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The Interpretation of Spirometric Measurements in Epidemiologic Surveys

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Spirometry is a fundamental tool in pulmonary epidemiology. Published standards provide specific information on instrumentation, techniques of testing, calculation of results, and physiologic mechanisms. They do not provide guidelines on how to interpret the test results once obtained, e.g., on such questions as which predicted values to use, what value is abnormal, how many people in the general population are likely to be abnormal? It is with these questions that this paper is concerned. Standard normal values in wide use are not ideal but should be utilized for all subgroups of the population investigated, as well as for the comparison population. Conventional definitions of abnormality lack statistical rationale and result in many false-positive and some false-negative results. This is especially true for fixed ratios such as forced expiratory volume (−1 sec)/forced vital capacity <0.70. A statistical definition of abnormality would place 95% of the normal population above the lower limit (lower 95% confidence limit). Such a definition may be more applicable to overt than to early disease. The spirometric values of well-defined diseased groups must be characterized before it is possible to state that *abnormality* (a value below the lower limit of normal) means *disease*. The distribution of values (including the mean and standard deviation) should be used to assess epidemiologic risk factors. Prevalence rates separate abnormal from normal subjects. Such data may be used to identify those requiring preventive intervention, medical care, or compensation. Pathogenic mechanisms can be more easily isolated when abnormal subjects are separated from the majority of normal. Frequencies of spirometric abnormality in standard or normal populations serve as a reference to compare rates of similar abnormality in a population under investigation.

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Several excellent guides to the use of spirometry have been published in the last 5 years. These include: (i) "The Assessment of Ventilatory Capacity," a Statement of the Committees on Environmental Health and Respiratory Physiology of the American College of Chest Physicians (1) in 1975; (ii) "Clinical Pulmonary

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Function Testing: A Manual of Uniform Laboratory Procedures," edited by R. E. Konner and A. H. Morris (2) and published by the Intermountain Thoracic Society Standardization Task Force in 1975; (iii) "Chronic Obstructive Pulmonary Disease," a handbook of the American Lung Association (3) in 1977; (iv) an American Thoracic Society Statement based on the Snowbird Workshop on Standardization of Spirometry (4) held in 1977; and (v) a definitive supplement to the *American Review of Respiratory Disease*, the Epidemiology Standardization Project (5) published in December 1978, for which Benjamin G. Ferris served as principal investigator. These are excellent references for definitions and physiologic rationale of the various tests, standards for calculation and reproducibility of results, calibration of equipment, instrument response, and other engineering details. These matters might be called the "hardware" of spirometry. Another aspect of spirometry needs fuller discussion for the benefit of many who use it as an epidemiologic (and clinical) tool. This might be called the "software": What do the results mean? Are they "normal" or "abnormal" and what do these terms mean? It is with this aspect of spirometry that this paper will be concerned.

I. RECORDING AND MEASURING

A. Performance Artifacts: The Need for Recording Flow-Volume or Spirometric Curves

Curves should be recorded whenever spirometry is performed. Erroneous results brought about by improper or incomplete performance are often detectable only from the curve. This is especially true of early termination of expiration (Figs. 1 and 2), since this can occur when most of the forced vital capacity (FVC) has already been expired and its value may be read as "normal." Early termination increases mean and instantaneous flow rates at middle and low lung volumes derived from the maximum expiratory flow-volume (MEFV) curve, as well as the ratio of the forced expiratory volume −1 sec (FEV_1) to FVC.

