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## Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids

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### Abstract

TOP

Nitric oxide (NO) is produced in large amounts in the noses of normal individuals. We have measured NO by chemiluminescence in the noses and exhaled air of subjects with symptomatic

allergic rhinitis, some of whom had concomitant asthma, during the pollen season and compared this with values measured in normal subjects and in patients treated with nasal and/or inhaled glucocorticoids. We found that nasal levels of NO were significantly ( $p < 0.001$ ) elevated in patients with untreated rhinitis ( $1527 \pm 87$  ppb,  $n = 12$ ) compared with normal individuals ( $996 \pm 39$  ppb,  $n = 46$ ) or subjects treated with nasal steroids ( $681 \pm 34$  ppb,  $n = 10$ ), whereas exhaled NO in patients with untreated rhinitis was similar to that in normal subjects ( $10 \pm 2$  ppb vs  $7 \pm 0.6$  ppb, respectively). In five subjects who were nasally challenged with allergen, there was a significant decrease in nasal NO 1 hour after challenge, and this was significantly correlated with increased rhinitis symptoms. In patients with rhinitis and concomitant asthma, nasal NO was also significantly elevated ( $1441 \pm 76$  ppb,  $n = 16$ ) but not when they were treated with nasal or inhaled steroids; whereas exhaled NO was elevated in untreated patients and in patients treated with nasal, but not inhaled, steroids. Our data suggest that the increase in exhaled NO in patients with allergic rhinitis is likely to be due to increased local production, caused by long-term exposure to allergen, which is suppressed by locally administered steroids. Measurement of nasal NO may be useful to study the inflammatory response in rhinitis and its response to antiinflammatory treatments. (J Allergy Clin Immunol 1997;99:58-64.)

|               |                                               |
|---------------|-----------------------------------------------|
| <b>iNOS</b>   | Inducible nitric oxide synthase               |
| <b>L-NAME</b> | N <sup>G</sup> -nitro-L-arginine methyl ester |
| <b>NO</b>     | Nitric oxide                                  |
| <b>NOS</b>    | Nitric oxide synthase                         |

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**Key Words:** [Nitric oxide](#), [allergic rhinitis](#), [inducible nitric oxide synthase](#), [glucocorticoids](#)

Nitric oxide (NO) is formed by many cells in the respiratory tract and may be detected in the exhaled air of animals and human beings.<sup>1,3</sup> There is evidence for an increased concentration of NO in the exhaled air of patients with asthma<sup>3,5</sup> and bronchiectasis<sup>6</sup> and in the exhaled air of individuals who have had upper respiratory tract infections.<sup>7</sup> This increase in exhaled NO may reflect increased expression of an inducible form of the enzyme NO synthase (NOS) in response to inflammatory stimuli, such as cytokines, suggesting that exhaled NO may be useful to monitor inflammation in the respiratory tract. The concentrations of NO in nasal air are considerably higher than those measured in orally exhaled air,<sup>8,10</sup> and this has suggested that the high concentration of exhaled NO may be contaminated by NO derived from the upper respiratory tract. The source of NO in the nose is uncertain, but recent evidence suggests that it may derive from the very high levels in the paranasal sinuses.<sup>11</sup> However, immunohistochemical studies suggest that NO may also be derived from NOS expressed in the nasal mucosa.<sup>12</sup> Little is known about the effects of disease on nasal NO, although a recent report suggests that levels may be elevated in patients with seasonal rhinitis.<sup>13</sup> It is not certain whether these elevated levels of NO in rhinitis are derived from the

inducible enzyme that is inhibited by glucocorticoids.

We have measured nasal and exhaled NO in patients with symptomatic seasonal rhinitis, some of whom also had asthma, who were either untreated or receiving treatment with topical glucocorticoids.

Methods

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Subjects

We studied 46 normal nonsmoking subjects and 22 patients with seasonal atopic allergic rhinitis who did not have asthma (Table I).

