

Provoking Factors in Bronchial Asthma

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Asthmatic patients were identified as having asthma on the basis of lung function studies (76%), objective physical findings of asthma (11%), or a strong history of asthma (13%). Each of the 234 patients so identified was assigned to an asthma subgroup determined by careful clinical assessment of the major provoking factor or factors for his asthmatic episodes; minor provoking factors were also identified. Only 20% of the patients had asthmatic episodes provoked by a single factor. Most asthmatics had at least one major and one or more minor provoking factor(s). Reagin-mediated mechanisms constituted the major provoking factor in 25% of patients and were a minor provoking factor in an additional 20% of the patients. Thus, in only 45% of the patients, were reaginic mechanisms responsible for some part of their asthmatic episodes.

"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that change in severity either spontaneously or as a result of therapy."¹ Such a broad definition does not deal with two important practical questions. Which patients who have symptoms suggesting asthma actually have asthma? What provoking factors initiate bronchospastic episodes in a

clearly defined population of asthmatic individuals?

Although answers to these questions might clarify and perhaps improve the care of individual patients, other more basic research activities^{2,3} are essential to the resolution of many problems that currently prevent full understanding of the pathogenesis of the asthma syndrome. Nonetheless, the ability to identify the asthmatic patient and to define those factors that provoke asthmatic attacks can provide an invaluable setting for correlating more basic laboratory data with specific variants of asthma.

A patient with intermittent bronchospasm, observed during a period of time by a physician, may have at one time exacerbation of his disease (requiring isoproterenol treatment to relieve his airway obstruction and separate him from other types of fixed-airway diseases) and at another time, may be in remission, with normal lung function studies (requiring methacholine provocation to verify the existence of bronchospasm). Thus, serial lung function testing, utilizing treatment or provocation, has been shown by us in a previous communication to be an accurate system for selecting patients who have bronchial asthma.⁴

As stated in an earlier publication,⁵ we have also characterized asthmatic patients on the bases of those provoking factors that appeared to initiate their particular asthmatic attacks. This report summarizes our experi-

ences in characterizing each new asthmatic patient entering our unit during a one-year period.

PATIENTS AND METHODS

All new patients registered in the Allergy-Immunology Division at Scripps Clinic and Research Foundation between July 1, 1971, and June 30, 1972, were potential participants in the study. Although many patients were referred to us because of asthma, all patients were asked if they had ever experienced wheezing, shortness of breath, chest tightness, or cough, and whether bronchodilator treatments had relieved such symptoms.

Methods for Documenting Asthma

If the patients answered any of the above questions affirmatively, every attempt was made to document their bronchospasm by the systematic approach outlined in Table 1. The entry methods are listed by choices (1st through 6th) based upon the degree of reliability of each method in detecting bronchospasm. The methods (in order of choice) include (1) a 20% improvement in one second forced expiratory volume (FEV₁) five minutes after inhaling isoproterenol (response to isoproterenol); (2) a 20% reduction in FEV₁ five minutes after inhaling successively one breath of 5 mg/ml of methacholine and up to five breaths of 25 mg/ml of methacholine (methacholine challenge: not started until January 1, 1972)⁶; (3) a greater than 30% improvement in FEV₁ within three days after starting corticosteroid therapy (improvement in FEV₁ days after therapy); (4) provocation of bronchoconstriction by other challenge procedures (other objective tests) (one patient developed bronchospasm during a bronchial chal-

Received for publication March 7, 1974; accepted June 28, 1974.

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lenge with allergens and this constituted the method of entry into the study for that patient); (5) a history of asthma combined with physical findings of asthma during the evaluation time (history and physical); and (6) a strong history of wheezing and dyspnea but no evidence of bronchospasm at the time of evaluation (history alone).

The reliability of methacholine challenge in separating normal individuals from asthmatics has been well documented.⁴ Normal individuals did not develop bronchospasm after the doses of methacholine employed. However, 10% of known asthmatics also did not develop bronchospasm, but these patients would be characterized as having asthma by one of the other modalities described above.

