Evidence is accumulating that elevated levels of serum IgE may play a role in the pathogenesis of chronic airflow obstruction. We examined this question using data on 863 subjects drawn from two cohort studies which we have followed over a period of nine to 11 years. One, the Portland cohort, represents a working population aged 25 to 55 years at baseline. The second, the Screening Center cohort, spans a wider age range (18 to 87 years at baseline) and is biased towards respiratory disease. Spirometric tests and respiratory symptom questionnaires have been administered five times over a nine-year period for the Portland cohort, and over an 11-year period for the Screening Center cohort. IgE was measured one time towards the end of the follow-up. Our data confirm the finding that smokers tend to have higher IgE levels than nonsmokers. For the combined sample, geometric mean levels of IgE were 31.0 IU/ml among smokers and 17.4 IU/ml among nonsmokers. Levels among ex-smokers were intermediate. Among smokers, IgE was not related to either amount smoked or pack-years. Cross-sectionally, FEV1 was inversely related to IgE in the Screening Center cohort, but not in the Portland cohort study. Among smokers, this association was only present for those subjects with symptoms of chronic bronchitis (chronic cough/sputum production). We found no association of IgE with longitudinal rate of decline of FEV1, in either cohort. These findings are consistent with other studies and support the hypothesis that serum IgE is inversely related to function level cross-sectionally, but is not predictive of rate of decline of lung function.

Considerable attention has been given in recent years to the possible role of serum immunoglobulin E (IgE) in the development of chronic airflow limitation and other respiratory disorders.1-5 This interest emerged from the findings of Gerrard et al and others in the early 1980s that smokers demonstrated elevated levels of IgE compared to nonsmokers, and that this excess IgE may be qualitatively different from the IgE seen in nonsmokers. Support for this latter hypothesis came from studies showing the lack of an age-related decline in IgE among smokers and the further observation that smokers showed a decrease in allergy skin test reactivity to common aero-allergens, despite their higher IgE levels.6 Subsequent studies have found positive correlations between elevated levels of IgE and a number of respiratory disorders, as well as cross-sectionally measured forced expiratory volume in one second (FEV1).7,8,12 Only one study has reported on the association between serum IgE and longitudinally-measured rate of decline of lung function. Taylor and coworkers9 followed 227 men for 7.5 years and found no evidence that elevated levels of IgE were associated with an accelerated rate of decline of FEV1.

We have followed two cohort studies over a period of nine to 11 years with biannual spirometric testing, single breath N4 test, and a respiratory symptom questionnaire. Towards the end of our follow-up, serum IgE was measured in a total of 863 subjects. In this article we present our data on the association between serum IgE and both cross-sectional FEV1 and rate of decline of FEV1. We also compare our findings on the distribution of IgE with those from previous studies, and reasons for similarities and dissimilarities are discussed.

Materials and Methods

Study Population

Data reported are derived from two cohorts which were followed over a nine to 11 year period. One, the Portland cohort, was a random sample of 507 Multnomah County employees first tested in 1974. Follow-up testing for this cohort was conducted in 1976, 1978, 1981 and 1983. The other, the Screening Center cohort, originally consisted of 1,024 subjects first tested in 1971 through 1972 at an emphysema screening center sponsored by the local lung association. Since the major objective of the follow-up in this group was to evaluate the role of the single breath N4 test in identifying the smoker most likely to progress to clinical airflow obstruction, only those subjects with a normal FEV1 were initially invited to participate in the follow-up. These included both nonsmokers and smokers with normal single breath N4 test results, and smokers with abnormal single breath N4 tests. All exsmokers were excluded. Follow-up testing for this cohort was done in 1975, 1977, 1980 and 1982. Those
subjects refusing to participate in the 1975 test were again invited to participate in 1980 and 1982, as were those who were initially excluded due to abnormal FEV1 levels.

Both cohort studies have been described elsewhere in terms of methods of selection and initial (cross-sectional) assessment of lung function.\textsuperscript{23,24} In view of the important question of generalizability of the data, it should be noted that the Portland cohort started as a random sample of a working population, aged 25 to 54 years (mean 38) at the time of the initial survey, while the Screening Center cohort consisted largely of a volunteer group of individuals (mean age 47 years) who presented themselves for pulmonary function tests in response to extensive media advertising. Cross-sectional data indicate that the Portland cohort is representative of the young and middle-aged working population in Portland and that the Screening Center cohort is biased towards respiratory disease.