Table I. Clinical characteristics of the subjects

| Subjects                                                      | No. | Age (yr) | Sex (M/<br>F) | Atopic<br>status | FEV <sub>1</sub> (%<br>predicted) | FVC (%<br>predicted) |
|---------------------------------------------------------------|-----|----------|---------------|------------------|-----------------------------------|----------------------|
| Normal control<br>subjects                                    | 46  | 32 ± 4   | 40/6          | 6                | 95 ± 5                            | 96 ± 4               |
| Asthma + allergic<br>rhinitis (untreated)                     | 16  | 36 ± 4   | 8/8           | 13               | 85 ± 5                            | 87 ± 4               |
| Asthma + allergic<br>rhinitis (inhaled<br>steroids)           | 15  | 33 ± 3   | 9/6           | 14               | 87 ± 4                            | 90 ± 5               |
| Asthma + allergic<br>rhinitis (nasal<br>steroids)             | 11  | 34 ± 4   | 5/6           | 11               | 87 ± 5                            | 89 ± 5               |
| Asthma + allergic<br>rhinitis (nasal and<br>inhaled steroids) | 8   | 33 ± 5   | 3/5           | 8                | 86 ± 4                            | 89 ± 5               |
| Allergic rhinitis<br>(untreated)                              | 12  | 37 ± 3   | 5/7           | 12               | 94 ± 6                            | 95 ± 6               |
| Allergic rhinitis<br>(nasal steroids)                         | 10  | 31 ± 3   | 4/6           | 9                | 92 ± 7                            | 94 ± 6               |
| Allergic rhinitis<br>(allergen<br>challenge)                  | 5   | 32 ± 3   | 5             | 5                | 99 ± 2                            | 102 ± 4              |

FVC, Forced vital capacity.

We also studied 50 patients with asthma and seasonal allergic rhinitis (hay fever) (Table I ■). None of the patients were current smokers, and two had been ex-smokers for more than 6 years. All the

asthmatic subjects had a history of wheezing or chest tightness and were previously diagnosed by a doctor as having asthma, and all patients had a clinical history of seasonal allergic rhinitis for at least 2 years. None of the patients with seasonal rhinitis had perennial rhinitis, nasal polyposis, sinus disease, chronic nasal obstruction, or other serious illness. A positive cutaneous response (skin prick test that produced a 3 mm wheal) to a defined antigen (cat dander, house dust mite, grass pollen, *Aspergillus fumigatus*) was identified in 46 of 50 patients with asthma and in six of 46 control subjects. All had FEV<sub>1</sub> values greater than 80% of predicted value. The patients with asthma and rhinitis were divided into four groups: untreated (received either no regular treatment or inhaled  $\beta_2$ -agonists alone,  $n = 16$ ), treated with inhaled glucocorticoids (beclomethasone dipropionate, budesonide, or fluticasone propionate 200 to 800  $\mu\text{g}$  daily for >3 weeks,  $n = 15$ ), treated with nasal steroids (beclomethasone dipropionate, budesonide, or fluticasone propionate 150 to 400  $\mu\text{g}$  daily for >3 weeks,  $n = 11$ ), and treated with nasal and inhaled steroids ( $n = 8$ ).

We studied 22 patients who had a clinical history of seasonal rhinitis during the grass pollen season in the United Kingdom (June and August) at a time when they were experiencing symptoms; 21 of these subjects had positive skin prick test results. None had perennial rhinitis, nasal polyposis, chronic nasal obstruction, or other serious illness. These patients were divided into two groups: untreated (received either no regular treatment or nasal antihistamines,  $n = 12$ ) and treated with nasal steroids (beclomethasone dipropionate, budesonide, or fluticasone propionate 200 to 400  $\mu\text{g}$  daily for >3 weeks,  $n = 10$ ).

In addition, five subjects with seasonal rhinitis (Table I ■) were studied out of season and underwent bilateral nasal allergen challenge with grass pollen. There was no history of upper respiratory tract infection in any subject for at least 4 weeks before the study. Patients did not consume any caffeine for 2 hours or use aerosol bronchodilators for 8 hours before any challenge.

All subjects gave their written consent to participate in the study. The study protocol was approved by the Ethics Committee of the Royal Brompton Hospital.

## Lung function measurements

Lung functional parameters were measured by spirometry (Vitalograph, Buckingham, U.K.).

