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Upper airway inflammatory diseases and bronchial hyperresponsiveness

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Inflammatory processes of the upper airway may alter the responsiveness of the lower airway. For example, bronchial hyperresponsiveness may be seen in patients with allergic rhinitis. This could represent coexistent but unrecognized asthma, but also suggests that IgE-dependent inflammation may occur in the lower airway that can increase bronchial hyperresponsiveness without at the same time precipitating obvious obstruction. Clearly, allergic rhinitis is a risk factor for asthma. A second example of the interaction of upper airway inflammation and bronchial hyperreactivity are reports that viral upper respiratory tract infections may cause otherwise healthy persons to respond abnormally to inhaled histamine or irritants for several months after the infections. These same viruses usually precipitate attacks in patients with asthma, who already have hyperresponsive airways. Both of these examples suggest that inflammatory processes occurring totally or primarily in the upper airway may participate in the pathogenesis of lower respiratory tract hyperresponsiveness and asthma. (J ALLERGY CLIN IMMUNOL 1988;81:1036-41.)

Bronchial hyperreactivity is defined as an abnormal responsiveness of the airways, expressed as increased air flow obstruction on exposure to a variety of physical, chemical, and pharmacologic bronchoprovocational agents.[1] It is equally well expressed by the prompt reversal of obstruction by beta adrenergic agonists or other bronchodilators. Hyperresponsiveness is almost always present in asthma and is sometimes considered pathognomonic; it may also be seen in cystic fibrosis, chronic bronchitis, and other lung diseases.

Bronchial hyperreactivity is usually thought of as an abnormality of the lower respiratory tract. Recently it has been described in two disorders in which the lower respiratory tract is usually normal. Patients with allergic rhinitis, who are at risk for asthma subsequently, frequently exhibit increased bronchial hyperresponsiveness; and acute viral upper respiratory tract infections may induce bronchial responsiveness. This de novo induction of hyperresponsiveness during airway infection suggests a mechanism that may explain the frequent associations of upper respiratory tract infections with wheezing episodes in patients with asthma and also why some healthy persons can develop persisting bronchial hyperresponsiveness.

Abbreviation used
FEV_1: Forced expiratory volume in 1 second

The mechanism underlying hyperresponsive airways is not known, but it has been suggested that abnormalities may exist in mucosal permeability, in autonomic control of bronchial smooth muscle, or in the smooth muscle itself.[1] Most hypotheses presume an abnormality in the lower respiratory tract, and so offer explanation for abnormal responses seen in diseases apparently limited to the upper respiratory tract. The access of molecules from the lumen of the respiratory tract to submucosal structures is limited in the normal state by the maintenance of "tight junctions" between epithelial cells. These junctions may be disrupted after exposure to pollutants[2] or to IgE-mediated inflammation.[3] However, abnormal bronchoconstriction also occurs when histamine is given parenterally to patients with asthma,[4] so this cannot be the sole mechanism. The caliber of the lower airways is under balanced autonomic control. Vagal efferent nerves decrease airway caliber, and the afferent input to these reflexes may originate in irritant receptors in either the lower or upper tract mucosa.[5] A major balancing factor is sympathetic tone, and decreased beta adrenergic responsiveness has been shown in

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asthma,[6] chronic bronchitis,[7] and viral upper respiratory tract infections.[8] Abnormalities of the bronchial smooth muscle, either hypertrophy or increased mass or abnormal response characteristics, have been proposed as mechanisms for hyperreactivity.[9]

The usual method of estimating bronchial reactivity is by use of bronchoprovocational agents, and the two most common challenges are exercise and inhalation of methacholine or histamine. The techniques for exercise challenge have been described in detail.[10] In general, 6 minutes of strenuous exercise is required to cause significant and reproducible airflow changes, so this test has been applied almost exclusively in children and young adults. Isocapneic hyperventilation, in which the ventilatory changes associated with exercise are reproduced voluntarily, is becoming more widely used as a substitute.[11]

Inhalation challenges are usually conducted using histamine or methacholine.[12, 13] After determining a baseline control response to inhaled saline solution, the agonist is inhaled, beginning with low concentration (0.025 to 0.03 mg/ml) and progressing stepwise with increasing doses, usually doubling at each step ($\Delta \geq 20\%$). Pulmonary function tests are measured after each step, and the test is stopped when a significant response occurs. The results are expressed as the dose or concentration causing pulmonary function tests to change a given amount from control values (usually a 20% change in FEV_1 or peak expiratory flow rate). This dose is called the PD_{20} FEV_1, expressed as breath units (1 breath unit is one inhalation of 1 mg/ml), or as the PC_{20} FEV_1 for the concentration (in milligrams per milliliter) causing a 20% change in FEV_1. Distilled water inhaled for increasingly longer times has also been used to demonstrate hyperreactivity.[14] The results of all of these tests correlate reasonably well with one another and thus appear to measure the same abnormality.

