Assessment of airway hyperresponsiveness in chronic stable asthma

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Airway reactivity and disease severity were investigated in 24 subjects with stable chronic bronchial asthma. Disease severity was determined by assigning a disease severity score (DSS) representing six clinical and therapeutic parameters. Airway hyperresponsiveness was assessed in two ways: airway reactivity score (ARS) based on the number of positive responses to a question concerning exposure to 22 nonspecific inhaled irritants and methacholine challenge testing and determining the cumulative dose causing a 20% reduction in FEV_1 (CMD_{20}). A significant correlation between DDS and CMD_{20} ($r = 0.57$; $p < 0.003$) and DSS and ARS ($r = 0.67$; $p < 0.0003$) attested to the important influence of airway hyperresponsiveness on disease severity. Significant correlations for ARS with CMD_{20} ($r = -0.60$; $p < 0.002$) suggested the consistency with which the ARS estimated methacholine hyperresponsiveness. We found no statistically significant correlations between DSS, ARS, or CMD_{20} and the age of subject, duration of asthma, or other host characteristics. There was not a significant correlation between the degree of airway obstruction and DSS or ARS noted. The results of this investigation demonstrate the value of the use of clinical information for assessing airway hyperresponsiveness and disease severity in patients with chronic stable asthma. Both ARS and DSS are useful clinical tools for estimating methacholine reactivity. (J ALLERGY CLIN IMMUNOL 1990;85:17-26.)

A number of factors contribute to the variability in severity of bronchial asthma, including viral respiratory infections, environmental or occupational agents, allergens, psychologic or emotional influences, adequacy of drug treatment, physical stimuli, such as cold air, and both particulate and gaseous irritants.[1-15] In particular, the sensitivity to airborne irritant exposures has reported significance, and therefore, the identification of subjects in a screened population who have increased airway responsiveness to irritants has important clinical and prognostic implications.[11, 12, 16] The use of currently available standardized questionnaire information for discrimination between subjects with and subjects without increased airway responsiveness or for identifying subjects with bronchial asthma may not be adequate.[17-19] As far as disease severity is concerned, there are reported studies with pharmacologic testing to quantify the degree of airway hyperresponsiveness and the history of drug treatments to document the severity of asthma.[13, 20] Few investigations address disease severity of asthma or degree of airway hyperresponsiveness with clinical information.[13, 21-24] The present investigation evaluates a method for quantifying both disease severity of

Abbreviations used

DSS:	Disease severity score
ARS:	Airway reactivity score
CMD_{20}:	Cumulative dose of methacholine causing a 20% fall in FEV_1
FEF_{25-75}:	Forced expiratory flow rate between 25% and 75% of FVC

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chronic stable asthma and the degree of airway hyperresponsiveness on a clinical basis with a questionnaire with a scoring system. The scoring system appears applicable to practicing physicians because the results of our investigation suggest that both the asthma severity and the degree of airway hyperresponsiveness can be quantified with clinical information.

MATERIAL AND METHODS

Study population

Individuals studied were 24 subjects with asthma, 17 female and seven male individuals whose mean age was 42.5 years (range, 24 to 73 years). A preliminary spirometric study documented reversible airway obstruction, and each subject fulfilled the criteria for the diagnosis of bronchial asthma.[25] Each subject had follow-up on an outpatient basis for at least 6 months, and, in many cases, for several years so that the usual clinical state of the disease was well-known by the investigators. All patients studied were extensively investigated to exclude any other significant medical illness, such as cardiac, liver, renal, or endocrine diseases. Subjects studied were admitted to the Clinical Research Unit of the Cincinnati General Hospital, and informed consent was obtained from each patient before study. The patients were studied when their asthma was clinically stable and when the disease state at time of investigation was considered to reflect the patient's usual clinical status during the previous 6 months. Those individuals who developed acute asthma attacks or transient clinical worsening of their disease were not scheduled for study. Clinical stability of asthma was certified in most patients by having each patient complete a personal symptom diary 2 weeks before the study; this information was reviewed by the investigators. Particular attention was directed to documenting prior and current medications. All subjects studied (except two patients) received medication, generally either a theophylline preparation or corticosteroids as the primary drugs for relief of symptoms. The use of β-adrenergic agonist drugs was limited because the subjects were also taking part in an investigation concerning β-adrenergic receptor status in asthma, and these drugs were not prescribed.[26] Those patients taking β-agonist medication had the drug stopped at least 2 weeks before the study.