## Nasal allergen challenge

A specific allergen extract (freeze-dried grass pollen extracts; ALK, Copenhagen, Denmark) was insufflated as a single dose of 500 biological units into each nostril, providing a total dose of 1000 biological units, by means of a hand-held pump spray that delivered 0.13 ml with each squirt. Symptoms were graded as described below. After the antigen challenge, subjects were asked to record their symptom scores hourly for 6 hours on a diary card. NO was measured before the challenge, and at 1, 2, 4, and 6 hours afterward.

During the nasal challenge, subjects were instructed to record their nasal symptoms every hour by using a numerical scoring system based on the following scale: sneezes, 0 (none), 1 (1 to 5), 2 (6 to 10), and 3 (>10); both rhinorrhea and nasal congestion, 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The maximum possible score was 9. The early-phase response was defined as symptoms occurring immediately after the nasal antigen challenge and ending at 1 hour after the dose of allergen was administered.

## NO measurements

Exhaled NO was measured by using a modified chemiluminescence analyzer (model LR2000; Logan Research, Rochester, U.K.), sensitive to NO from 1 to 5000 ppb (by volume), and with a resolution of 1 ppb, which was designed for on-line recording of exhaled NO concentration, as previously described.<sup>3 14</sup> This feature obviates the need for collection in a reservoir, with its variable loss of reactive NO, and provides greater sensitivity (with a response time <0.5 seconds) and high reproducibility. In addition to NO, the analyzer also measured CO<sub>2</sub> (resolution, 0.1% CO<sub>2</sub>; response time, 200 milliseconds) and sample pressure and volume in real time. The sampling rate of the analyzer was 250 ml/min for all measurements. The analyzer was calibrated daily by using certified NO mixtures (90 ppb and 500 ppb) in nitrogen (BOC Special Gases; Surrey Research Park, Guildford, U.K.). Ambient air NO was recorded before and after each subject was studied.

Measurements of exhaled NO were made by slow exhalation (5 L/min) from total lung capacity for 30 seconds through a wide-bore Teflon tube, bypassing the analyzer, and thus with minimal resistance to flow; NO (end-exhaled) was sampled from a side arm. The value corresponding to the plateau of the end-exhaled CO<sub>2</sub> reading (5% CO<sub>2</sub>) was taken as representative of an alveolar sample. In these measurements subjects wore a nose clip, and the pressure during expiration was kept constant ( $3 \pm 0.4$  mm Hg) by using a visual display of expiratory flow measured by pressure and volume sensors in the analyzer. Nasal NO was measured with a Teflon tube inserted into one of the nares while the subject held his or her breath (i.e., with no active exhalation). This allowed analysis of the local NO concentration with free flow of ambient air (250 ml/min) from one nostril to the other and subsequent direction into the analyzer. Baseline values at each visit were taken after subjects quietly rested for at least 15 minutes.

## Statistics

All the results were expressed as means  $\pm$  SEM. Comparisons between groups were made by repeated-measures two-way analysis of variance with Bonferroni's correction for multiple comparisons. A *p* value of less than 0.05 was considered significant.

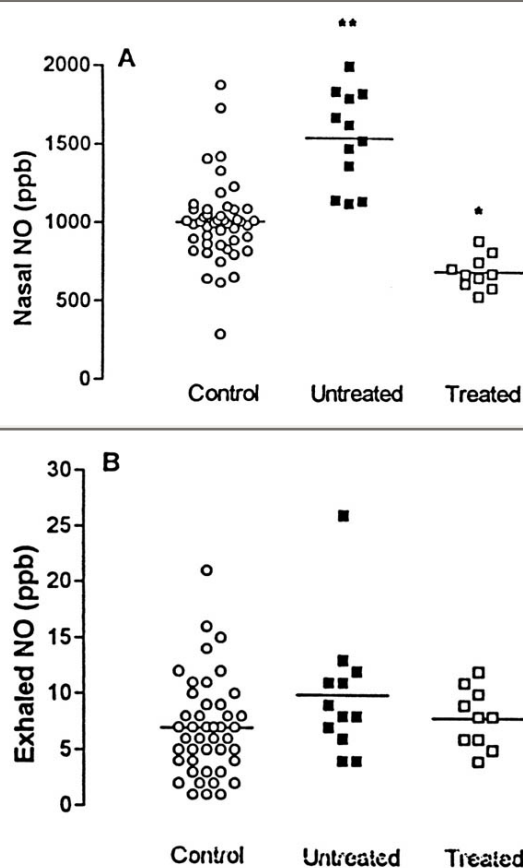
## Results

TOP

### Nasal and exhaled NO in rhinitis

Nasal NO was significantly ( $p < 0.001$ ) elevated in patients with untreated seasonal rhinitis during the pollen season, compared with control subjects without rhinitis or asthma (Fig. 1, Table II).