We attempted to use one of the first three choices for each patient entering the study, resorting to choices 5 and 6 if the early choices could not be employed. No test or entry method was assumed to be totally reliable and we were particularly interested in avoiding overly rigid criteria for entrance into the study.

Characterization of Asthmatic Patients

For each patient entering the study, present age, age at onset of asthmatic symptoms, sex, physician who cared for their asthma previously, and current place of residence (inside or outside of San Diego County) were recorded. With a few exceptions, each patient's history and physical examination findings were evaluated for the presence of allergic rhinitis; the patients underwent chest and sinus roentgenography, nasal smear for eosinophils, and immediate wheal and flare allergen skin testing. Selected patients underwent the following special tests: aspirin challenges,⁶ bronchial inhalation challenge,^{5,7} isoproterenol challenge,⁸ and serum precipitin analysis for fungal precipitating antibodies.⁹ Other appropriate diagnostic studies, such as otorhinolaryngologic consultations, sinus and sputum bacterial and fungal culture studies, more extensive lung function studies (such as lung volumes, diffusing capacity, flow rates, arterial blood gases, helium distribution studies; ventilation and perfusion lung scans, cardiovascular consultations, bronchoscopies, barium swallow roentgenograms, and urinary 5-hydroxyindole acetic acid analysis, were reserved for patients whose history, or results of physical or routine testing suggested the need for such investigations. When the evaluation of the patient's condition was completed, data collected from flow sheets were first analyzed by the physicians caring for the patient

and then analyzed again in combined conferences. One or more of 21 clinical syndromes or provoking factors was then assigned to describe each patient's asthmatic attacks. Furthermore, if the patient's asthma could be provoked by more than one factor, a major factor was designated if in the judgement of the attending physicians, based on both clinical and laboratory data, it initiated more than 50% of the asthmatic attacks for the patient with intermittent asthma or appeared to be associated with continuous asthma in other patients. All additional provoking factors were recorded as minor.

Patients were assigned to each subgroup (listed in Table 2 and immediately below) on the bases of clinical judgement within the following prearranged guidelines:

Reagin-Mediated.—A history of asthma provoked by one or more known allergens in the patient's environment, when combined with reproducibly positive wheal and flare skin tests (as described in the article by McDonald et al⁶) to intradermal injections of such allergen extracts, allowed us to make this association. A reagin mediated factor was excluded in those patients with negative wheal and flare skin tests, or those whose only positive skin test reactivity was to allergens not present in the patient's domiciliary or working environment. When positive skin tests to available allergens did not correlate with the history, bronchial inhalation challenges were employed^{5,7} as much as possible (this was done in 27 patients).

Sinusitis.—Sinus roentgenograms were interpreted as being abnormal if complete opacification, air fluid level, or mucoperiosteal thickening was detected in one or more paranasal sinus. We sought evidence for a causal relationship between abnormal sinuses and asthmatic attacks, with histor-

ical correlation between a flare of upper-respiratory tract symptoms, such as nasal congestion, purulent nasal discharge, paranasal pain, combined with abnormal roentgenograms and the onset of asthmatic symptoms. In addition, we looked for improvement in asthma after successful treatment of sinusitis with antibiotics, antral irrigations, or surgical drainage of appropriate sinuses. Bacteriologic data were sought and used in directing antibiotic treatment, but were not considered essential for assigning patients to this category. Other studies¹⁰ from this institution have shown that overt bacterial infection is in fact infrequently found in diseased sinuses of asthmatic patients.

Upper-Respiratory Tract Infection (URI).—A patient whose asthmatic attack appeared to begin with a common upper-respiratory tract "cold" and terminated three to seven days later as the respiratory illness resolved was assigned to this group. The above assignment was a clinical impression alone since in this study there was no attempt to isolate viruses from upper-respiratory tract passages. On the bases of other investigations,¹¹ it seems likely that such infections are usually caused by viruses. Frequently, patients in this subcategory were from the younger age groups.