DSS

The clinical severity of asthma was quantitatively determined for each subject by use of a DSS. A numerical value was based on six parameters expressing clinical features of asthma regularly present during the previous 6 months. Each of these six components of the DSS was arbitrarily divided into five categories, representing increasingly more severe features of the specific parameter. The decision for inclusion of various clinical categories and ranking was initially based on the experience of the investigators who examined their own clinical practices in an informal way during a period of several months to come to grips with the problem. Repeat application of the DSS in individual patients might vary from day to day, depending on the clinical status of the subject on that day. However, the DSS was developed to provide a rough estimate or "average" clinical status of a subject during a specific 6-month period. We did not have the opportunity of performing serial administrations of the DSS during a period of several weeks or months and therefore cannot estimate its accuracy or repeatability. The DSS represents our effort to use subjective clinical information in a somewhat quantitative manner. The six clinical parameters were

1. Number of acute asthmatic attacks that required physician's treatment (including medication by injection) at office, emergency room, or hospital (score 1 to 5: none, at least one, two, three or four, or more than four attacks).
2. Frequency of attack of wheezing and/or chest tightness that occurred during an average day (score 1 to 5: none, at least once, two, three or four, five or more occurrences).
3. Frequency of attacks of wheezing and/or chest tightness that occurred during an average night (score 1 to 5: sleep through the night, awakened once, awakened twice, awakened 3 to 4 times, or awakened by asthma almost hourly).
4. Cough score on an average day or night (score 1 to 5: no cough, occasional cough but not seriously disturbing, quite troublesome during attacks only, very troublesome and frequent, or distressing most of the time, day or night).
5. Degree of shortness of breath with exertion (score 1 to 5: can walk indefinitely, gets short of breath with strenuous exertion, shortness of breath with moderate exertion, such as climbing one or two flights of stairs, walking four or five blocks, shortness of breath with minimal exertion, such as climbing one-half to one flight of stairs, performing housework, or walking one-half block, and shortness of breath at rest).
6. Therapy that the patient required to control asthma (score 1 to 5: none, β-agonist bronchodilators used intermittently only, oral theophylline used continuously, regular use of cromolyn, or aerosol or oral corticosteroids).

The range of scoring for the DSS with the above system was 6 to 30, with a minimum possible score of 6 and a maximum score of 30.

ARS

The clinical assessment of airway responsiveness was accomplished by inquiring as to which of 22 nonspecific irritants caused worsening or precipitation of asthma symptoms. Each subject was asked, "Is your asthma worsened by, or do the following produce wheezing, chest tightness, and/or coughing?" The time period in question was the previous 6 months. Our clinical experience was that the irritants listed represented relatively indigenous environmental exposures that the subjects would likely encounter in a 6-month period of time. We did not inquire as to whether there were "irritants" listed that were not encountered by an individual patient during the study period. Irritants listed

were (1) heat, (2) cold, (3) rain or dampness, (4) sudden change in temperature, (5) dust, (6) tobacco smoke, (7) cooking or frying odors, (8) fumes, (9) perfume, (10) household spray, (11) soap powders, (12) antiperspirants, (13) cut grass, (14) varnish, (15) household cleaners, (16) respiratory infections, (17) cosmetics, including aftershave lotion, (18) ammonia (Lysol [Lehn & Fink Products, Division of Sterling Drug, Inc., Montvale, N.J.] or Chlorox [Chlorox Co., Oakland, Calif.]), (19) solvents (including alcohol and nail polish remover), (20) crude oil, including gasoline, (21) sawdust, and (22) periods of high air pollution.

The number of positive responses were recorded as a percentage of the total, providing an ARS. A score of zero was indicated if all responses were negative, and a score of 100 was indicated if all responses were positive.

Pharmacologic assessment of airway responsiveness

Methacholine challenges were performed on all 24 subjects with a modification of a method reported previously.[27] Beta-adrenergic agonist medication was stopped at least 2 weeks before study, and theophylline preparations were stopped at least 12 hours before the investigation. Individuals receiving corticosteroids were administered their usual dosage on the morning of the study. Oral corticosteroid dosages ranged between 5 and 20 mg daily, most receiving 5 mg/day. The usual dose of the aerosol corticosteroid was three of four puffs per day. Ten of 24 subjects had baseline FEV_1 values <65% of predicted. Because we believed it was important to study a wide range of clinical situations, from patients with mild to severe asthma, a proportion of subjects we examined had markedly abnormal spirometric tests. We were particularly cautious in performing methacholine challenge tests in individuals with severe functional changes. We initiated testing at very low methacholine concentrations and progressed slowly with small increment doses and careful monitoring procedures. We did not experience significant adverse response in any of the subjects tested, and prompt reversal of changes were noted in all subjects, either spontaneously or with administration of rapid-acting (isoproterenol) inhaled aerosol bronchodilator.

