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EDITORIAL

Bronchial hyperresponsiveness and cytokines in virus-induced asthma exacerbations

In recent years studies employing new sensitive molecular methods of identification for the most common upper respiratory tract viruses (coronavirus and rhinovirus) have demonstrated that viral infections are associated with the majority of asthma exacerbations in children and adults in the community [1,2]. These data are supported by other recent studies demonstrating that virus infections are associated with more severe exacerbations of asthma requiring hospital admission in both adults and children [3] and also in asthma mortality where winter peaks of asthma deaths in adults suggest a viral aetiology [4]. These studies and many previous studies on the same subject (reviewed by Pattemore *et al.* [5]) have over recent years stimulated a great deal of research to elucidate the mechanisms by which upper respiratory virus infections induce exacerbations of asthma.

Many of these studies have involved wild type infections occurring *in vivo* and have led to the identification of a number of possible pro-inflammatory mechanisms. The use of experimental infections, however, allows a more invasive approach to be taken, which in recent years has included bronchoscopy with bronchial lavage and biopsy. These studies have demonstrated that an experimental rhinovirus cold in both normal and asthmatic subjects is associated with a bronchial mucosal $CD3^+$, $CD4^+$ and $CD8^+$ lymphocyte infiltrate, as well as eosinophilia, which in asthmatic subjects was persistent [6]. The addition of allergen challenge to experimental infection results in conversion of early asthmatic reactors to late asthmatic reactors [7], with increased bronchoalveolar lavage eosinophilia and histamine levels [8].

Two of the areas that have provoked a great deal of interest over recent years are the roles of bronchial hyperresponsiveness in virus-induced asthma and the possible role that pro-inflammatory cytokine release plays, not only in the induction of bronchial hyperresponsiveness but also in the inflammatory response in general. In this issue of the journal a further detailed study employing experimental rhinovirus infection reports on both these aspects, demonstrating that bronchial hyperreactivity is induced and that IL-8 may play a role in the induction of bronchial hyperreactivity and therefore possibly in exacerbations of asthma [9].

In this study atopic asthmatic subjects were challenged with rhinovirus 16 or placebo and the severity of the cold and asthma symptoms monitored along with bronchial hyperreactivity, pulmonary function, nasal lavage IL-8 levels and peripheral blood lymphocyte and neutrophil counts. Of the rhinovirus-inoculated subjects, eight developed severe colds and the other 11 developed mild colds. There was no significant change in pulmonary function in either group, though there was a trend in both severe and mild groups for a decrease in FEV_1 of about 5% on the third day after inoculation. There were significant increases in bronchial hyperreactivity in both groups and increases in nasal lavage IL-8 levels on day 2 and day 9. In accordance with previous observations there was also a peripheral blood lymphopenia and neutrophilia. Correlations were observed between the increase in IL-8 level at day 2 and the severity of cold symptoms, the change in PC_{20} and neutrophil and lymphocyte counts. The authors concluded that the severity of a cold induced by experimental rhinovirus infection is related to the increase in airway hypersensitivity to histamine and that release of chemokines such as IL-8 may play a role in this process.

There were a number of interesting features to this study which differ from many previously conducted studies. First is that the method of virus inoculation differed from previous similar studies in that subjects received not only nasal spray and nasal drops as is commonplace but also inhalation via the nasal passages of a nebulized solution of virus. The total dose of virus given was similar to that in previous studies but the changes in histamine reactivity and also the fact that an exacerbation of asthma was induced in the one subject with the most reactive airways suggest that this model may be getting somewhat closer to virus-induced exacerbations of asthma in real life.

The discrepancy between the severity of illness induced by experimental colds and that observed in real life has been a source of criticism of studies such as these and the authors may have pointed the way to try and mimic the real life situation more closely. Clearly the danger is that one does not wish to induce real life exacerbations of asthma in such studies but a demonstrable decrease in airway function and an increase in asthma symptoms is clearly desirable. The authors have achieved a non-significant trend in the former case and a significant increase in asthma symptoms in the latter. I would recommend that any future studies wishing to investigate the mechanisms of virus-induced asthma should employ similar methods to those used in this study. It may be profitable in future studies to monitor small airway function rather than simply PEF or FEV, which are rather crude measures of large airway function.

This study [9], along with that of Cheung *et al.* [10] and

others [6,8], clearly demonstrates that increases in bronchial reactivity can be demonstrated in atopic or asthmatic subjects and also that they may be prolonged [10]. There is now little doubt that bronchial hyperreactivity can be reliably induced by both experimental and wild type virus infections in atopic and asthmatic subjects, though the role of bronchial hyperreactivity in relation to asthma itself is more complex [11]. Bronchial hyperreactivity can also be induced in normal subjects, though less reliably and of lesser severity [12].

The role of cytokine release in virus-induced asthma has been a subject of much study recently and a wide variety of cytokines including IL-1β, IL-6 [13], IL-8 [14], IL-11 [15], TNF$_\alpha$ [13], interferon-α and -γ [13], RANTES and MIP1-α [16] have been found in association with viral infection.

Much more difficult, however, is to determine the possible pathological role of these cytokines. This study goes a little way towards achieving that end in demonstrating that the amount of IL-8 induced by the experimental colds correlates not only with cold and asthma symptoms, but also with the changes in PC_{20} and in peripheral blood cell counts. These data are in accordance with our own observations, which have demonstrated increased IL-8 levels in wild type virus infections during exacerbations of asthma in school children (the majority of these infections were rhinovirus infections [14]). There were also increased levels of the neutrophil product myeloperoxidase, a correlation between the levels of myeloperoxidase and the severity of nasal symptoms, and the IL-8 purified from these samples was biologically active in neutrophil chemotaxis assays, suggesting that IL-8 was playing an active role in recruiting and activating neutrophils [14].

These observations, taken with those of Grünberg *et al.* [9], are consistent with the hypothesis that IL-8 may be playing a pathological role, though it is equally possible that it is protective and/or simply a marker of the severity of virus infection. In order to determine whether IL-8 and other cytokines are playing a pathological role, studies similar to those cited above will need to be carried out, and an assessment of the severity of viral infections made using virus titrations. It is also desirable to study asthmatic subjects suffering colds but no exacerbation of their asthma, and exacerbations of asthma induced by the same virus types. Most importantly, comparisons between normal subjects undergoing colds and asthmatic subjects undergoing virus-induced exacerbations of asthma will also need to be performed before the true importance of these potential mediators in virus-induced asthma can be assessed.

A further interesting finding of this study, although not one of its primary aims, was confirmation of previous observations that neutralizing antibodies to rhinovirus are less protective in asthmatic subjects than in normal subjects where they do appear to have some protective function [12]. This question is intriguing as although it has long been known that local antibody responses are more protective than systemic, systemic antibodies have long been thought to play an important protective role, particularly IgG_1 and IgG_4 [17]. This aspect of the difference between the normal and asthmatic response to virus infections is clearly a subject that would merit further study.

The authors of the present study are to be congratulated on the thoroughness of the methods they employed, as a result of which they have made a number of important and interesting observations. This study by no means answers all the questions that the role of viruses in asthma have provoked but it provides a very good example of how these questions may be answered in further similar studies in the future.

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