Many investigators believe that subject effort is best monitored by the MEFV

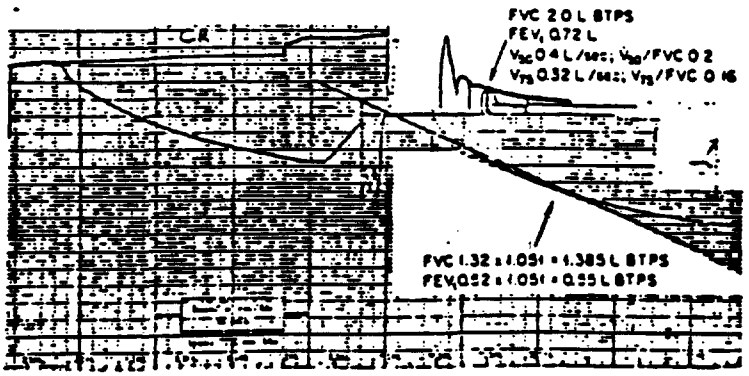

FIG. 1. The last two of many spirograms (water spirometer) compared with the MEFV curve (inset) obtained at the same session, showing significantly greater FVC and FEV_1 when effort was monitored with the MEFV curve. (Displays are ATPS for spirographic and BTPS for MEFV curves.)

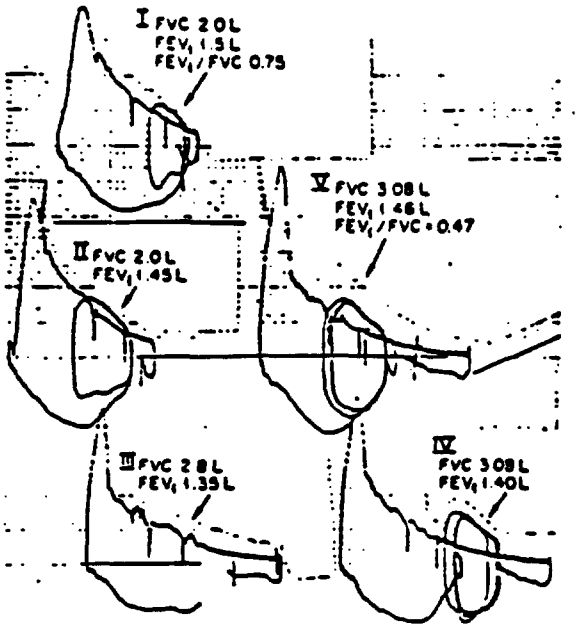

FIG. 2. Multiple MEFV curves made during one session. The FVC and FEV_1 in efforts I and II are virtually identical but were not accepted because of evidence of early cessation of expiration on the MEFV curve, as confirmed by the next three curves. Efforts IV and V again show virtually identical values for FVC, which are 54% greater than those initially obtained. No attempt was made to record full inspiratory loops.

curve (6–8). Figure 1 shows the last two of many spirograms performed by a patient with airway obstruction in 1971; they were reproducible and believed to represent maximum effort. The inset is the MEFV curve performed during the same session (one of the first such curves recorded in our clinical laboratory). Note the significantly greater FVC and FEV_1. We have reviewed spirographic tracings obtained in our laboratory before 1970, when MEFV curves were introduced, and found many which reveal early termination. In subjects with normal values, the flow rates and flow-volume ratios calculated from these tracings were somewhat high. In some patients with clinical airflow obstruction, the values were those of restrictive rather than obstructive impairment, while in others, the degree of obstruction was consistently underestimated.

Because of performance artifacts and the wide range of "normal" values, apparently normal results do not mean optimum, reproducible values. Should less than maximal values be used, the calculated regression equations—which may then be used as controls, as baselines for longitudinal studies, or to assess risk factors for various groups—will be in error.

The errors introduced by an incomplete or poorly performed effort point out the importance of the technician (or physician) performing the test. His instructions, encouragement to maximal effort, and eye for detecting departures from accept-

able procedure are paramount. No computer-programmed monitoring system can easily replace these qualities. His experience will cause him to obtain additional efforts when existing ones seem to be reproducible and maximal (Fig. 2), and allow him to avoid wasting time and energy in getting repeated inadequate curves from the subject who simply cannot perform.