Purulent Sputum.—Patients whose asthma exacerbated during a time when they were expectorating thick, discolored (yellow, green, grey) phlegm in the absence of sinusitis or a URI were assigned to this group. Allocation to this group was based only on the presence of purulent sputum coinciding with a flare of asthmatic symptoms and signs. Pathogenic bacteria were rarely recovered from transtracheal aspirates of some of these patients, and viral or mycoplasma agents were not demonstrated in any.¹²

Postviral Onset.—Those patients whose asthma symptoms began shortly after a "flu-like" illness (symptoms of respiratory inflammation, fever, myalgias, fatigue, cough) and whose asthma continued after termination of the "flu" to the time of evaluation were assigned to this category. It was possible to differentiate this group from the prior two categories because of the persistence of asthma long after the assumed termination of the inciting "infection."

Aspirin Intolerance.—Either an unequivocal history of asthma within three hours after ingesting aspirin or provocation of asthma during controlled aspirin challenge⁶ constituted the marker event for assignment to this group. The expected clinical course of most untreated patients with aspirin intolerance is to have continuous and relatively severe asthma even though

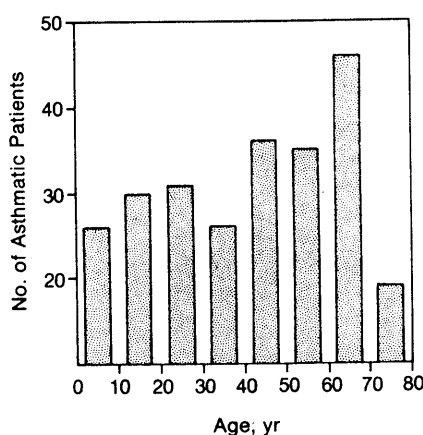


Fig 1.—Distribution of the ages of asthmatic patients by decades.

Table 1.—Method for Establishing Presence of Asthma for Each Patient Entering Study

Documentation of Asthma		Entry Date Into Study, No. of Patients (%)*			First-Year Total— July 1971– July 1972
Order of Choice	Method	July–December 1971	Jan–July 1972	χ^2	
1st	Response to isoproterenol (>20% $\uparrow$ FEV ₁)	50(54)	51(36)	NS	101(43)
2nd	Methacholine challenge (>20% $\downarrow$ FEV ₁)	ND	60(43)	$P < .001$	60(26)
3rd	Improvement in FEV ₁ , days after therapy	6(6)	7(5)	NS	13(6)
4th	Other objective tests	1(1)	ND	NS	1(1)
5th	History and physical findings	19(20)	8(6)	$P < .01$	27(11)
6th	History alone	17(18)	15(11)	NS	32(13)
Total (%)		93(100)	141(100)		234(100)

* χ^2 indicates population differences in two six-month study periods; NS, not significant; ND, not done.

they avoid ingestion of aspirin.

Asthmatic Bronchitis.—Those patients who had daily coughing or sputum production (bronchitis) or both, usually with fixed bronchial airway obstruction in addition to 20% or greater changes in FEV₁ during serial lung function testing, were judged to have this combination of bronchial syndromes. Improvement in results of lung-function studies was in most cases incomplete, with the best FEV₁/TVC values being below 60%. (TVC is total vital capacity.)

Uncertain (Unknown).—When no provoking factors could be identified or no dominant major factor could be separated from other factors, patients were assigned to this group.

Miscellaneous.—Isoproterenol Abuse.—Using criteria outlined by Reisman,⁸ patients were identified on the basis of a history suggesting overuse of their symptom-mimetic nebulizer coupled with lung-function evidence of unsustained bronchodilation after isoproterenol inhalation.

Irritants.—A history of asthmatic attacks in direct relationship to inhalation of irritant fumes, such as smoke and smog, was obtained from these patients.