**Fig. 1.** NO levels in the nose **(A)** and in exhaled air **(B)** in normal subjects (*open circles*), patients with untreated rhinitis (*filled squares*), and patients with rhinitis treated with topical steroids (*open squares*). Significance of difference from control subjects: \*\* $p < 0.001$ , \* $p < 0.05$ .



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Table II. Nasal and exhaled NO in normal subjects and patients with allergic rhinitis

|                  | Normal subjects | Patients with allergic rhinitis |                |
|------------------|-----------------|---------------------------------|----------------|
|                  |                 | Untreated                       | Nasal steroids |
| No.              | 46              | 12                              | 10             |
| Nasal NO (ppb)   | 996 ± 39        | 1527 ± 87*                      | 681 ± 34†      |
| Exhaled NO (ppb) | 7 ± 0.6         | 10 ± 2                          | 8 ± 1          |

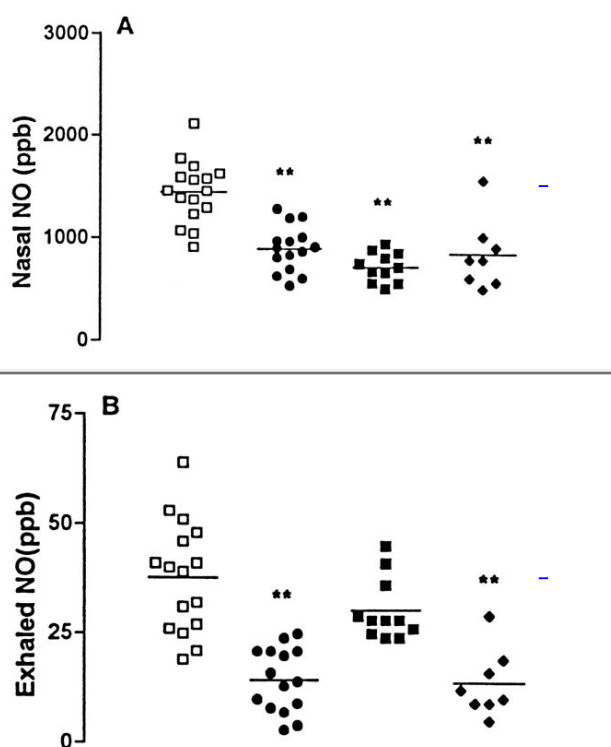
Data are expressed as means ± SEM. Significance of difference in NO and FEV<sub>1</sub> from the group of untreated patients ( $p$  value) was determined by analysis of variance.

\* $p < 0.001$ .

† $p < 0.05$ .

In patients with both rhinitis and asthma who were not receiving either nasal or inhaled glucocorticoids, there was also a significant ( $p < 0.001$ ) elevation of nasal NO (Fig. 2, Table III).

**Fig. 2.** NO levels in the nose **(A)** and in exhaled air **(B)** in patients with concomitant rhinitis and asthma who were untreated (*open squares*), treated with inhaled steroids only (*filled circles*), treated with nasal steroids only (*filled squares*), or treated with combined nasal and inhaled steroids (*filled diamonds*). Significance of difference from untreated patients: \*\* $p < 0.001$ .



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Table III. The effect of treatment with inhaled and/or nasal glucocorticoids on nasal and exhaled NO in patients with asthma and allergic rhinitis

|                  | Untreated | Inhaled steroids | Nasal steroids | Inhaled + nasal steroids |
|------------------|-----------|------------------|----------------|--------------------------|
| No.              | 16        | 15               | 11             | 8                        |
| Nasal NO (ppb)   | 1441 ± 76 | 892 ± 57*        | 713 ± 42*      | 836 ± 119*               |
| Exhaled NO (ppb) | 38 ± 3    | 14 ± 2*          | 30 ± 2         | 14 ± 3*                  |

Data are expressed as means  $\pm$  SEM. Significance of difference from untreated subjects ( $p$  value) was determined by analysis of variance.