ALLERGIC RHINITIS

Allergic rhinitis has been said to be a risk factor for development of asthma. When examined, 29% to 57% of adults with asthma have coexisting rhinitis,[15, 16] but it is not clear that the rhinitis precedes the asthma. From the studies of Broder et al.[16] of the entire population of a small town in Michigan, it would appear that rhinitis does not precede asthma very often. When first studied in 1959-1960, 579 persons were identified as having allergic rhinitis. When restudied 3 to 5 years later, only 6.4% of these persons had asthma. Nevertheless, this rate was substantially higher than the 2.0% of new cases of asthma identified in persons without allergic rhinitis during this period.

Allergic rhinitis in childhood may be associated with development of asthma more frequently. Anderson et al.[17] examined 8806 children enrolled in the National Child Development Study of England, Scotland, and Wales; this represented 51% of a cohort observed since birth during a single week in March 1958. At age 7, 11, and 16 years they completed a questionnaire, were interviewed, and were examined by a school physician. A total of 24.7% had had wheezing during childhood, but the point prevalence at 7, 11, and 16 years was only 8.3, 4.7, and 3.5%, respectively. Those with allergic rhinitis and sneezing attacks at age 7 years were 7.1 times more likely to have had wheezing sometime during childhood.

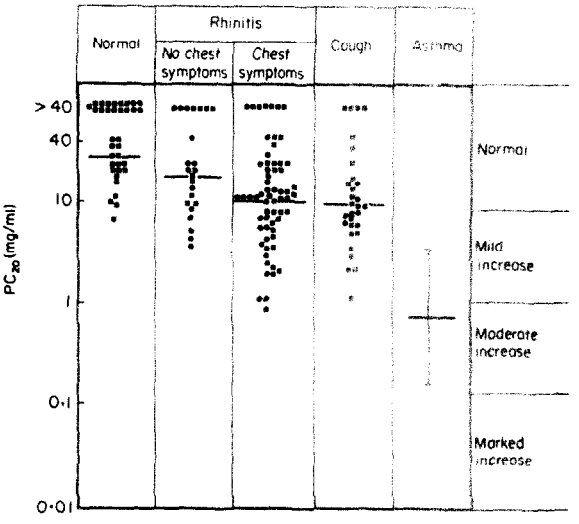

FIG. 1. Responses to histamine inhalation challenge in adults with allergic rhinitis, cough, or asthma, compared with normal persons. Geometric mean value of PC_{20} (±1 SD) for 156 patients with asthma is shown in column 5. (From Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Clin Allergy 1977;7:235-43.)

Allergic rhinitis may be a risk factor for development of asthma, and is further suggested by the frequent association with airway hyperreactivity. A comparison of responses to histamine bronchoprovocation in healthy volunteers and in patients with allergic rhinitis and asthma is illustrated in Fig. 1. Twenty-nine percent of those with reaction to bronchial challenge testing can be demonstrated as having a current or past history of asthma.[11, 12, 18, 19] However, persons with allergic rhinitis are clearly less responsive than those with asthma, even when allergic sensitivity as assessed by skin tests or leukocyte histamine release studies is comparable.[20, 21]

The significance of the association between allergic rhinitis, asthma, and abnormal airway responsiveness with regard to the pathogenesis of asthma is unknown. As a first approach to understanding this association,

it is worth considering the link between allergy and abnormal airway reactivity. Based on reports of a clustering of abnormal methacholine responsiveness among atopic families, some investigators have suggested a possible genetic basis for this link.[22] Another possibility is that hyperresponsiveness arises in atopic persons as an acquired abnormality, perhaps as a consequence of inflammatory changes in the lower respiratory tract. Cockcroft et al.[23] have shown controlled intrapulmonary deposition of allergen in the laboratory. Environmental allergen exposure[24] can produce a transient increase in histamine and methacholine responsiveness in allergic patients who develop late-phase asthmatic reactions. These changes are of the same order of magnitude as found in normal persons after viral respiratory tract infections or after exposure to pollutants.[25-28] Although the cause of the increase in reactivity is unknown, a possible mechanism is suggested by the demonstration that mucosal permeability may substantially increase after antigen challenge in sensitized monkeys.[3] A final piece of evidence linking allergic inflammation is the demonstration that when patients with asthma who are allergic to house dust mites are isolated from their antigen, bronchial reactivity decreases significantly over several months.[29]