Exercise.—A history of asthma occurring during or immediately after engaging in physical exercise was obtained. Treadmill studies were not carried out.

Meteorologic.—Patients assigned to this category had a history of asthmatic episodes associated with changes in barometric pressure, temperature, and humidity.

Emotional.—Attacks of asthma followed episodes of anxiety, fear, or anger. Anxi-

ety per se, during an asthmatic attack, was interpreted as a normal response to a sense of suffocation and such patients were not included in this category. These criteria can be expected to select only the most obvious psychophysiologic respiratory reactions and might not include more subtle varieties.

Cardiac Asthma.—In these patients, evidence of failure of the left side of the heart associated with bronchospasm that cleared after treatment of cardiac disease was sought.

Esophageal Disorders.—Hiatus hernia and reflux esophagitis were associated with asthma, which could be corrected by treatment of the esophageal disorder.

Carcinoid Tumors.—Evidence of the tumor (flushing, diarrhea, wheezing, and elevated urinary 5-hydroxyindole acetic acid) was sought by the usual diagnostic methods.

Bronchial Obstruction.—Foreign body, tumors, and other causes of endobronchial obstruction that can lead to "wheezing" were also taken into consideration.

Pulmonary Emboli.—Patients in whom wheezing and dyspnea occurred in association with documented pulmonary emboli were assigned to this category.

Humoral Antibody.—In some patients IgG antibody directed against endobronchial antigens (such as *Aspergillus* and *Candida*) may be associated with bronchospasm through immunologic and unknown mechanisms.

History of Asthma. Methacholine Bronchial Challenges Negative.—Despite a convincing history of asthmatic attacks,

methacholine inhalation did not induce bronchospasm in these patients.

No History of Asthma. Methacholine Bronchial Challenges Positive.—This group was composed of patients with rhinitis and no history of lower respiratory symptoms who developed bronchospasm after provocation with inhaled methacholine.

Statistical analysis of populations with χ^2 and Yates correction was carried out with an advanced statistical calculator (Wang 462). P values $> .05$ were recorded as not significant (NS).

RESULTS

A total of 234 newly registered patients were found to have bronchial asthma during the one year entry period. Table 1 shows the number of patients who entered the asthma study through each of the six selection methods during the six months of 1971 and 1972 and the total one-year period. For 101 of the 234 (43%) patients who had symptomatic asthma at the time of entry, isoproterenol produced more than 20% improvement in their FEV₁ values. Symptomatic pediatric patients tended to enter the study through the 5th entry method along with some adults who could not adequately perform lung function studies (27 of 234 patients or 11%).

After Jan 1, 1972, a total of 60 of 234 patients (26%) who were asymptomatic at the time of evaluation and had normal FEV₁ values or less than a 20% increase in FEV₁ values after isoproterenol inhalation developed bronchospasm after inhalation of methacholine. Only 32 (13%) of the patients entered the study without some type of objective evidence for asthma (ie, on the basis of history alone).

At the time of entry into the study, the 234 patients were divided into age groups as shown in Fig 1. The mean age for all entering participants was 41 years, and the mean age for onset of asthma was 28 years. Thus, on the basis of history, the participants had experienced attacks of bronchospasm or continuous asthma for an average of 13 years prior to the evaluation of their condition at our institution. There were 107 (46%) male and 127 (54%) female patients. One hundred seventy-two patients (74%)

Table 2.—Incidence of Major Provoking Factors and Associated Minor Provoking Factors