\textbf{Measurements}

Testing on each occasion has included a respiratory symptom questionnaire and spirometric study. Serum IgE and atopic status were measured toward the end of the study.

\textbf{Questionnaire.} The questionnaire used in 1971 and 1972 was closely modeled on the British Medical Research Council questionnaire\textsuperscript{25} and was self-administered. On all other occasions we have used the Respiratory Symptom Questionnaire\textsuperscript{26} recommended by the ATS Division of Lung Diseases in 1972 for epidemiologic studies. This questionnaire was the predecessor of the current American Thoracic Society-Division of Lung Diseases (ATS-DLD) Respiratory Symptom Questionnaire.\textsuperscript{27}

From the questionnaire, nonsmokers were defined as those who were smoking <1 cigarette/day; smokers, persons who were smoking \(\geq 1\) cigarette/day; exsmokers, persons who had smoked regularly in the past (\(\geq 1\) cigarette/day), but were smoking <1 cigarette/day at the time of testing.

Persons were designated as symptomatic if: 1) they had a cough or sputum production on most days for at least three months of the year (cough/sputum), or 2) they complained of attacks of shortness of breath with wheezing or had wheezing in the absence of a cold or on most days (wheezing). Asthma was defined as (self-reported) doctor-diagnosed asthma. In this report, smoking status and respiratory symptoms were defined as at the time of IgE determination.

\textbf{Spirometry.} In 1971 and 1972, we used a Stedal-Wells spirometer. Each subject performed at least three forced expiratory vital capacity maneuvers from which the forced vital capacity (FVC) and FEV1 were obtained (the maximal value achieved). From 1974 on, spirometry was performed using one of three Vitalograph bellows spirometers. Volume signals from all three spirometers were corrected to absolute volumes using a single super syringe. We corrected for the static temperature sensitivity of each Vitalograph and the different dynamic temperature sensitivities of the four spirometers, as described elsewhere.\textsuperscript{28}

On each test occasion after 1972, a minimum of five forced expiratory vital capacity measurements were obtained, from each of which FVC and FEV1 were measured. For both FVC and FEV1, maximal value achieved was used. FEV1/FVC ratio was calculated as the ratio of the two maximal values. All volumes were corrected to BTPS conditions. All spiographic readings for all years were inspected for quality by one of the authors. We followed the published guidelines for acceptability of forced expiratory volume-time curves,\textsuperscript{28} and only data from acceptable curves were used.

Rate of change over time for FEV1 was calculated as the slope of the least squares regression line derived from all available and acceptable measurements over the study period. For our cross-sectional analyses, only spirometric data obtained at the time of IgE determination were used.

\textbf{IgE.} We collected blood from 507 people in the Screening Center and 356 in the Portland cohort study. All of the Portland and most (84 percent) of the Screening Center cohort study blood samples were drawn between 1980 and 1981. The remaining Screening Center samples were drawn in 1982. The samples were stored at \(-70^\circ\mathrm{C}\) from the time of collection until analysis in 1983. IgE determinations were carried out by the Tucson SCOR Project using the PRIST method. Additional details concerning their methodology are given elsewhere.\textsuperscript{29} Each serum sample was assayed in duplicate and IgE levels for each individual are reported as the mean of the two determinations. All values were recorded as IU/ml.

\textbf{Atopy.} Skin prick tests were administered on 288 subjects in the Portland cohort as part of the 1983 follow-up. Five allergens common to the Portland area were used, as well as positive and negative controls (Hollister-Stier Laboratories, Spokane, Washington). The five allergens were Bermuda grass (1:20), dematiaceae mold mix (1:100), English plantain (1:20), house dust (1:10) and western grasses (1:100). Histamine phosphate (equivalent to histamine base (1 mg/ml)) was our positive control and glycerine (50 percent solution) was our negative control. Wheal size was measured as a sum of diameters along the major and minor axes. Individuals were classified as atopic if, for any agent other than histamine, the wheal size (sum of diameters) exceeded that for glycerine by 5 mm or more. Ninety-nine percent of our prick-tested subjects had a positive response to the histamine control, and all of the histamine responses exceeded those for glycerine by 4 mm or more.