The methacholine challenge (methacholine chloride, J. T. Baker Chemical Co., Phillipsburg, N.J.) was performed as follows: compress air was passed through a No. 40 DeVilbiss nebulizer (DeVilbiss Co., Somerset, Pa.) at 10 L/min, generating an aerosol of methacholine that was transported through a short connecting tube into a plexiglass mixing chamber leading to a one-way valve and mouthpiece for the patient; the expiratory side of the one-way valve connected to a 13 L Collins spirometer (Warren Collins, Inc., Braintree, Mass.) for measurement of the expired volume; of the methacholine aerosol had a mean aerodynamic diameter of <2 μm. The aerosol was allowed to accumulate in the chamber for at least 60 sec before the patient started inhaling. Then the subject, with noseclips, breathed normally from the system, and expired volume was monitored continuously on the moving spirometer drum. The subject began breathing at functional residual capacity, maintaining a normal tidal volume until approximately 5 L of air had been expired, and then the mouthpiece was removed. Spirometric studies were performed at 120 sec. At 5 minutes, the methacholine dose was increased if this was necessary. The increased dose was accomplished either by increasing the expired volume (i.e., 6, 8, 10 L, etc.), increasing the chamber concentration of methacholine solution, or both, depending on the percentage change in FEV_1 noted after the previous inhalation. At any methacholine concentration, the amount of methacholine delivered (i.e., inspired) was estimated by multiplying the expired volume by the chamber concentration (i.e., 5 L × 10 μg/L = 50 μg). Repeated testing in the same patients demonstrated good reproducibility of results (±15%). The results of the methacholine challenge tests were recorded as the CMD_{20} or the cumulative methacholine dose (micrograms) necessary for a positive test. The test was considered positive when there was a ≥20% fall in FEV_1; otherwise, additional methacholine was administered until the total cumulative dose of about 2000 μg was administered. The CMD_{20} was calculated by performing a log-dose transformation of the data and performing a linear regression against the percent fall in FEV_1. Experience in our laboratory has demonstrated that a concentration of 1000 μg of methacholine with the generation system described above corresponds to a methacholine concentration of about 4 to 8 mg/ml, and 2000 μg correlates to a dose of approximately 16 to 32 mg/ml. Baseline values were obtained with the same procedure but breathing normal saline.

Pulmonary function tests

Baseline pulmonary function studies were performed according to accepted criteria.[28] FVC and FEV_1 were measured with a precalibrated 12 L dry-rolling seal spirometer (model No. 220 Cardiopulmonary Instruments, Houston, Texas). Predicted values for FVC and FEV_1 and for FEF_{25-75} were measured according to Morris et al.[29] The output of the spirometer was displayed on a rapid-writing X-Y recorder (model 750A, Cardiopulmonary Instruments).

Data analysis

Data were analyzed by analyses of variance, comparing the various individual parameters. In addition, analyses of covariance was performed with clinical scores as dependent variables and other parameters as covariances.[30] Because of the uncertainty of the distribution of our biologic data, nonparametric analyses were made on some of the data. Spearman's rank correlations were calculated for a number of variables.[31]

RESULTS

Demographic data

Some characteristics of the 24 subjects studied are presented in Table I. The mean ± SD age was 42.5 ± 12.9 years, with a range of 24 to 73 years. Nine individuals were younger than 35 years of age, whereas six subjects were older than 50 years. There were 17 women and seven men. Most patients had

