the effect of relatedness to a patient; their more recent follow-up raises question about this influence. Our data show the effect of both factors. It seems clear that in addition to phenotype, other genetically determined biochemical factors will be discovered in the future to explain this added familial relationship.

REFERENCES


Q. (Zwilling): Because the study population was obtained by their familial relationship to patients with lung disease, will this affect the ability to generalize your conclusions to the total population?
A. (Madison): Only a small number of the study population were drawn by their familial relationship to a known patient. Upon analyzing the data, the effect of this potential bias was small.

Q. (Burrows): Why were no initial abnormalities in lung function present in those who deteriorated at a fast rate?
A. (Madison): We don't know.

Multiple Factors in Airways Obstruction*

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A number of risk factors have been described that influence the development of COPD. It is important not only to identify them, but to assess their relative importance in airflow limitation. The purpose of this report is to present observations on the relationship of various factors in subjects who participated in a genetic epidemiologic study of COPD and to suggest a ranking of their contribution in the development of airflow limitation.

STUDY POPULATION

The Hopkins study population comprises several groups of patients along with their relatives, neighborhood controls, teachers, and other groups.1,2 For the examination of potential risk factors, all patients were included. Thus, for this analysis, only those subjects over 20 years of age and not ascertainment on the basis of their own health status were considered: 2,539 subjects as shown in Figure 1. In an interview, questions regarding smoking habits, family history, socioeconomic status, and other factors of epidemiologic interest were included. Tests of pulmonary function included spirometry for assessment of airways obstruction. From blood samples, determinations of ABO blood types and protease inhibitor types were made. The ability to secrete water-soluble ABH antigens into body fluids was determined from saliva samples. A binary variable multiple regression procedure was carried out to adjust for 12 factors: familial component, age, sex, race, smoking history, socioeconomic status, alcohol intake as well as genetic markers: Pi type ABO blood type, AB blood type, ABH secretor status, and PTC taste ability. Thus, the mean FEV1% or percentage of persons with aberrant FEV1% indicated for each factor has been adjusted for the 11 other factors in the matrix.

The forced expiratory volume in one second as a percentage of forced vital capacity (FEV1%) was used as the index of obstruction. An FEV1% of <68 was defined as "aberrant."

RESULTS AND DISCUSSION

Comparisons of Mean Adjusted FEV1%

Figure 2 contains the mean adjusted FEV1% for groups with and without the various risk factors. The greatest difference of means (6.6) was found when comparisons of subjects more than 45 years old were made with subjects 20-44 years old. Smokers of one or more packages of cigarettes daily had a mean FEV1% 4.6

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less than never smokers. Individuals from the lowest fifth of the socioeconomic groups (compared to those from the upper fifth), first degree relatives of COPD patients (compared to first degree relatives of non-pulmonary patients, neighborhood controls, and teachers), mean (compared to women), and nonsecretors of ABH antigens (compared to secretors) had FEV1% approximately 2 (range 1.8-2.3) below their respective comparison groups. ABO blood type and race had smaller differences of only borderline significance; and the differences with Pi type and amount of alcohol intake were not statistically significant. One finding, which was quite unexpected, was that heavy drinkers, whether classified according to wine, beer, straight liquor, or mixed drink intake were no more obstructed than light drinkers when adjustments for differences in smoking habits, SES, and other factors were made.

**Figure 1.** Population selected for study. Note that only nonpatient groups are included in the present analysis.

**Figure 2.** Risk factors and airways obstruction.

**Figure 3.** Risk factors and aberrancy of forced expirations.
Comparisons of Rates of Aberrancy

Clearly, a number of factors are associated with lower mean FEV\textsubscript{i}\%. However, some of these differences are small. In fact, it might be argued that a 2 percent difference in the FEV\textsubscript{i}\% of a patient is trivial. On the other hand, if the FEV\textsubscript{i}\% has even minor shifts in the mean, given the same variance, marked differences in the numbers of subjects in the tails of the distribution may be involved. For this reason, we calculated adjusted rates of aberrancy, that is, the proportion of subjects with FEV\textsubscript{i}\% <68, for the groups and compared these rates in terms of ratios. Results are shown in Figure 3. Note that subjects 45 years of age or older have 3.8 times as large a proportion of individuals with an FEV\textsubscript{i}\% <68 as subjects 20-44 years old when adjustments for other factors are made. The rate of aberrancy for cigarette smokers (1 + packs daily) is more than three times that of never-smokers; for those from the lowest SES it is 2.4 times that of those from the highest SES; for 1° relatives of COPD patients, 1.7 times that of 1° relatives of nonpulmonary patients and other controls; for men, 1.6 times that of women; and for nonsecretors, 1.4 times that for secretors. Relative rates of aberrancy of Pi variants, subjects with A blood type, whites, and heavy drinkers were closer to one, and only ABO type attained statistical significance.