\textbf{Statistical Methods.} For some analyses, pulmonary function data were expressed as percent predicted to adjust for differences between groups with respect to age, height and sex. We used regression equations derived from the asymptomatic nonsmokers in our own cohort studies to determine the predicted values.

We used analysis of covariance to describe the dependence of IgE on age, sex, smoking status and atopic status. Chi-square goodness-of-fit statistic for likelihood ratios was used to evaluate the significance of competing models.\textsuperscript{30} Dependence of IgE on amount smoked and duration of smoking for current smokers, and on time since quitting for exsmokers, was assessed using standard linear regression analysis.

For dichotomous outcome measures such as the prevalence of wheeze and asthma, we used a chi-square test for trend\textsuperscript{32} to assess the overall strength of association with IgE. We also used logistic regression analysis to adjust this association for auxiliary variables such as age and sex. In addition to using a discrete version of IgE (<40 IU/ml, 40 to 100 IU/ml, >100 IU/ml) in these analyses, we also used Ln IgE as a continuous variable. Unless otherwise noted, the two measures gave equivalent results and only the former is presented in this paper. The dependence of continuous measures, such as rate of decline of FEV1 and percent predicted FEV1 on IgE, were examined using analysis of covariance as described above. Unless otherwise stated, the term statistical significance is taken to imply \(p<.05\), and all significance levels are one-sided. All analyses were done on a Harris 900 minicomputer using either the Statistical Package for Social Sciences (SPSS)\textsuperscript{33} or the General Linear Interactive Modelling (GLIM)\textsuperscript{34} statistical software packages.

A total of 31 subjects (3.6 percent) were excluded from our cross-sectional analyses of FEV1, due to unacceptable data. For our analyses involving longitudinal rate of decline of FEV1, we excluded those subjects with fewer than three acceptable values. This included 10 percent of those Screening Center subjects for whom IgE data was available, and 3 percent of the Portland cohort subjects. Among the remaining 799 subjects, 88 percent were tested at least four times and the mean length of follow-up was 8.7 years for the Portland cohort and 10.2 years for the Screening Center cohort.

\textbf{Results}

Demographic information on the cohorts is given in
Table 1—Characteristics of Sample

<table>
<thead>
<tr>
<th></th>
<th>Portland Cohort (n = 536)</th>
<th>Screening Center Cohort (n = 507)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>47%</td>
<td>57%</td>
</tr>
<tr>
<td>Women</td>
<td>53%</td>
<td>43%</td>
</tr>
<tr>
<td>Age*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (yrs) ± SD</td>
<td>45 ± 9</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>Range</td>
<td>33-61</td>
<td>26-94</td>
</tr>
<tr>
<td>Smoking status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>Ex</td>
<td>34%</td>
<td>21%</td>
</tr>
<tr>
<td>Non</td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td>Prevalence of respiratory symptoms†</td>
<td>28%</td>
<td>49%</td>
</tr>
</tbody>
</table>

*Status at time of IgE determination
†Chronic cough, sputum or wheeze

Table 1. The Screening Center cohort is, on an average, older and covers a much wider age range than does the Portland cohort. It also shows a higher prevalence of respiratory symptoms. The lower proportion of ex-smokers in the Screening Center cohort is due to their having been excluded from the initial follow-up for this cohort. Thus, ex-smokers in this cohort were predominantly smokers in 1971 who subsequently quit.

Distribution of IgE

Despite the differences between the two cohorts, their distributions of IgE as a function of age, sex and smoking status were similar based on an analysis of variance, and their data are combined for Figures 1 and 2. Similar to other studies, we found smokers to have elevated levels of IgE relative to nonsmokers. This was true both overall and for each cohort study separately. As shown in Figure 1, the distribution of Ln(IgE) in smokers is shifted toward the higher end of the Ln(IgE) scale. Higher IgE levels for smokers can also be seen in Figure 2, along with the fact that smokers fail to show the age-related decline in IgE which nonsmokers show. This decline in nonsmokers is restricted primarily to the over-70 years age group. In the Portland cohort, where the oldest subject was 61-years-old, and among Screening Center subjects under 70 years of age, there is no significant association between age and IgE. It is only when the older subjects are included that the decline in IgE with age becomes significant. Among smokers, neither amount smoked nor pack-years was correlated with IgE. The distribution of IgE among ex-smokers was intermediate to that observed for smokers and nonsmokers and was not related to time since quitting.