Major Factors	Patients in 1971-1972, No.(%)	Sole Cause of Asthma Attacks	Associated Minor Factors†								
			Reagins	Sinusitis	URI	Purulent Sputum	Postviral Onset	Aspirin Intolerance	Asthmatic Bronchitis	Uncertain	Miscellaneous
Reagins	58(25)	12	...	5	17	6	5	1	2	2	45
Sinusitis	20(9)	3	8	...	0	0	1	0	1	2	19
URI	17(7)	6	9	0	...	0	1	0	2	0	10
Purulent spu- tum	6(3)	3	2	0	0	...	0	0	0	1	1
Postviral	16(7)	1	3	2	0	2	...	0	0	1	22
Aspirin intoler- ance	21(9)	2	6	13	1	1	1	...	0	0	12
Asthmatic bronchitis	40(17)	2	7	3	4	8	1	1	...	1	31
Uncertain	23(10)	2	6	5	5	4	0	0	0	...	30
Miscellaneous*	15(7)	2	5	2	2	1	0	0	1	3	...
Asthma history/ MCH-test — ‡	14(6)	11	0	3	0	0	0	0	0	0	0
No asthma history/ MCH-test + ‡	4(2)	3	1	0	0	0	0	0	0	0	1
Total No. of Patients (%)	234(100)	47 (20)	47 (20)	33 (14)	29 (12)	22 (9)	9 (4)	2 (1)	6 (3)	10 (4)	171 (73)

* The miscellaneous major factor, with number of patients in parenthesis, were isoproterenol abuse (1), irritants (7), exercise (1), meteorological changes (1), emotions (1), and pulmonary emboli (1).

† Total number of patients for each minor provoking factor was 234.

‡ MCH-test indicates methacholine bronchial challenge test.

Table 3.—Incidence* of Allergic Rhinitis, Positive Wheal and Flare Skin Tests, and Abnormal Sinus Roentgenograms in Each Subgroup of 234 Asthmatic Patients

Major Factors	Total No. of Patients in One yr	Reagin Mediated (Allergic) Rhinitis		Wheal and Flare Skin Test		Abnormal Sinus Roentgenograms	
		%	χ^2	% Positive	χ^2	Opacification or Air Fluid Level, %	Mucoperiosteal Thickening
Reagins	58	60	$P < .001$	100	$P < .001$	16(50)	24
Sinusitis	20	40	NS	55	NS	55	45
URI	17	47	NS	65	NS	6(16)	25
Purulent sputum	6	33	NS	67	NS	0(5)	60
Postviral	16	38	NS	56	NS	13	25
Aspirin intolerance	21	14	NS	50(20)	NS	62	19
Asthmatic bronchitis	40	8	$P < .01$	51(39)	NS	0(36)	47
Uncertain	23	22	NS	57	NS	25(20)	35
Miscellaneous †	15	33	NS	77(13)	NS	0(13)	54
Asthma history/ MCH-test — ‡	14	14	NS	38(13)	NS	25(12)	50
No asthma history/ MCH-test + ‡	4	50	NS	75	NS	0(3)	33
Total Patients	234	34%		66% (229)		20% (212)	35% (212)

* The χ^2 calculated for incidence in each subgroup compared to that in the total population figures in parentheses indicate number of patients tested in each subgroup when less than total number in that subgroup. NS indicates not statistically significant.

† Miscellaneous major factors, with number of patients in parentheses, were isoproterenol abuse (1), irritants (7), exercise (1), meteorologic changes (1), emotions (4), and pulmonary embolism (1).

‡ MCH-test indicates methacholine bronchial challenge test.

had been under the care of other physicians: 66 (38%) by internists, 50 (29%) by general practitioners, 39 (23%) by allergists, 11 (6%) by pedia-

tricians, 3 (2%) by otorhinolaryngologists, and 3 (2%) by other physicians. Of the 234 patients, 51% resided in San Diego County.