Thus, it appears that even small decreases in the mean FEV\textsubscript{i}\% of a group may be associated with large increases in the numbers of individuals having aberrant values. While interactions of the various risk factors are not considered in this report, it is quite clear that important factors related to the development of COPD include age, smoking, SES, family relationship, sex, and secretor status.

REFERENCES


Q. (Flenley): Because cigarettes produced a number of years ago had more toxic materials than those manufactured now, can this be a factor in the association between age and lower FEV\textsubscript{i} percentage?
A. (Cohen): It is possible that this is responsible for part of the association; however, our study has not addressed this point.
Q. (Mittman): Is the FEV\textsubscript{i}/VC the best variable to use?
A. (Cohen): We believe that the absolute FEV\textsubscript{i} is useful; but for cross sectional data, we feel, FEV\textsubscript{i}/FVC is the most suitable index because height adjustments are not necessary and patients with low FEV\textsubscript{i} because of restrictive disease are not mislabelled.

A Longitudinal Study of Smokers and Nonsmokers
5-6 Year Follow-up Using Spirometry and the Single Breath N\textsubscript{2} Test

Sonia Buist, M.D., and I. Nagy, M.D.

Three hundred forty-two smokers and nonsmokers, first tested at an emphysema screening center in Portland in 1971/72, were followed-up for five to six years, using a respiratory symptom questionnaire, spirometric tests and the single breath N\textsubscript{2} test. Subjects were tested three times during the study period. Since the major objective of this study was to evaluate the role of the single breath N\textsubscript{2} test in identifying the smoker most likely to progress to chronic airflow obstruction, only nonsmokers and smokers without clinical airflow obstruction (defined as an abnormal 1-sec forced expiratory volume [FEV\textsubscript{1}] were included.

Lung aging, as measured by spirometric variables, was very slow in the nonsmokers. The fastest rate of decline in function was seen in male smokers who initially had mild function impairment, defined as an abnormal single breath N\textsubscript{2} test. Nine male smokers (7% of all male smokers and 10% of male smokers with an abnormal single breath N\textsubscript{2} test) developed an abnormal FEV\textsubscript{1}, during the course of the study; all had an abnormal single breath N\textsubscript{2} test at the start of the study.

We conclude that men are more at risk of developing clinical airflow obstruction than are women, and that the single breath N\textsubscript{2} test is usually abnormal for several years before the FEV\textsubscript{1} becomes abnormal. However, since not all smokers with an abnormal single breath N\textsubscript{2} test subsequently develop an abnormal FEV\textsubscript{1}, the predictive value of the test, in terms of accurately identifying the susceptible smoker, is still in question. It seems likely that other factors which interact with smoking need to be identified and used in association with the single breath N\textsubscript{2} test in order to identify the susceptible smoker during the preclinical stage of the disease process.

Q. (Mittman): Because many smokers have abnormal closing volume measurements, yet only a minority develop clinical disease, doesn’t this reduce the value of the single breath nitrogen test as a predictor for lung disease?
A. (Buist): The predictive value of the single breath N\textsubscript{2} test appears to be very poor. On the other hand, it may well give important information concerning the natural history of chronic airflow obstruction. At this point, I don’t think the longitudinal studies using this test have gone on for long enough to adequately answer the question of the predictive value. It may turn out, for example, that a combination of the single breath N\textsubscript{2} test and spirometry may be a good predictor.

Q. (Mittman): Wasn’t the single breath test as a prediction of disease doomed to failure from the start because you saw many smokers with abnormal tests, yet we all know only a few get disease?
A. (Buist): Your question is difficult to answer. We believe many factors are important in predicting development of disease.

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