent in five of the six patients and was accompanied in two of these five by the appearance of split products of complement.

One patient exhibited dual immediate and delayed asthmatic responses to inhalation of rat serum proteins. This patient study is shown in Figures 3 (immediate response) and 4 (delayed response). In Figure 3 the early response, which occurred within minutes of challenge with rat serum protein, was characterized by a marked fall in FEV₁. This occurred within ten minutes

![Figure 2. Time course of changes in systemic arterial plasma histamine in four patients. No patient had detectable plasma histamine prior to challenge.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21018/)

![Figure 3. FEV₁, plasma histamine, symptoms and complement studies of the immediate phase of one subject's dual asthmatic response following inhalation of whole rat serum.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21018/)
of challenge and was accompanied by a rise in systemic arterial plasma histamine, but no elevation of mixed venous plasma histamine. CH₃0 fell only marginally; however, split products of C3 were detected within minutes of challenge and remained present throughout all of the early phase. The immediate phase lasted approximately one hour and was accompanied by a moderate degree of wheezing. This was followed by an asymptomatic period of three hours during which the FEV₁ rose towards normal. Symptoms of the delayed phase commenced at 2:10 in the afternoon and these were accompanied by a gradual fall in FEV₁. This delayed response was preceded and also accompanied by a modest rise in mixed venous plasma histamine, but no elevation in the systemic arterial plasma histamine. Split products of C3 were present throughout the immediate phase and most of the delayed phase and finally were not detected at 3:40 pm. They were therefore present for approximately five hours after challenge compared to less than 30 minutes in the patient with only an immediate response (Fig 1). The prolonged activation of serum complement, together with the systemic release of histamine, possibly from circulating basophils, suggested that allergen may have been absorbed systemically. To test this hypothesis, an oral challenge with lyophilized rat serum in a gelatin capsule was carried out. The results of this study are shown in Figure 5 and they clearly demonstrate a significant fall in FEV₁ and FEF₂₅₋₇₅ commencing within 20 minutes of challenge and continuing for nearly one hour following the oral challenge. A control challenge with human gamma globulin (HGG) produced no significant change in either FEV₁ or

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21018/)
These studies indicate that allergen challenge in asthmatic subjects leads to lung release of histamine in the immediate phase followed by peripheral metabolism resulting in mixed venous levels generally being lower than systemic arterial blood levels. This is frequently associated with changes in the level of complement activity and accompanied by the appearance of split products of the complement components in some subjects. By contrast, the delayed asthmatic reaction in our patient appears to be due to activation of complement and the systemic release of histamine possibly from circulating basophils following absorption of allergen either from the respiratory or gastrointestinal tracts.

REFERENCES

DISCUSSION
Question: Are the levels of blood histamine found in your study enough to cause symptoms if injected intravenously? If this is the case, shouldn't we be able to block these effects with adequate doses of antihistamine?
Dr. Allen: That is an interesting point. Blood histamine is really only a reflection of tissue histamine levels which may be ten to a hundred to a thousand fold higher. Thus, doses of antihistamine may not be effective in controlling tissue reactions, and in fact we don't know if they even get to the tissue sites where histamine is acting.