TABLE I. Characteristics of subjects with bronchial asthma

Subject	Sex	Age (yr)	Hgt (cm)	Wgt (kg)	Smoker	Asthma (yr)	FEV_1 (%)	DSS
1	F	38	138	59	No	2	71	15
2	F	24	155	60	Yes	18	70	15
3	F	47	163	110	No	1	71	28
4	F	40	163	96	No	38	75	14
5	F	32	158	104	No	4	74	20
6	M	31	173	69	No	6	16	25
7	M	33	168	64	No	8	103	6
8	F	61	158	71	No	8	57	21
9	F	53	150	83	No	53	74	22
10	F	38	155	60	No	32	96	12
11	F	36	160	97	No	23	62	18
12	F	42	155	133	No	13	56	18
13	M	42	177	110	Yes	17	86	23
14	M	73	177	93	Yes	4	40	15
15	M	32	167	89	No	2	78	10
16	F	44	162	66	No	2	78	11
17	F	52	160	59	Yes	19	26	15
18	F	48	166	71	Yes	9	40	17
19	F	34	154	117	No	32	57	20
20	M	34	177	104	No	6	58	13
21	M	66	175	85	Yes	66	14	9
22	F	62	159	82	No	30	37	17
23	F	28	154	86	Yes	24	53	15
24	F	30	175	81	No	1	100	15

TH, Theophylline; *CS*, corticosteroids, either aerosol or oral.

had asthma for more than 10 years, the mean ± SD duration being 18.1 ± 17.3 years; 11 subjects had had asthma for less than 10 years and eight subjects for more than 20 years. Most subjects were nonsmokers; only seven were smokers (mean, 30 pack per year for the seven subjects).

Results of the pulmonary function tests revealed the FEV_1 percent predicted to be abnormal in 20 individuals (mean ± SD was 62.2 ± 24.3%; median, 66%; range, 14% to 103%); 12 subjects had less FEV_1/FVC than 65%, whereas 12 had values that were ≥65% (mean ± SD, 64.5 ± 15.5%; range, 23% to 81%). Mean ± SD values for FEF_{25-75} predicted was 46.6 ± 23.5% (range, 13% to 95%); mean ± SD for FVC percent predicted was 78.4 ± 23.2% (range, 21% to 108%).

DSS and airway responsiveness

Individual DSS and ARS scores are presented in Table I. There was variability in DSS, but most scores were between 15 and 20. Only one subject had a minimal score of 6, and no subject had a maximum score of 30. The mean ± SD for DSS was 16.4 ± 5.2 (median, 15; range, 6 to 28). The ARS ranged from a low to 14 to a high of 95. The mean ± SD was 61.6 ± 22.2 (median, 68). Ten subjects had values of 70 or higher, whereas five subjects had values of <40. Two subjects were taking no medication; 13 patients were receiving corticosteroids, either by aerosol or orally. Mean CMD_{20} for the 13 subjects receiving corticosteroids was 188.4 μg compared to 428.5 μg for the 11 subjects not taking this form of medicaton ($p < 0.05$).

CMD_{20} ranged between 11 and 2138 μg (mean ± SD was 298.5 ± 474 μg; median, 160 μg). Subjects with lower CMD_{20} tended to demonstrate more airway obstruction. This is illustrated in Fig. 1 in which patients are divided into two groups, depending on whether the FEV_1/FVC is more or less than 65%. Great individual variability is noted. Individuals with FEV_1/FVC <65% had a mean CMD_{20} of 120 μg, whereas subjects with values >65% demonstrated a mean concentration of 478 μg (p is not significant). Pearson's correlation coefficients documented a significant correlation between FEV_1 percent predicted and CMD_{20} ($r = 0.50$; $p < 0.01$). A similar correlation was noted for Spearman's rank correlations, $r = 0.49$ and $p < 0.001$. Correlations be-

ARS	Drugs		CMD_{20} (μG)
	TH	CS	
77	+	0	94
36	+	+	200
82	+	+	15
77	+	0	213
82	+	0	121
64	+	+	42
14	0	0	2138
77	+	+	17
72	+	0	53
27	+	+	552
68	+	+	26
95	+	0	11
68	+	+	697
73	+	+	186
50	+	+	109
41	+	0	1194
68	+	+	27
68	+	0	272
95	+	+	236
41	+	0	134
31	0	0	202
68	+	+	42
73	+	0	282
31	+	0	300