In Table 2, the number of patients whose asthma seemed attributable to a major provoking factor are listed. Despite the addition of methacholine

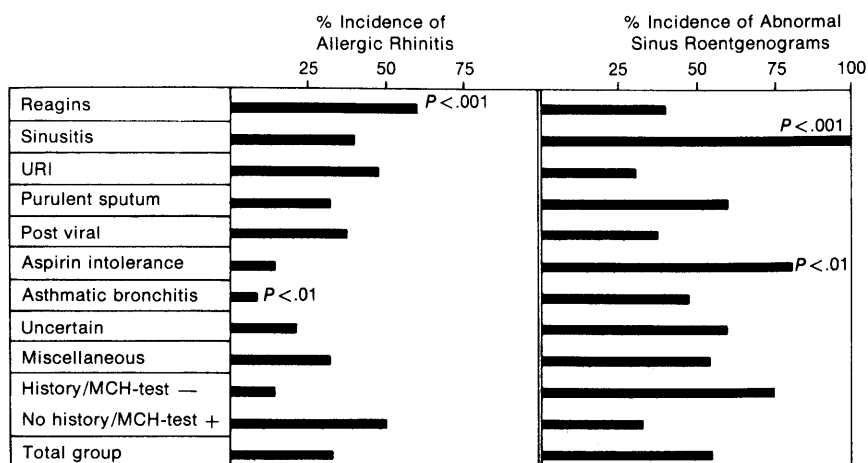


Fig 2.—The percent incidence of allergic rhinitis and abnormal sinus roentgenograms for each major asthma subgroup. χ^2 with Yates correction was done to compare incidence for each subgroup to incidence in total population of 234 asthmatic patients. Those incidences that were significantly different are recorded. (See Table 3 for additional statistical details). URI indicates upper-respiratory tract infection. MCH-test indicates metacholine bronchial challenge test.

challenge with the entry of 48 more patients during the second six months of the study, there was no significant change in the incidence of provoking factors in the two periods. The most frequent provoking factors were reagin and asthmatic bronchitis. If the categories labeled URI, sinusitis, postviral, and purulent sputum were combined into one, however, this combined group becomes the most frequent as a provoking factor, barely exceeding the reagin-mediated group. Aspirin intolerance was designated as a major "provoking" factor, even though in patients in this group the asthma generally continues despite the patients' avoidance of aspirin. It is our belief that aspirin-induced asthma may reflect a fundamental biochemical anomaly not present in other asthmatic patients.

In the miscellaneous group there were no patients in the categories of cardiac asthma, esophageal disorders, carcinoid tumors, or foreign bodies obstructing bronchi. Although the majority of patients' sera were tested for precipitating antibodies to *Candida*, *Aspergillus*, and mixtures of molds, only one serum contained precipitating antibodies. This finding was judged to be unimportant in the patient's asthma.

For each major factor, the prevalence of associated minor factors are

recorded in the same line on the right half of Table 2. As indicated by the second column, only 20% of the patients had asthma that was provoked by a single factor. Most of these had been categorized as having reagin-mediated asthma or asthma following a URI. This small group was contrasted to the majority of asthmatic patients who developed bronchospasm after provocation by a major factor and by one or more minor factors.

The association between allergic rhinitis, positive wheal and flare skin tests, abnormal or normal sinus roentgenograms, and different subgroups of asthmatic patients are recorded in Table 3. Two thirds of all asthmatic patients were found by dermal testing to have wheal and flare responses consistent with the presence of a specific reaginic antibody. Approximately one third of all asthmatics had associated allergic rhinitis (Fig 2). In contrast, as expected, there was a significantly increased incidence of allergic rhinitis in the reagin group and a decreased incidence in the asthmatic bronchitis group.

Abnormal sinus roentgenograms were found in 55% of the patients. Within the major subgroups, there was no difference in incidence of abnormal sinus roentgenograms as compared to the total population except

for the sinusitis group (a matter of selection) and the aspirin intolerance group. Sinusitis has long been known to be a hallmark of the latter.

The condition of all patients spontaneously returning to this institution from January to November 1973 was evaluated again to determine if those provoking factors operative in 1971-1972 were still operative in 1973. Patients who did not return because their asthma improved or who continued to be satisfied with the care rendered by their local physician were not contacted. Table 4 shows both the numbers of patients in each major subcategory who returned for follow-up during 1973 and, within this group, the number of patients for whom the clinical assessment of the major provoking factor was changed during the interval.