\* $p < 0.001$ .

Exhaled NO levels were not significantly different in patients who had rhinitis but not asthma from values in normal control subjects but were significantly ( $p < 0.001$ ) elevated in untreated patients who had both rhinitis and asthma (Fig. 2 ■).

### Effect of treatment with topical glucocorticoids

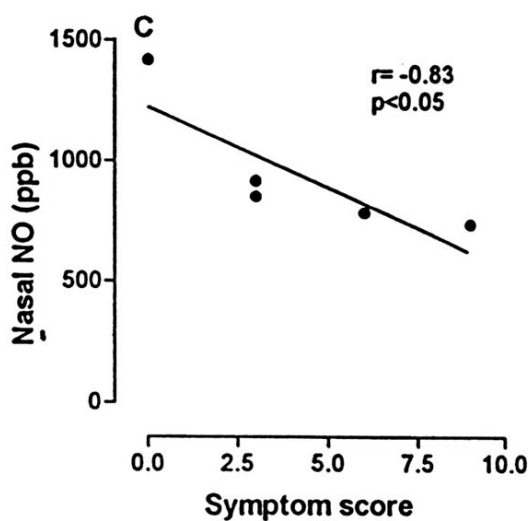
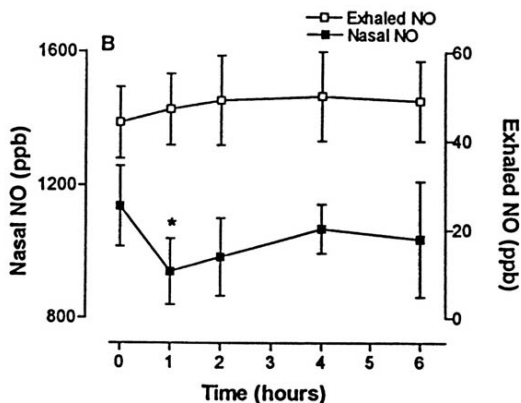
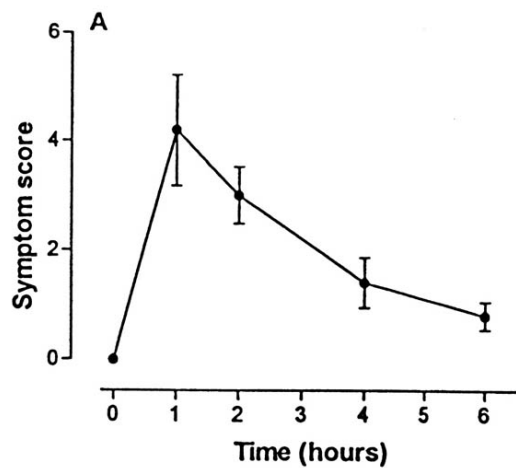
Nasal NO was significantly reduced in patients with allergic rhinitis treated with nasal glucocorticoids in comparison with the untreated group of patients with rhinitis ( $p < 0.001$ ) and normal subjects ( $p < 0.05$ ) (Fig. 1 ■, Table II ■).

Nasal NO was lower in patients with seasonal allergic rhinitis with asthma treated with nasal steroids ( $p < 0.001$ ), inhaled steroids ( $p < 0.001$ ), or nasal + inhaled glucocorticoids ( $p < 0.001$ ) in comparison with an untreated group of similar patients (Fig. 2 ■, Table III ■). Exhaled NO did not differ in the group of patients receiving nasal steroids ( $p > 0.05$ ) but was significantly reduced in patients treated with inhaled ( $p < 0.001$ ) or nasal + inhaled glucocorticoids ( $p < 0.001$ ) in comparison with an untreated group of similar patients. There were no significant differences in FEV<sub>1</sub> between the groups.

### Effect of allergen challenge

Nasal challenge with grass pollen extract in five atopic subjects resulted in immediate nasal symptoms (symptom score,  $7 \pm 0.8$ ), which gradually declined to baseline at 6 hours (Fig. 3).