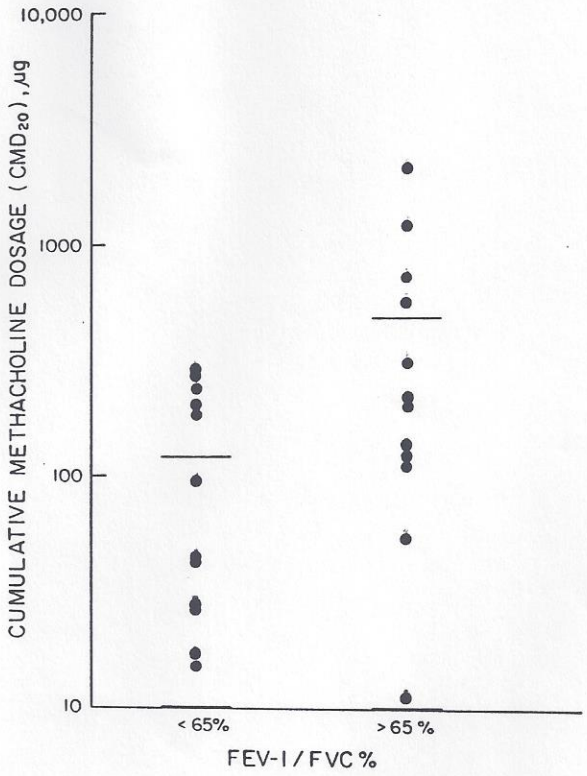

FIG. 1. Results of individual methacholine challenge tests expressed as the CMD_{20} in 24 subjects with asthma. The two groups, consisting of 12 patients each, are based on whether or not the FEV_1/FVC is more or less than 65%.

TABLE II. Correlation coefficients for several variables

	CMD_{20}	FEV_1	FEV_1/FVC	ARS	Age	Duration (yr)	DSS
DSS	−0.56	−0.16	−0.05	0.67	0.05	−0.13	—
p Value	0.003	NS	NS	—	NS	NS	—
ARS	−0.60	−0.31	−0.22	—	0.18	−0.01	0.67
p Value	0.002	NS	NS	—	NS	NS	0.0003
FEV_1	0.05	—	0.76	0.31	−0.48	−0.25	−0.16
p Value	0.001	—	0.0001	NS	0.02	NS	NS
CMD_{20}	—	0.50	0.40	−0.58	−0.18	−0.16	−0.49
p Value	—	0.01	NS	0.003	NS	NS	0.02

NS, Not significant.

tween FEF_{25-75} predicted and CMD_{20} was $r = 0.46$; $p < 0.03$. Values for FVC percent were not significant.

Because of the observed relationship between CMD_{20} and the degree of airway obstruction (Fig. 1), the importance of the initial lower FEV_1 among individuals was considered.[43] To take into account the differences in FEV_1 among individual subjects studied, the CMD_{20} was divided by percent predicted FEV_1. A statistically significant correlation between CMD_{20} divided by percent predicted FEV_1 and DSS was noted ($r = 0.58$; $p < 0.004$). A similar relationship for CMD_{20} percent FEV_1 was demonstrated for ARS ($r = 0.61$; $p < 0.002$). Individual data are presented in Table I.

We found a poor correlation between the degree of airway obstruction and DSS ($p > 0.05$). The correlation by rank testing was −0.020. Patients with a

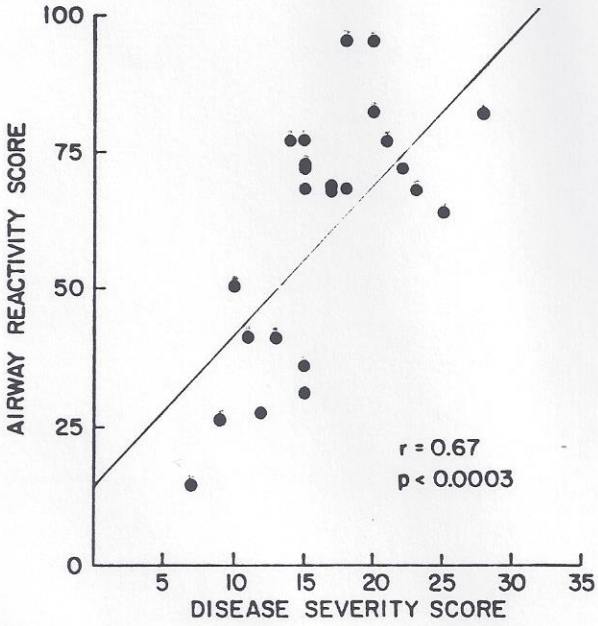

FIG. 2. Relationship between ARS and DSS. A statistically significant positive correlation is illustrated between the two; $r = 0.67$; $p < 0.0003$.

higher DSS did not always demonstrate lower FEV_1 measurements. Pearson's correlation coefficients for several variables are listed in Table II. Significant correlations were noted between the DSS and CMD_{20} ($p < 0.003$), between DSS and ARS ($p < 0.0003$), but not pulmonary function tests results, age, or duration of asthma. Similar results were noted for ARS (Table II). Spearman's rank correlations elicited similar results. In contrast, a very poor correlation was noted between ARS and FEV_1 (or FVC) percent predicted and Spearman's rank correlations for ARS and FEV_1 percent predicted. Spearman's rank correlations for ARS and FEV_1 percent predicted was -0.27 ($p < 0.01$).

