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Natural History of Adult-Onset Asthma

Insights from Model of Occupational Asthma

Longitudinal studies from childhood to adult years have yielded risk factors for the persistence of childhood asthma (1). Yet, little is known of the natural history of adult-onset asthma. Occupational asthma has been suggested as a useful “human model” of adult extrinsic asthma (2). In this issue of the *Journal* (pp. 367–372), Maghni and coworkers provide evidence that patients with occupational asthma who retain their bronchial hyperresponsiveness for several years after removal from exposure to the causing agent exhibit persistent airway inflammation, characterized by eosinophilia and neutrophilia in induced sputum (3).

The study of Maghni and coworkers (3) is not solely of interest to investigators of occupational diseases, but is also of interest to most chest physicians. The wide interest is justified because occupational asthma is estimated to account for approximately 15% of the adult asthmatic population (4). Asthma remains the most commonly reported occupational lung disease in most industrialized countries. More interestingly, trends from long-standing surveillance schemes in Finland and the UK show little change in the incidence of occupational asthma over the past 10 years (5,6).

The study by Maghni and coworkers (3) offers the opportunity to employ occupational asthma as a model for studying the natural history of adult-onset asthma in general. There are advantages to using this model for that purpose: the agent causing the disease is well identified; the onset, duration, and intensity of exposure can be determined more precisely than in non-occupational asthma; complete removal of the cause of the disease is feasible, making it possible to characterize the long-term consequences of a respiratory sensitization without interference from further exposures to the inciting agent. A pioneering study by Chan-Yeung and coworkers (7) documented higher numbers of eosinophils and neutrophils in bronchoalveolar lavage fluid of 10 patients who failed to recover from western red cedar asthma after removal from exposure for at least 1 year. Investigations using bronchial biopsies revealed airway inflammation and remodeling in workers studied not very long after cessation of exposure (6–18 months) (8–9). Original findings of the study by Maghni and coworkers (3) include an increase in eosinophils; neutrophils, and their product, myeloperoxidase; and the neutrophil chemoattractant, interleukin-8, in subjects with persistent airway hyperresponsiveness many years after the last exposure (on average, 6.8 years). Of note, the study involved only a minimally invasive technique (induced sputum). The large number

of subjects examined (103) and the lack of difference in the outcome measurements between asthma caused by high- and low-molecular weight agents suggest that these findings may represent a common feature of persistent occupational asthma.

The use of airway responsiveness to methacholine for evaluating control of asthma may seem to conflict with the recommendations of international guidelines that are based solely on symptoms and lung function. There is some evidence, however, that a treatment strategy aimed at reducing airway hyperresponsiveness is more effective in the management of asthma (10). An approach based on airway hyperresponsiveness may be further justified in a long-term study of occupational asthma because airway hyperresponsiveness tends to improve more slowly after cessation of exposure than do symptoms and lung volumes (11, 12). As a consequence of this criterion, Maghni and coworkers (3) excluded patients without measurement of airway hyperresponsiveness. The main reasons that methacholine challenge was not performed were related to the severity of asthma; accordingly, the relationships between functional outcome and inflammatory features at the time of the follow-up applies to subjects with milder asthma. Because of evidence that conditions at diagnosis strongly influence the prognosis (12), it is possible that the results would have been different had all subjects been included in the study. The ideal design of a study for prospectively assessing the consequences of occupational asthma is to include measurements of airway inflammation and lung function before and after removal from exposure to causal agents. Because sputum was not examined before cessation of exposure, the data of Maghni and coworkers (3) does not characterize the starting degree of inflammation, nor do the data indicate whether or not patients with persistent inflammation actually improved during follow-up.

Despite these limitations, the remarkable persistence of airway inflammation and its characteristics have important implications. Because reexposure to the offending agent was excluded, airway inflammation appears self-sustained (without needing a specific exogenous stimulus). Low-molecular weight chemicals responsible for occupational sensitization once inhaled may attach proteins, although these compounds are unlikely to remain in the body for years. The same consideration is even more valid when the sensitizing agent is a protein. If the mechanism of airway inflammation in these patients with persisting asthma is independent of exogenous stimulation, avoiding allergen will not be sufficient to produce a favorable outcome. The question there-

fore arises whether prolonged antiinflammatory therapy might benefit. A few (relatively short-term) controlled clinical trials have explored the benefit of inhaled steroids after removal from the workplace (13, 14). Various clinical and functional parameters, including bronchial hyperresponsiveness, exhibit improvement, but no case of definite cure of asthma has been documented. Most current treatment strategies are focused on eosinophilic airway inflammation. A substantial part of the inflammatory response in persistent occupational asthma, however, appears to involve interleukin-8-mediated neutrophil influx or a mixed eosinophil/neutrophil response (3). Inflammatory mechanisms not involving eosinophilic inflammation are also common in general asthma (15). Indeed, sputum neutrophils were the only cell higher in patients with severe asthma than in patients with mild to moderate asthma in a large cross-sectional European study (16). The availability of non-invasive tools for assessing airway inflammation and the model of occupational asthma may help us better understand the mechanisms responsible for asthma, and lead to the development of new treatment strategies.

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Modulation of Alveolar Fluid Clearance by Acute Inflammation The Plot Thickens

Although many proinflammatory mediators have been measured in biological fluids from patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (1), the pathophysiological significance of a given biological marker is not always apparent from isolated measures of concentrations or immunologic activity. A variety of factors can influence the biological activity of a proinflammatory mediator. For example, the simultaneous presence of inhibitors such as antiinflammatory cytokines, soluble receptors, receptor antagonists, or autoantibodies can markedly alter the biological activity of a given cytokine or other proinflammatory molecule (2). Effects of proinflammatory molecules may also vary depending on the target cell that is studied. Finally, proinflammatory mediators may have complex and unrecognized effects on other physiological systems in addition to their direct involvement in the inflammatory cascade. One example of this type of complex relationship is the increasingly recognized interplay between inflammation, coagulation, and fibrinolysis in sepsis and ALI/ARDS (3). Thus, moving from

simple measures of biological markers to measures of biological activity both *in vitro* and *in vivo* has the potential to greatly enhance our understanding of the pathophysiology of clinical ALI/ARDS.

In this issue of the *Journal* (pp. 407–412), Sloniewsky and coworkers (4) take an important step in this direction with their investigation of the effect of the proinflammatory cysteinyl leukotriene, leukotriene D₄, on alveolar epithelial sodium transport and the activity of the alveolar epithelial Na,K-ATPase. Before this report, investigation of the role of leukotriene D₄ in the pathogenesis of ALI/ARDS has focused principally on its deleterious proinflammatory and permeability-enhancing effects. Sloniewsky and coworkers report that leukotriene D₄, found in substantial levels in the pulmonary edema fluid of patients with ALI/ARDS (5, 6), can increase alveolar epithelial fluid transport both *in vitro* and in the isolated perfused rat lung through increased activity and membrane localization of the Na,K-ATPase (4). This effect is mediated through the CysLT receptor 2, which