**Fig. 3.** Effect of nasal allergen challenge on exhaled NO in patients with seasonal rhinitis studied out of season. **A**, Symptom score after allergen challenge. **B**, Nasal and exhaled NO levels at the same time points. Mean values  $\pm$  SEM of five patients are shown. Significance of difference from baseline: \* $p < 0.05$ . **C**, Correlation between nasal NO and symptom scores.



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Nasal NO was significantly reduced at 1 hour ( $942 \pm 83$  ppb) after nasal allergen challenge compared with baseline values ( $1138 \pm 96$  ppb,  $p < 0.05$ ) but had recovered at 4 hours. There was a significant negative correlation between nasal NO and symptom scores at 1 hour after allergen challenge ( $r = -0.97$ ,  $p < 0.005$ ).

## Discussion

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We have confirmed that the levels of NO in the nose are considerably greater than levels in exhaled air and that the levels in patients with symptomatic allergic rhinitis are significantly higher than levels

in subjects without rhinitis. Furthermore, patients with rhinitis treated with nasal steroids had significantly lower nasal NO levels than untreated patients with rhinitis and even normal subjects. Surprisingly, nasal allergen challenge out of season, which induced acute symptoms of rhinitis, resulted in a rapid fall in nasal NO; and the magnitude of this fall correlated with severity of symptoms.

The high levels of NO in the nose are consistent with previous reports,<sup>8 10 14</sup> and we have confirmed that levels of nasal NO are elevated in patients with symptomatic rhinitis.<sup>13</sup> The source of NO in the nose is uncertain, but it is possible that it is derived from the high level of expression of inducible NO synthase (iNOS, type II NOS) in paranasal sinuses.<sup>11</sup> However, immunocytochemical studies have also demonstrated expression of NO synthases in human nasal mucosa. Normal subjects express the endothelial type of NOS (ecNOS or type III NOS), whereas subjects with rhinitis show expression of iNOS in nasal epithelial cells.<sup>12</sup> In addition, the neuronal form of NOS (nNOS, type I NOS) is localized to nerves within the nose,<sup>15</sup> although it is unlikely that nerves would make a significant contribution to nasal NO. These data suggest that the increased levels of NO in nasal air of patients with rhinitis may be derived from iNOS expression in the nasal mucosa. There is a close analogy to the increase in exhaled NO levels found in asthmatic patients,<sup>3 5</sup> which may be derived from the increased expression of iNOS in airway epithelial cells of patients with asthma.<sup>16</sup> The mechanism of increased iNOS expression in allergic rhinitis and asthma may be similar, and similar proinflammatory cytokines have been detected in the nasal mucosa of patients with rhinitis, as in bronchoalveolar lavage fluid of asthmatic patients.<sup>17 18</sup> Proinflammatory cytokines induce iNOS expression in cultured human airway epithelial cells in vitro because of increased transcription of the iNOS gene.<sup>19 20</sup> Bacteria that colonize the nose are another possible source of NO, because some strains produce NO.<sup>21 22</sup> However, this is unlikely, and previous studies have shown that antibiotics do not affect nasal NO.<sup>8</sup>

The functional significance of increased NO production in rhinitis is not yet certain. NO is a potent vasodilator and might be expected to contribute to the mucosal swelling in rhinitis. In animal studies there is evidence that the NO synthase inhibitor N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME) increases plasma exudation in the lower airways.<sup>23 24</sup> Topical application of L-NAME blocks the plasma exudation induced by nasally administered histamine in nonallergic subjects and allergen in patients with allergic rhinitis, suggesting that NO may play a role in plasma exudation in the human nose.<sup>25</sup>

We found that patients with rhinitis who were treated with nasal steroids had significantly lower values of nasal NO than untreated patients. This is consistent with our previous studies of inhaled glucocorticoids in patients with asthma. Asthmatic patients treated with inhaled steroids have normal levels of exhaled NO,<sup>3</sup> and the elevated levels of NO in exhaled air are reduced by either oral or inhaled glucocorticoids.<sup>26 27</sup> Furthermore, reduction in the dose of inhaled steroids in patients with asthma that is controlled results in an increased level of exhaled NO.<sup>28</sup> It is likely that glucocorticoids inhibit the induction of iNOS, resulting in decreased production of NO. In epithelial