The relationship between DSS and ARS is graphically depicted and a good correlation is illustrated in (Fig. 2) ($r = 0.67$; $p < 0.0003$). A semilog plot demonstrating the relationship between DSS and CMD_{20} ($r = -0.57$; $p < 0.003$) is illustrated in Fig. 3. A higher DSS correlated with greater responsiveness to methacholine is illustrated. A similar relationship between ARS and CMD_{20} ($r = -0.60$; $p < 0.002$) is illustrated in Fig. 4. As expected, more clinically apparent reactivity to nonspecific inhaled irritants is associated with greater sensitivity of the airways to methacholine.

Stepwise multiple regression analyses were performed to determine the contributions of various independent variables on DSS and ARS. With one variable in the model, statistically significant correlations are noted for ARS and DSS with CMD_{20}, but not for FEV_1 percent predicted (data not presented). The correlation did not significantly improve by the inclusion of additional measurements. Substitution of other independent variables for CMD_{20}, such as age, duration of asthma, or FEV_1 percent predicted (or other pulmonary function tests) did not significantly correlate with DSS and ARS. Stepwise multiple regression analyses incorporating more than one independent variable demonstrated variables such as age, duration of asthma, and degree of airway obstruction (i.e., as measured by FEV_1 percent predicted) did not significantly influence correlations with DSS and ARS.

DISCUSSION

The results of the present investigation suggest that the degree of airway responsiveness to nonspecific stimuli in subjects with chronic stable asthma can be estimated by use of an ARS. In some respects our study is comparable to the study reported by Mortagy et al.[16] who surveyed two populations with a self-administered questionnaire consisting of questions denoting "bronchial irritability" as induced by "12 environments," including cold air, smoky atmospheres, traffic fumes, and common household chemicals, such as hair sprays, perfumes, bleaches, etc. The designation, "bronchial irritability syndrome," was applied to those subjects reporting bronchial irritability symptoms and demonstrating increased histamine reactivity with a provocative dose of 0.5 gm/L causing a 20% fall in FEV_1. There were no normal subjects reporting symptoms who had provocative dose values of 0.5 gm/L causing a 20% fall in FEV_1. Although the relationship between clinical asthma and "bronchial irritability" was considered to be unclear, 27% of this group had a physician's diagnosis of asthma. The investigators concluded that the bronchial irritability syndrome was a definable entity for epidemiologic studies and patient care.

The application of an "established" questionnaire for distinguishing subjects with nonspecific hyperresponsiveness appears to be unreliable, likely caused by the make up of questions used.[17, 18, 32] Negative results were reported by Dales et al.[18] after examining responses to a standardized American Thoracic Society-Division of Lung Disease respiratory questionnaire. A high proportion of subjects with mild to moderate airway hyperresponsiveness were demonstrated to be asymptomatic with this questionnaire, suggesting it is deficient in detecting asthma.[19] Other negative studies were studies of Desjardins et al.[17] who administered a modified questionnaire proposed by the International Union Against Tuberculosis and a Dutch study with a modified British Medical Research Council standardzied questionnaire.[32]