B. "Best Effort"

There is agreement that for FVC and FEV_1 the largest values be used, even if these do not come from the same effort. For calculation of forced expiratory flow $(FEF)_{25-75}$, FEF_{75-85}, and instantaneous flow rates, a "best effort" or "best curve" must be selected. This has been simply and workably defined (4) as the curve with the largest sum of FVC and FEV_1. In our experience with many thousands of subjects on epidemiologic surveys, the "best curve" as defined above usually contains the largest individual values (≈3%) for FVC and FEV_1. Successive MEFV curves are overlain at high gain and are virtually identical for most subjects (Fig. 3).

II. NORMAL VALUES

A. What Is a Normal Population?

With Hutchinson's publication "On Capacity of the Lungs and on Respiratory Function with a View of Establishing a Precise and Easy Method of Detecting Disease by Spirometer" in 1846, it was recognized that spirometric measurements can be interpreted only be comparing them to values derived from a "normal" population. A *normal* population is one from which abnormal subjects are excluded. This must be distinguished from a *general* population, which should reflect the distribution of impairment, symptoms, specific disease states, smoking habits, and occupational or environmental exposures in a community.

The normal values for North Americans in wide use until recently (9, 10) were derived from a narrow range of subjects, generally hospital personnel or patients with nonpulmonary illness. In the last decade, a broader range of subjects has been studied (11–19), and individuals have been excluded because of:

(1) an objectively obtained history of respiratory (sometimes including cardiac) disease and symptoms (11, 13–15, 17–19);
(2) abnormal physical findings (13, 18);
(3) an abnormal chest roentgenogram (13, 18);
(4) a history of smoking (13, 15, 17, 18);
(5) likely exposure to pulmonary hazards (11, 15).

It may be seen that most series lack physical or roentgenographic examination. Many series have relied on volunteers; the proportion of those asked who actually participated has generally not been stated. The ethnic composition may not be specified, or may be limited to a specific group (11, 13). Several recent series have included smokers (13, 19) "because they are found in an average population" (13), thus confusing a normal with a general population. Even the definition of "smoker" has varied. One investigator (18) excluded smokers but defined a subject as a smoker only if he had smoked more than a pack of cigarettes a day for 5 years.