The only significant difference in the distribution of Ln (IgE) between the cohort studies, based on the ANOVA, involved an interaction between sex and smoking status. In both cohorts, smokers had signifi-
significantly greater IgE levels than nonsmokers, but only in the Screening Center cohort were IgE levels significantly greater for males than for females. Among Portland cohort subjects for whom atopic status was measured, sex was still not significant after adjusting for atopy, and smoking status still was significant. IgE was, of course, significantly elevated among atopic subjects.

**Relation to Respiratory Symptoms**

Both cohorts showed a positive correlation between prevalence of asthma and IgE level among both smokers and nonsmokers (Fig 3). Associations were strongest for nonsmokers. Among smokers, increased asthma was only seen among subjects with IgE levels in excess of 100 IU/ml. For nonsmokers in both cohort studies, IgE was also positively correlated with wheeze (Fig 4). There was a weaker (nonsignificant) association with wheeze among Portland cohort smokers, and no association between IgE and wheeze was seen among Screening Center cohort smokers. There was no association with cough/sputum production in the Portland cohort. For the Screening Center cohort, a weak association was seen overall, but it was not significant for any of the smoking groups. For exsmokers in both cohorts, associations between IgE and each of the above respiratory symptoms were weak or nonexistent.

Reanalysis of the above data using logistic regression to adjust for age and sex generally confirmed the results of the unadjusted analyses. The only exception was for asthma among smokers in the Screening Center cohort. The unadjusted analysis indicated a marginally significant association with IgE (p = .07). For our adjusted analysis, we found a significant association for male smokers (p = .01) but not female smokers (p = .67) based on the logistic regression trend chi-square.
Relation to FEV$_1$

Figure 5 shows the proportion of subjects in each cohort with an FEV$_1$ <80 percent of predicted in relation to serum IgE. In the Screening Center cohort, but not the Portland cohort, elevated levels of IgE were significantly associated with reduced cross-sectional levels of FEV$_1$. The association among smokers only held for those with cough/sputum production, for whom the proportions in the three IgE groups (<40, 40 to 100, >100 IU/ml) were 39, 53 and 65 percent respectively (p<.01). Among smokers not reporting cough/sputum production, these proportions were 31, 38 and 30 percent. There was no association between cross-sectional FEV$_1$ and IgE for exsmokers in either cohort. We found the same results when we correlated IgE and percent predicted FEV$_1$ as continuous measures, and also when we used the FEV$_1$/FVC ratio in place of percent predicted FEV$_1$. In the Portland cohort, the lack of association between IgE and FEV$_1$ among smokers persisted even when we restricted our analysis to those smoking at least one pack per day. Logistic regression analysis confirmed these findings and further showed that the association among nonsmokers in the Screening Center cohort was only present for males.

Table 2 shows longitudinally-measured rates of decline for FEV$_1$, as a function of IgE for each cohort. Only among smokers in the Screening Center cohort was there evidence of an association between IgE and rate of decline of FEV$_1$. The trend was inconsistent, however, and the rate of decline for smokers with IgE levels >100 IU/ml was not significantly different from that for smokers with IgE levels <40 IU/ml. For the 288 subjects in the Portland cohort that underwent skin prick tests, we also adjusted our analysis for atopic status. We found no association between IgE and rate of decline of FEV$_1$ among either group.

We also looked at variability about each individual’s regression line of FEV$_1$ over time as a measure of reversible airflow obstruction. In terms of a standard linear regression analysis, this variability corresponds to the “mean square error” or “residual mean square”. We found no association between this measure and IgE in either cohort, even after adjusting for age, sex and smoking status.