Most epidemiologic studies of asthma focus on re-

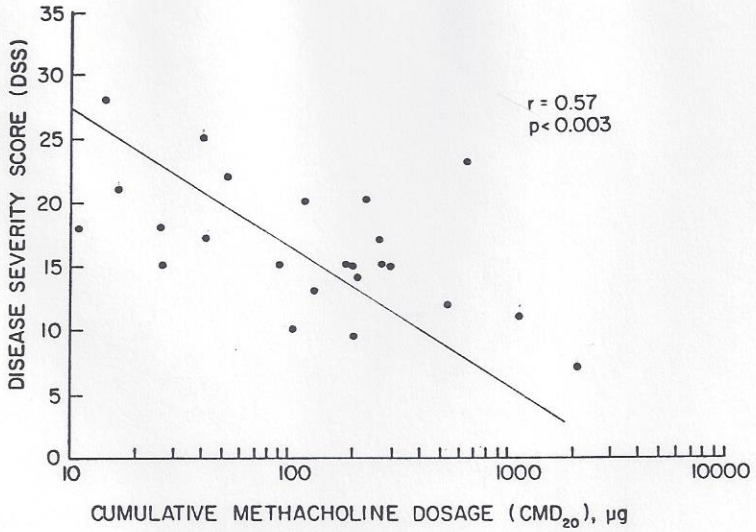

FIG. 3. Relationship between DSS and CMD_{20}. Data are presented on a semilog plot and illustrate a significant negative correlation between the two; $r = -0.57$; $p < 0.003$.

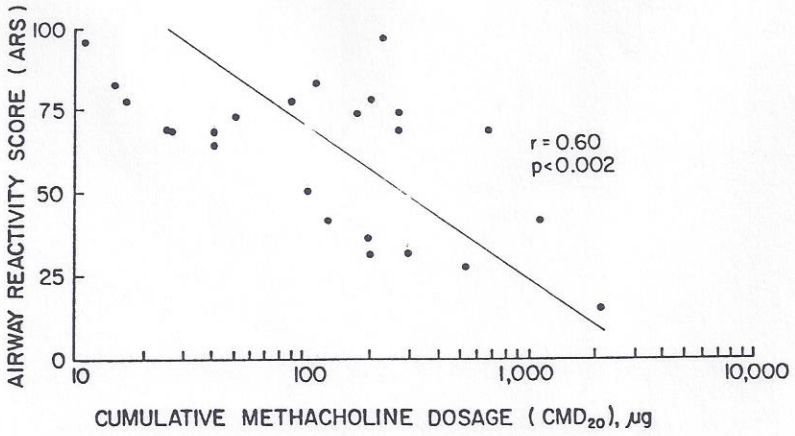

FIG. 4. Relationship between ARS and CMD_{20}. A significant negative correlation is illustrated; $r = -0.60$; $p < 0.002$.

spiratory symptoms, such as cough, phlegm, and exertional breathlessness that better detect "chronic bronchitis" than do questions as "attacks of chest tightness with difficulty breathing," which appears more appropriate for asthma.[19] The results of our ARS questionnaire, which specifically addressed 22 common airborne and physical irritants, several with odors, was strongly correlated with the methacholine CMD_{20}. Many patients with asthma complain that odors make their symptoms worse.[33-36] The mechanism to explain why odors worsen asthma is not discerned, but consideration must be made to both chemical and neural reactions occurring in the bronchial mucosa with a psychologic component playing a role.[33]

We have not determined the sensitivity of the ARS in recognizing airway hyperresponsiveness, but rather we studied its value in appraising patients with well-defined asthma. We believe that in this setting, it has important clinical and therapeutic uses. It is clear that further studies are necessary to document its efficacy in a variety of clinical situations. Although our data look encouraging, both the ARS and DSS questionnaires we devised require further refinement and psychometric testing, including test-retest reliability and interitem correlations.

An emphasis on airway hyperresponsiveness and disease severity has therapeutic significance. The identification of suitable patients for certain medications might be accomplished by simply asking the patients about their response to certain nonspecific irritants. Sodium cromolyn and aerosol corticosteroids are recommended as a therapeutic modality for re-

ducing airway hyperresponsiveness and inflammation.[13] Anticholinergics may alleviate irritant-induced vagally mediated bronchospasm that may account for a significant portion of airway obstruction in some patients with asthma.[37-39]

Troublesome asthma symptoms, such as persistent cough, dyspnea, and chest tightness can contribute to clinical disease severity that may not be expressed by the degree of airway obstruction.[6, 11, 40, 41] In our investigation, DSS more closely correlated with CMD_{20} and ARS than FEV_1 percent predicted. The coefficients of determination was 45% for ARS, 24% for CMD_{20}, and 2.6% for FEV_1 percent. These data also imply that perhaps 55% to 76% of the DSS was influenced by other factors than airway hyperresponsiveness.