Of the 234 patients, 82 (39%) patients returned; 66 of these 82 (80%) were judged to still have the same major provoking factor responsible for their asthmatic episodes. However, in a few asthmatic patients, URIs now seemed to be more important provocateurs than were the prior reagin-mediated mechanisms. In others, the certainty of sinusitis as a provocateur was less clear, and reagin-mediated mechanisms seemed to have become paramount in a few other patients. Thus, a modest but definite tendency toward changing patterns of provocation is apparent even during a relatively short re-evaluation interval.

During the first six months of the study, we performed orally administered aspirin challenges only on patients who had abnormal sinus roentgenograms or nasal polyps or those who were dependent on corticosteroids and did not give a reliable history of aspirin intolerance.⁶ Using these strict criteria, of the 22 patients (out of 93) (24%) who underwent aspirin challenges during the first six months of the study, three (3%) developed bronchospasm during the three-hour test period. As indicated in Table 2, these three patients were then included with patients whose aspirin intolerance had been identified by a reliable history. During the last six months of the study, asthmatic

Table 4.—Assessment of Major Factors in Patients One Year After Initial Evaluation

Major Factors*	No. of Patients 1971-1972 (1 yr)	No. of Patients Returning in 1973 (%)	Changes in Assignment of Major Factors From Initial to Follow-up Examination									
			No Change	Reagin	Sinusitis	URI	Purulent Sputum	Postviral Onset	ASA Intol- erance	Asthmatic Bronchitis	Uncertain	Miscellaneous
Reagins	58	23(40)	19	...	0	3	0	0	0	0	1	0
Sinusitis	20	9(45)	5	0	...	1	0	0	0	0	3	0
URI	17	7(41)	7	0	0	...	0	0	0	0	0	0
Purulent sputum	6	0	0	0	0	0	...	0	0	0	0	0
Postviral	16	6(38)	3	2	0	1	0	...	0	0	0	0
Aspirin intolerance	21	7(33)	7	0	0	0	0	0	0	0	0	0
Asthmatic bronchitis	40	12(30)	12	0	0	0	0	0	0	...	0	0
Uncertain	23	8(35)	7	0	0	0	0	0	0	1	...	0
Miscellaneous	15	3(18)	1	1	0	0	0	0	0	0	1	...
Asthma history/ MCH-test —	14	5(36)	5†	0	0	0	0	0	0	0	0	0
No asthma history/ MCH-test +	4	2(50)	0	2	0	0	0	0	0	0	0	0
Total No. of Patients (%)	234	82/234(39)	66/ 82 (80)	5/ 82 (6)	0	5/ 82 (6)	0	0	0	1/ 82 (1)	5/ 82 (6)	0

* URI indicates upper-respiratory tract infection. Miscellaneous major factors, with number of patients in parentheses, were isoproterenol abuse (1), irritants (7), exercise (1), meteorological changes (1), emotions (4), pulmonary emboli (1). MCH-test indicates metacholine bronchial challenge test.

† No evidence of asthma during followup examinations in all five patients.

patients were selected for aspirin challenges on the bases of availability of the patient for challenge and the absence of aspirin intolerance by history. A significantly ($P < .025$) increased number, 57 (40%), of the 141 asthmatic patients in the six-month 1972 group underwent aspirin challenges as a result of changes in the protocol. However, only four of the 141 (3%) patients had bronchospastic responses during orally administered aspirin challenges, a number not significantly different from that of the previous six months. These data support the correctness of the original assumption⁶ that certain marker criteria in asthmatic patients can help in predicting which asthmatic patients are most likely to experience bronchospasm during aspirin challenge.