The increase in bronchial hyperresponsiveness in allergic rhinitis related to allergen-induced inflammatory changes or alterations in mucosal permeability of the lower airways may be related to natural environmental exposure to aeroallergens, resulting in IgE-mediated reactions, not only in the upper respiratory tract but in the lower respiratory tract, and to effects on the lower airways that are subclinical or not sufficient to cause perceived symptoms. The evidence for this is circumstantial, but nonetheless compelling. When patients with hay fever and asthma are compared, there are insignificant differences in allergen sensitivity in terms of skin sensitivity or leukocyte histamine release.[21] A number of investigators have shown that patients with allergic rhinitis who have never had asthmatic symptoms demonstrate physiologic alterations typical of acute asthma after inhalation of an appropriate allergen in the laboratory.[20-22] Patients with asthma remain slightly more hyperresponsive than do those with hay fever, especially when the FEV_1 response is measured.[20-22] Nevertheless, the differences are small and there is considerable overlap between groups. Why these patients respond to inhaled allergen in the laboratory but not after natural environmental exposure is not entirely clear, but the most likely explanation is that the amount of allergen encountered under natural conditions is far less than that used in laboratory experiments, and that the ability to sustain a clinical response under conditions of lower levels of allergen exposure depends on preexisting abnormal airway reactivity.[22, 29] Hence patients with marked increases in airway responsiveness, those with asthma, for example, may sustain a substantial airway response after a mild allergic reaction, and patients with modest increases in responsiveness, such as those with allergic rhinitis, experience little if any clinical effect. Despite the absence of a clinically perceptible airway response in these patients, it seems plausible that allergic stimulation is capable of causing inflammatory changes as well as subclinical airflow obstructions. Although there is no direct evidence to support this, there are reports of subtle abnormalities of lower airway function in patients with hay fever during intervals of environmental allergen exposure and symptomatic rhinitis.[30]

Classifying a patient as having clear-cut asthma or clear-cut rhinitis is often difficult. Some may deny symptoms of wheezing or chest tightness but admit to having cough during a particular pollen season. A history of wheezing is predictive of airway reactivity in only 35% to 49% of patients.[31] It seems reasonable to view patients with symptoms of clear-cut asthma and those with exclusive symptoms of rhinitis during a particular pollen season or with exposure to animal dander as representing either end, respectively, of a spectrum of allergic respiratory bronchial responsiveness.

Thus, although there are common underlying abnormalities in hay fever and asthma, it is still not known whether the existence of active allergic airway disease as expressed as allergic rhinitis somehow modifies the lower respiratory tract, leading progressively to hyperresponsiveness and eventually to clinical asthma. Based on studies showing that allergen exposure can result in increased airway responsiveness, it is tempting to speculate that this is the case.[23, 24] Existing data emphasize the importance of obtaining a careful clinical history regarding chest symptoms of patients with allergic rhinitis, and beginning bronchodilator therapy when such symptoms are reported.

UPPER RESPIRATORY TRACT INFECTION

Acute viral upper respiratory tract infections have been clearly associated with exacerbation of asthma in children and in adults.[30-33, 35, 38-44] There is no association between acute bacterial infections of the upper respiratory tract and exacerbation of asthma. The effects of chronic upper respiratory tract infections (such as chronic sinusitis) are discussed elsewhere in this symposium.

The most informative studies in children were conducted by McIntosh et al.[38] and by Minor et al.[40] In

TABLE I. Association of viral infection with attacks in patients with asthma

Study	Year	n	Age (yr)	Wheezing episodes with positive viral cultures		Viral illness with wheezing	
				n	%	n	%
Children							
Freeman and Todd[32]*	1962	30	0-5+			34/62	55
McIntosh et al.[38]	1973	32	1-5	58/139	42	58/102	57
Horn and Gregg[39]	1973	47	5-7.8			41/62	66
Minor et al.[40]	1974	16	3-11	23/43	53	42/61	69
Shapiro et al.[41]*	1974	44	5-7.8	9/44	20		
Minor et al.[42]	1976	41	1.3-18.1	17/71	24	17/32	53
Horn et al.[43]	1979	22	1-15	35/72	49		
Adults							
Huhti et al.[44]*	1974	63	15-77	27/142	19		
Minor et al.[42]	1976	8	22-60	3/17†			
Horn and Gregg[39]	1973	19	Not stated			8/21‡	38
Hudgel et al.[33]	1979	19	24-67	8/76	11		
Halperin et al.[30]	1985	21	19-37			4/19‡	21

*Hospitalized patients.
†States only that 3/17 positive cultures were in adults.
‡Rhinovirus.