Methacholine challenge testing is a well-established clinical tool[11, 12, 21, 42-46] but can be affected by a number of influences, including suggestion,[47] deep inspiration,[48] adequacy of aerosol deposition,[49] pretest pulmonary function status,[50] selection of the proper physiologic measurement to monitor the airway response,[51] a number of infectious, environmental, and clinical factors,[11-13] the patient's ability to cope with their disease,[9] and emotional lability.[7] Investigators have reported correlations between a greater sensitivity to methacholine or histamine and worsening clinical features of asthma, including wider diurnal variation in flow rates, more exercise-induced bronchospasm, amount of medication required for asthma control, and greater bronchial response to allergens.[11-13, 20, 42, 52] In our study, the age of the patient and the duration of asthma did not correlate with disease severity, which is similar to some studies,[42, 53] but is in contrast to the study reported by Spector et al.[54] Most of our patients were nonsmokers; therefore, the influence of irreversible small airway obstruction from cigarette smoking on airway hyperresponsiveness and disease severity may not be an important consideration.[51, 55] Although corticosteroids are known to reduce methacholine sensitivity and CMD_{20} was lower in the group receiving this medication, we do not believe their use had a significant effect on the outcome of our study.[13, 56] No patient receiving a β-agonist medication before the study required significant change in medication when these drugs were stopped.[26] Theophylline preparations are reported not to affect airway responsiveness.[13]

We attempted to regulate the details of the methacholine-challenge aerosol delivery and methodology, to make sure of proper selection of patients with stable asthma and with well-defined disease, and to standardize our research protocol to address important variables. We investigated preselected subjects with well-defined chronic asthma and with verified hyperresponsive airways who were studied in a laboratory setting, in contrast to epidemiologic studies of populations in which previous clinical status is unknown. Although we can not be absolutely sure that there were not other factors influencing the patient's results, it is our observation that in our well-defined patient population with stable disease, many of the confounding variables were relatively well identified. Our investigation focused on a simple method for estimating the degree of airway hyperresponsiveness and severity of disease with select clinical information provided by the patient. Our findings support the contention that in chronic stable asthma, the inherent responsiveness of the airways to nonspecific stimuli is a notably important factor in influencing clinical features of the disease and a dominant factor in determining disease severity.

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Comparison of the generation of platelet-activating factor and leukotriene C_4 in human eosinophils stimulated by unopsonized zymosan and by the calcium ionophore A23187: The effects of nedocromil sodium

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The generation of platelet-activating factor (PAF) and leukotriene C_4 (LTC_4) from normodense human eosinophils (EOSs), stimulated with unopsonized zymosan or calcium ionophore A23187, has been studied. There was a zymosan time- and dose-dependent increase in both PAF and LTC_4 production. A plateau of 0.11 ± 0.04 ng of PAF per 10^6 EOSs (mean ± SEM; n = 7) and of 1.38 ± 0.58 ng of LTC_4 per 10^6 EOSs (n = 5) was reached at 5 × 10^5 zymosan particles at 37° C for 30 minutes. Under optimal conditions, 91 ± 1% of the PAF and 66 ± 13% of the LTC_4 remained cell associated. Calcium ionophore A23187 induced a time- and dose-dependent increase in the quantities of PAF and of LTC_4 generated by EOSs. A plateau of 31 ± 13 ng of LTC_4 per 10^6 EOSs (n = 5) was reached at 1 μmol/L of calcium ionophore A23187 at 37° C for 15 minutes. The dose response for PAF generation reached 4.2 ± 0.8 ng/10^6 EOSs (n = 8) at 10 μmol/L of calcium ionophore A23187 at 37° C for 15 minutes and had not plateaued; 90 ± 5% of the generated PAF was cell associated. In vitro preincubation of EOSs with 10^{-8} to 10^{-4} mol/L of nedocromil sodium for 15 minutes did not change the subsequent generation or cellular distribution of PAF or LTC_4 in EOSs optimally stimulated with either zymosan or calcium ionophore A23187. (J ALLERGY CLIN IMMUNOL 1990;85:26-35.)

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Arachidonic acid released from membrane phospholipids by the action of PLA_2 after cell activation can be metabolized by the cyclooxygenase or lipoxygenase pathways. The cyclooxygenase pathway leads to the generation of prostaglandins and thromboxane. The 5-lipoxygenase pathway leads to the elaboration of the leukotrienes, which in the human EOS is predominantly LTC_4.[1, 2] LTC_4 increases vascular permeability and is a potent constrictor of nonvascular smooth muscle.[3]