COMMENT

Most previous clinical studies of asthmatic patients do not clearly state the method used to identify the subjects of their clinical investigations.^{13,14} This is not surprising, since there is no universal test or procedure by means of which all asthmatic patients can be identified. Furthermore, the

very fact that some asthmatics are only intermittently symptomatic and have remissions and seeming "cures" makes it difficult to include all asthmatic patients in any one study population. In our prospective study, the majority (76%) of the asthmatic patients were identified by lung function tests. Of these, 26% were asthmatic patients who were in remission but in whom reversible bronchial obstruction could be provoked by methacholine challenge. Only 13% of the patients entered this study on the basis of a history of asthma alone.

Of the 234 asthmatic patients, 58 (25%) had asthma that was mediated by a reaginic mechanism as the major provoking factor. Reaginic mechanisms were judged to be minor provoking factors in 47 of the patients whose major mechanisms were of a non-reagin group. When both of these groups were combined, reagin-mediated factors were judged to contribute to asthma in 105 (45%) of the 234 patients. Other studies show the frequency of "allergic" (presumably reagin-mediated) asthma to vary from 56% to 66% of the total asthma population, depending upon the patients' age, nature of the population studied,

and the use of bronchial challenge as opposed to reliance upon skin tests and history alone.¹⁵⁻¹⁷

As indicated in Table 3, 154 (66%) of 229 patients in this study had positive wheal and flare skin tests to one or more test antigens. Therefore, there were 49 patients who had positive skin tests and were not considered to have reagin-mediated asthma. Thirty-one patients had positive skin tests to allergens that were not present in their environment and, therefore, could not account for their asthmatic episodes. Only nine of 27 patients who underwent bronchial challenge with extracts of aeroallergens to which they had reaginic antibodies developed bronchospasm in response to such challenges. The remaining 18 patients with positive skin tests and negative response to bronchial challenges were interpreted to have asthmatic exacerbations provoked by factors other than reagins. Combining these 18 patients with the 31 from above gives a total of 49 patients with reaginic antibodies that were not playing a role in initiation of bronchospasm. It has been well documented that positive direct or passive transfer skin tests can be found

in individuals who have never had clinical symptoms.¹⁸ From this and other data, we believe that the presence of reaginic antibodies does not in itself establish a causal relationship in the pathogenesis of asthma.

For the purpose of our clinical practice and this study, we have segregated the sinusitis, URI, purulent sputum, and post-viral reactions into separate categories that in combination represent the most important (26%) major provocateurs or associations with asthmatic attacks. Unfortunately, despite their importance it has been difficult to define and understand these reactions, particularly their roles in provoking asthma.

Although the majority of our patients in this study had roentgenographic evidence consistent with inflammation in their paranasal sinuses, in another study¹⁰ we found

only an occasional patient from whom we were able to culture bacteria from the affected sinuses. With a few exceptions, in asthmatic patients with flares of asthma coinciding with URIs or purulent sputum, we were unable to culture bacteria from transcricothyroid secretions.¹² However, our studies did not exclude the possibility that certain viruses might be associated with asthmatic exacerbations. This has been suggested recently by Minor et al¹⁹ who have shown a close temporal relationship between the presence of certain rhinoviruses and A₂/Hong Kong influenza viruses in nasal and pharyngeal secretions, with asthmatic exacerbations in children.

In looking carefully at other major and minor factors given in Table 2, one is struck by the heterogeneous and complex pattern of interactions

that characterize the asthmatic episodes in our patients. Such a pattern is consistent with the fact that there are underlying immunologic, physiologic, and biochemical derangements controlling the homeostasis of bronchial airway patency of asthmatics that leads to an increased susceptibility to many initiating and provoking factors. For their usefulness in biochemical and cellular investigations, however, those cases in which the asthmatic attacks are provoked by a single factor may provide more homogeneous settings for laboratory and clinical correlations, an ultimate goal toward which these studies are directed.

James R. McDonald, MD, and Stanley Z. Berman, MD, assisted with the collection of the clinical data.

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