Table 2—Mean Rates of Decline$^*$ of FEV$_1$(ml/yr) for Subjects Tested at Least Three Times

<table>
<thead>
<tr>
<th></th>
<th>Portland Cohort IgE Range (IU/ml)</th>
<th>Screening Center Cohort IgE Range (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;40</td>
<td>40-100</td>
</tr>
<tr>
<td>Current smokers</td>
<td>$-53 \pm 32^‡$</td>
<td>$-45 \pm 25$</td>
</tr>
<tr>
<td></td>
<td>(67)</td>
<td>(25)</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>$-39 \pm 23$</td>
<td>$-46 \pm 25$</td>
</tr>
<tr>
<td></td>
<td>(75)</td>
<td>(21)</td>
</tr>
</tbody>
</table>

*Means adjusted for age, height and sex using analysis of covariance
†2-tailed significance levels based on analysis of covariance F-test adjusting for age, height and sex.
‡All data expressed as mean ± SD (n)
DISCUSSION

Our results corroborate earlier studies documenting an elevation of serum IgE levels among individuals who smoke. Relative to nonsmokers, the distribution of IgE in smokers was both elevated and more dispersed. Smokers also failed to show the same age-related decline in IgE which nonsmokers showed. In one of two cohort studies, we also confirmed reports of an association between elevated levels of IgE and reduced cross-sectional FEV₁ among smokers with a positive history of respiratory symptoms. Among nonsmokers, we found this association among men both with and without a history of respiratory symptoms. In both cohort studies, elevated levels of IgE were not associated with an accelerated rate of decline in FEV₁ over a period of nine to 11 years, nor with the variation about individual regression lines. These results held for both smokers and nonsmokers. Our cohorts included adults with a wide range of ages, of all smoking habits, and with a function range which was similar to true population samples. One was a volunteer cohort population, possibly biased towards respiratory disease, and the other was a random sample of working civil servants. Thus, although our cohort studies were not true population samples, our subjects were probably reasonably representative of the general adult population.

Ever since the first studies showing an elevation of serum immunoglobulin among smokers, there has been interest in the possibility that this factor may help to identify the so-called susceptible smoker (i.e., the smoker who develops clinical airflow obstruction and an appreciable impairment of lung function). The possibility that the elevated IgE seen among smokers may be qualitatively different from the IgE of nonsmokers has been proposed. Also, it has been hypothesized that the excess IgE in nonatopic smokers may be a response to allergic stimuli that is not inhaled but that resides in the lower airways, and that this elevated IgE may be important in the pathogenesis of the "chronic asthmatic bronchitis" syndrome. Casterline recently reviewed these and other studies and discussed possible mechanisms to explain the findings.

In light of this interest, evidence as to the association between IgE and both cross-sectional lung function and longitudinal rate of decline of lung function is especially important. Both our study and the recent report by Taylor et al found no association between elevated levels of IgE and rate of decline of FEV₁ among large cohorts followed over a seven- to 11-year period. The report by Taylor et al focused primarily on the relationship between bronchial responsiveness and rate of decline of FEV₁, and the lack of association with IgE was noted only briefly. It is not clear, therefore, whether they adjusted for smoking or atopic status. In our study, atopic status was only ascertained for a small number of subjects, and thus, in the majority of our analyses we were not able to adjust for its effects. Nonetheless, we did find, among subjects in the Screening Center cohort, that elevated levels of IgE were associated with reduced cross-sectional levels of FEV₁. We confirmed the findings of the Tucson Epidemiologic Study and found that, in smokers, this association was limited to those with symptoms of bronchitis. Interestingly, however, the association among nonsmokers was present for subjects with and without these symptoms and was only seen for males.

The discrepancy between these longitudinal and cross-sectional findings is not necessarily surprising. It is quite possible that the type of disease associated with high IgE levels (which Burrows et al have labeled chronic asthmatic bronchitis) would result in considerable variability in FEV₁ over time rather than a consistent downward trend. If this were indeed the case, then cross-sectional analyses could be expected to have greater statistical power to detect these effects than longitudinal analyses. We examined this hypothesis by comparing the variability of individual regression lines for subjects with high and low levels of IgE. We found no evidence of increased variability over time among those with high levels of IgE. Other explanations are possible, and it is also not yet clear how much concordance should be expected between longitudinal and cross-sectional analyses. Clearly, more work needs to be done to explore the nature and extent of this hypothesized association.