cells glucocorticoids inhibit cytokine-mediated induction of iNOS,<sup>19 29</sup> and a biopsy study has demonstrated that patients receiving inhaled steroids have less expression of iNOS in epithelial cells than untreated patients with asthma.<sup>30</sup> It is therefore likely that nasal steroids have a similar inhibitory effect on iNOS expression in the nasal mucosa, thus reducing the nasal levels of NO. The fact that control of nasal symptoms with topically applied steroids is associated with reduced values of nasal NO suggests that the elevation of NO in allergic rhinitis is unlikely to be derived from paranasal sinuses, which should not be affected by steroids applied in nasal sprays. However, the levels of NO found in normal subjects and patients with rhinitis after administration of inhaled steroids may be derived from a constitutive form of NOS and may, at least in part, be derived from the paranasal sinuses. It is of interest that the values of nasal NO after administration of topical nasal steroids were significantly lower than values in normal subjects, suggesting that some of the NO, even in normal individuals, may be derived from iNOS expression in the nose.

Challenge of patients with rhinitis with allergen resulted in a significant fall in nasal NO, without any effect on exhaled NO levels. This change was maximal at 1 hour when symptoms were at a peak, and there was a significant correlation between the magnitude of the fall in nasal NO and the symptom score. A fall in nasal NO is surprising but may be due to inflammatory swelling of the nasal mucosa, resulting in blockage that may reduce the contribution from paranasal sinuses. Alternatively, the increase in blood flow and vascular permeability during the acute allergic response may itself facilitate the removal of NO from the nasal mucosa. In asthmatic patients we have not observed any such fall in exhaled NO during the early response to allergen.<sup>31</sup> However, we have observed an increase in exhaled NO during the late response to allergen, which is associated with an inflammatory response in the airway mucosa.<sup>31</sup> In this study we did not observe any increase in nasal NO 6 hours after allergen challenge, but none of the subjects experienced a late response in terms of symptoms within 6 hours. Long-term exposure to allergen may be expected to produce different effects and may result in induction of iNOS in the nasal mucosa.

The relationship between inflammation in the nose and lungs is complex, and many patients have concomitant asthma and rhinitis. In our study we report that the exhaled NO levels in patients with rhinitis but without asthma was not significantly different from values in normal subjects. However, in patients who had untreated asthma and rhinitis, the exhaled NO level was elevated as expected. There has been debate about whether NO measured in exhaled air is contaminated by the high levels of NO in the upper airways.<sup>8 10</sup> We have recently measured NO directly from the lower respiratory tract by means of a bronchoscope in normal and asthmatic subjects and have demonstrated that the levels are similar to those measured at the mouth when the exhalation is unobstructed.<sup>14</sup> Furthermore, the levels measured in the lower airways are elevated in asthmatic patients to the same extent as those measured in exhaled air.

As we have previously observed, asthmatic patients treated with inhaled steroids had levels of exhaled NO that were not significantly different from values in normal subjects. In patients who had both asthma and rhinitis, treatment with inhaled steroids had no effect on nasal NO, and treatment with nasal steroids had no effect on exhaled NO. This suggests that treatment of the inflammation in the upper airways has no effect on inflammation in the lower airways, at least as measured by exhaled NO. Concomitant treatment with inhaled and nasal steroids resulted in normal exhaled and nasal NO levels, as expected. However, we also found that nasal NO levels, as well as exhaled NO levels, were significantly lower in patients with rhinitis treated with inhaled steroids alone. This is

likely to be due to deposition of the inhaled glucocorticoid in the nose during the inhalation maneuver and suggests that inhaled steroids may be used to treat nasal and bronchial mucosal inflammation.

We have demonstrated that nasal NO is elevated in subjects with symptomatic seasonal rhinitis who are untreated and that treatment with nasal steroids is associated with normal levels. This strongly suggests that the elevated levels are due to iNOS expression in the nasal mucosa, and further studies examining expression of iNOS in rhinitis and the effects of therapy are now indicated. Nasal NO measurement is simple and noninvasive and may be a useful means of assessing nasal inflammation and the response to antiinflammatory treatment, such as glucocorticoids. Controlled trials are now needed to assess this formally. The role of NO in the regulation of nasal function remains to be elucidated, but experiments with NO synthase blockers in rhinitis would be of great interest, both in terms of the pathophysiology of rhinitis and of the development of more specific therapies for this common condition.

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