both studies, a group of children with asthma were studied prospectively with weekly viral cultures, documentation of infections with cultures and serology, and monitoring of respiratory symptoms. McIntosh et al. studied children aged 3 to 8 years during two winters, and documented 128 viral infections and 144 wheezing episodes, with 64 (42%) occurring simultaneously. Minor et al. studied school-aged children and found 48 viral infections and 61 wheezing episodes, with 32 coincident episodes. In studies of adults with asthma[30, 33, 39, 42, 44] and chronic bronchitis,[35] only 10% to 20% of exacerbations could be associated with acute viral illnesses. The available experience with asthma is summarized in Table I. The only prospective study of patients with asthma is that by Halperin et al.,[30] who evaluated 21 volunteers with well-characterized asthma who were experimentally infected with one of two rhinovirus serotypes. Only four volunteers (21%) showed an appreciable change in FEV_1 during infection. These five were not distinguishable from the other volunteers, but they did have a significant and persistent increase in bronchial hyperresponsiveness.

The consistently lower incidence of wheezing with viral infections seen in adults suggests that there may be age-related differences in the host response to viral infections. This suggestion is supported by the existence of bronchiolitis and croup in children. These two syndromes, the first seen with respiratory syncytial virus and the second with parainfluenza virus infection, are not seen in adults infected with the two viruses. Even more intriguing is the demonstration by Welliver et al.[36, 45] that those children who develop these two syndromes make a specific IgE antibody response to the virus, whereas those who are infected but have only upper respiratory tract symptoms do not. They suggested that the tendency of younger patients to make IgE antibodies to these two viruses was an important determinant for development of lower respiratory tract disease.

TABLE II. Agents associated with wheezing episodes in patients with asthma

Rhinovirus
Respiratory syncytial virus
Parainfluenza types 1, 2, 3
Influenza A
Influenza B
Coronavirus
Adenovirus
Mycoplasma pneumoniae
Other (enterovirus, herpesvirus, coxsackie virus)

The viruses associated with lower tract illness (Table II) are those usually found in acute "colds" in the general population. Respiratory syncytial virus and coronavirus have been recovered primarily in small children with asthma, and *Mycoplasma pneu-*

moniae and influenza have been found chiefly in adults. These agents vary so greatly in their pathobiologic characteristics that it is almost certain that several mechanisms are involved in inducing asthma attacks. Influenza, parainfluenza, and adenovirus, for example, cause widespread, severe epithelial damage in both the upper and lower tracts, with a significant inflammatory response and pneumonia.[46] Rhinovirus, on the other hand, produces trivial epithelial damage in the upper respiratory tract[47] and colonizes the lower tract in only a few infected patients.[48] Respiratory syncytial virus and parainfluenza virus are the only respiratory viruses that cause immediate hypersensitivity effects in the human airway. Both have been found to induce IgE antibodies in secretions when associated with wheezing, but not when associated with rhinitis.[36, 45]

Wheezing episodes in asthma have been clearly associated with acute infection, but the development of de novo bronchial reactivity in normal persons is much less clear. Parker et al.[18] first described abnormal methacholine responses during acute upper respiratory tract infections; however, the viral origin was not established in any case, and inasmuch as five of their 13 patients retained their abnormal response to methacholine, it is not clear whether they were normal before infection or whether the apparent "cold" simply worsened their underlying hyperresponsiveness. Empey et al.[26] demonstrated that bronchial responses returned to normal after as long as 3 months, but failed to identify the specific viral cause. A third study[49] showed abnormalities in bronchial response to exercise in cold air during acute upper respiratory tract infection. Three different agents were isolated—mycoplasma, rhinovirus, and respiratory syncytial virus—but differences with the three agents were not discussed.

It is important to specify viral origin in the development of bronchial hyperresponsiveness. As described previously, the pathologic processes of infection by different "common cold" viruses differ widely and have a major impact not only on the mechanism by which bronchial reactivity develops but also on whether it develops at all. For example, the two studies documenting influenza A infections[27, 50] demonstrate increased responsiveness in most patients, but two studies of rhinovirus infection demonstrate no change in response to histamine[48] or methacholine,[34] and a third demonstrated a twofold increase in histamine reactivity.[51] The differences between influenza A infection and rhinovirus support the hypothesis that mucosal disruption and inflammation are necessary for bronchial hyperreactivity. At the same time the question of de novo generation of hyperresponsiveness by viral infection remains unanswered because only the last study with rhinovirus provides data regarding the patient's status before infection.

SUMMARY

Bronchial hyperresponsiveness is seen in illnesses involving the upper respiratory tract. In allergic rhinitis, it appears to be coexistent and to constitute a risk factor for asthma. In acute respiratory tract infections, asthmatic attacks may occur coincident with viral infections, and infection with some specific viruses may cause normal persons to develop bronchial hyperresponsiveness. Bronchial hyperresponsiveness may take months to clear, and may predispose to conditions with long-term sequelae.

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