Interpretation of these results must be made with care for a number of reasons. Even though our analysis tacitly assumes that serum IgE level does not change over time, individual values may have varied over the course of the study. Therefore, it is uncertain how representative our values were of each subject's average IgE levels over time. Second, our cohorts have relatively few subjects with very large IgE levels. Our data may therefore not be sufficiently heterogeneous in relation to IgE to detect patterns which occur only in the extreme tails of the IgE distribution curve. Finally, neither our study nor most of the published studies of which we are aware has fully adjusted for the dependence, if any exists, of IgE on age, sex, atopy and other sociodemographic factors. Freidhoff and coworkers even suggested that the elevated IgE levels in smokers are a byproduct of the confounding effects of age and sex and that, once these factors are properly controlled for, smokers and non-smokers no longer show significant differences in IgE levels. While this conclusion seems questionable given the overwhelming evidence to the contrary, it is worth noting that the studies done to date have used very diverse population groups and that many of the differences in results may be explained by this fact. In our own cohort studies, for
example, we do not find an age-related decline in IgE among nonsmokers in the range 25 to 55 years; it is only among the older subjects that IgE shows a significant decline. This is consistent with other studies; those which include very young subjects (<25) or older subjects (>65) tend to report significant age associations,10,11,12,20 while those with a narrower age range report either weak or nonsignificant trends.9,11 Reports of elevated IgE among males are also inconsistent. While most studies show this trend, the differences are often nonsignificant, especially among healthy subjects in the age range 25 to 65 years.9,11,12,20

Again, our data reflect this pattern. In a young, healthy, working population (the Portland cohort), we did not find significant differences in IgE between males and females, but in an older, less healthy cohort (the Screening Center cohort), males did have significantly higher IgE levels than did females.

Perhaps most puzzling is the association between IgE and smoking. While most studies show smokers to have elevated IgE relative to nonsmokers, and ex-smokers to be comparable to nonsmokers, there is no clear evidence for an association between IgE and amount smoked. Although Burrows et al5 have found a positive relation between IgE and amount smoked, both the data presented here and those of Warren et al15 failed to show a positive correlation with dose or duration of smoking. Bahna and coworkers8,20 have actually found an inverse association between amount smoked and both IgE and IgD even though, overall, smokers had higher levels of both immunoglobulins than did nonsmokers.

From the discussion above, it is clear that our understanding of the relationship of IgE to respiratory disease and the factors influencing IgE levels is far from complete. If IgE is to be meaningfully related to symptomatic lung disease, we need first to understand more completely the underlying biologic relationship between IgE and factors such as age, sex, and smoking status. This will facilitate the development of a meaningful index which may then be used to standardize IgE levels so that “relatively” high values may be distinguished from “absolutely” high values. This concept has long been understood in the study of spirometric data, where the use of “percent predicted” and “Z-scores” are now standard practice for describing the influence of risk factors such as smoking on variables such as FEV1.

On the basis of existing knowledge, we conclude that elevated levels of serum IgE are probably associated with functional impairment. The nature of this association is not yet fully understood, however, and seems to be limited to cross-sectional data. Among smokers, this association also appears limited to those with symptoms of chronic bronchitis.

ACKNOWLEDGMENTS: We wish to thank Dr. Ben Burrows for his careful review of the manuscript and Linda Antolie and Kathy Turner for their help in its preparation. We also wish to thank Douglas Van Fleet, Diane Killian and Gary Schultz for their help in data collection and Anita Dunn, who carried out the IgE determinations.

REFERENCES


5. Gerrard JW. The biological importance of IgE. Immunol Allergy Practice 1984; 25:381-84


17. Recommended Standardized Procedures for NHLI Lung Program Epidemiology Studies. Bethesda: National Heart and Lung Institute, Division of Lung Diseases, 1971


21. Vollmer WM, Johnson LR, Buist AS. Relationship of response to a bronchodilator and decline in forced expiratory volume in one

Serum IgE, Cross-sectional and Longitudinal FEV1, Relationship (Vollmer et al)