relation to baseline FEV₁, the lack of a “response plateau,” and the lack of a response to hyperventilation, may not relate to asthma so much as they relate to disease severity or patient age. Finally, changes in responsiveness induced by allergen stimulation are not related to baseline AHR. This suggests that chronic persistent AHR may have underlying mechanisms that differ from those responsible for short-term changes in AHR induced by inflammation. Our ability to clarify these issues and to better define the structure-function correlates of AHR will depend on our ability to obtain and investigate airway tissue from humans with well-characterized clinical abnormalities.

REFERENCES

1. Willis T. Pharmaceutica rationalis. London: Thomas Dring, 1679; 78-85
2. Floyer J. A treatise of asthma. London: R. Wilkin, 1698

Exhaled Nitric Oxide Is Increased in Asthma*

Sergei A. Khartonov, MD; Deborah Yates, MD; David R. Springall, PhD; Lee Buttery, BS; Julia Polak, MD; Richard A. Robbins, MD; and Peter J. Barnes, DSc

Asthma is an airway disease which has been associated with cytokines released by inflammatory cells. Nitric oxide is a highly reactive gas formed from arginine by nitric oxide synthase (NOS). The inducible form of NOS (iNOS) is known to be induced by cytokines but decreased by corticosteroids. In this context, we hypothesized that lung epithelial cells could be stimulated by cytokines to express iNOS and that corticosteroids would decrease the cytokine-induced increase.

To test this hypothesis, the murine lung epithelial cell line, LA-4, and primary cultures of human bronchial epithelial cells were stimulated with cytokinx, a combination of TNF-α, IL-1β, and interferon-γ. Nitric oxide production was assessed by evaluating the culture supernatant fluids for nitrate, the stable end product of NO, and evaluating the cells for iNOS by immunocytochemistry and iNOS mRNA by Northern blot analysis.

Both murine and human cells demonstrated an increase

*From the National Heart and Lung Institute and Royal Postgraduate Medical School, London. Dr. Robbins is with the University of Nebraska Medical Center, Omaha.
in each of the different measures of NO production when cultured with cytomix (p<0.05, all comparisons) and each was decreased by dexamethasone 10^{-6} M (p<0.05, all comparisons). To determine if these in vitro observations are reflected in vivo, exhaled NO was measured in 64 normal subjects, 22 asthmatics not taking corticosteroids, and 36 asthmatics taking inhaled corticosteroids. Peak exhaled NO levels were increased in asthmatics not taking corticosteroids compared to normal control subjects (p<0.01) but not in asthmatics taking corticosteroids (p>0.05).

These data demonstrate that cytokines increase iNOS expression by lung epithelial cells which is decreased by corticosteroids and that these in vitro observations are mirrored by exhaled NO levels in asthmatics.

**Increased Sensitivity to the Consequences of Rhinoviral Infection in Atopic Subjects**

Philip G. Bardin, MD; D. Fraenkel; G. Sanderson; Martina Dorward; Sebastian Johnston, PhD; and Stephen Holgate, DSc

Rhinovirus (HRV) may be the predominant cause of asthma exacerbations in children as well as adults. Although worsening of existing airway disease is probably mediated by means of increases in airway responsiveness (AR), there is controversy as to whether atopic individuals are more susceptible to the consequences of rhinoviral infection. We hypothesized that an allergic diathesis modulates rhinoviral colds and have initiated studies employing experimental rhinoviral infection, measuring both upper airway symptoms, nasal albumin levels, and lower airway reactivity in normal and atopic individuals.

Twenty-two subjects (11 normal, 5 atopic, 6 atopic asthmatic) had preinoculation measurements of virus (HRV serotype 16) neutralizing antibody levels, IgE, skin tests, and AR performed. This was followed by HRV 16 colds, daily symptom scores and nasal washes, and a repeat of AR measurements.

Seventeen volunteers developed clinical colds as measured by symptom scores, and virus shedding was present in all subjects. The presence or absence of preinoculation antibody determined subsequent severity of colds in normal but not in atopic subjects. Atopic antibody-positive individuals developed severe colds in contrast to normal subjects who developed mild colds in the presence of neutralizing antibody (p=0.01). Both atopic and normal antibody-negative subjects developed severe colds. This differential response was matched by nasal albumin levels which were significantly increased during the cold in atopic (but not in normal) volunteers with preinoculation antibody present (p=0.01). The IgE levels were higher in atopic subjects but did not correlate with more severe cold scores. In the entire group, AR was significantly increased during the cold (p=0.05) as well as in all atopic subjects (p=0.02). This was also true in atopic asthmatics (p=0.02) but not in normal nonatopic volunteers (p=0.10). A significant correlation was found between symptom scores and AR (r=0.9, p=0.008) in asthmatic but not normal subjects.

Our data suggest that atopic individuals exhibit increased sensitivity to the consequences of HRV infection manifest both as severe upper airway cold symptoms and as amplified lower airway responsiveness. Atopic tissues may be "preprimed" and more susceptible to the detrimental effects of colds.