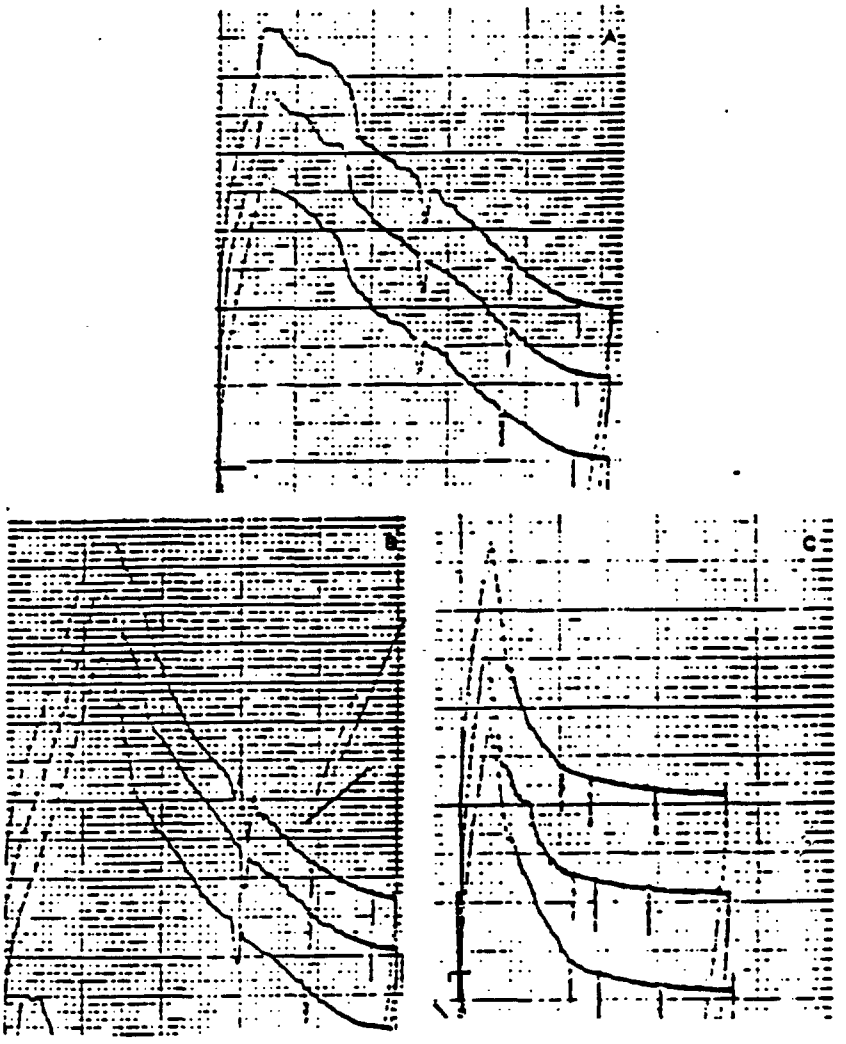

FIG. 3 (A–C). MEFV curves performed in triplicate by three consecutive subjects in a field survey, showing the consistency in configuration and results routinely obtained with motivated, well-coached persons. *All* efforts were recorded. The deflections of the pen are at 0.5, 1.0, and 3.0 sec.

What comprises a positive history has varied. It is often defined only as chronic bronchitis. At the other viewpoint, an editorial (20) advocated that a history or electrocardiographic evidence of coronary artery disease should exclude subjects from a normal population, since the FVC and FEV_1 are lower (21). This approach was followed in a survey of 2684 Israeli men aged 45 years and older (22).

Results reported for FVC and FEV_1 have either been the largest of three satis-

factory efforts or the mean best three of five. The Snowbird Workshop (4) concluded that "there is no need to obtain more than three acceptable tests." Both approaches involve at least three efforts, yet in a frequently cited series (11), spirometry was performed "at least twice" on each subject.

The results of spirometry have been used to define normal subjects for spirometric prediction equations. Normal values for the MEFV curve (including VC) were reported for subjects whose spirometry was *normal by "existing" standards* (18). In another study, persons with disease were excluded from the community sample from which the FVC and FEV_1 were derived (14). "Disease" consisted of symptoms and/or a spirometric abnormality, $FEV_1/FVC < 0.6$.

B. Which Normal Values to Use?

For most users of spirometry the question really is: *Which published normal values to use?* The references cited in the beginning of this paper (1, 2, 4, 5) make no recommendation on this important matter. Morris' data (11) are probably the most widely used: they have been cited in the American Lung Association handbook (3) and programmed by many manufacturers for their automated spirometers. Subjects, who came from a nonsmoking population living in an unpolluted rural valley, did not have histories or symptoms of respiratory disease. Problems with these data include:

(1) *Epidemiologic*

Applicability to urban populations.

(2) *Methodologic*

(a) Physical and roentgenographic examinations were not made; heart disease was not on the questionnaire.

(b) No more than two efforts were obtained from an unknown number of subjects.

(c) The Kory method was used for calculation of FEV_1. This results in a value which may be up to 179 cc smaller (23) than that obtained by the currently recommended method, extrapolation. The resulting difference in $FEV_1/FVC \times 100$ may be 4.5 for an FVC of 4 liters. The Kory method was used in several other series of predicted values (10, 12, 13).

Surveys of several large representative populations have provided regression equations for spirometric measurements. In the Tecumseh, Michigan, survey, 6365 subjects ≥10 years of age (5101 of whom were ≥16 years of age) were tested (24). Separate regressions were developed for FVC, FEV_1, FEV_1/FVC, $\dot{V}_{max_{50}}$, FEF_{25-75}, $FEF_{0.2-1.2}$, and peak flow (PF) for male and female subjects without cough, phlegm, or dyspnea in the age groups 10–15, 16–19, and 20–74 years. A wedge spirometer was used. Only two tracings were obtained and the best effort was defined as the one with the larger FVC. Schoenberg *et al.* (25) recorded MEFV curves in 3046 asymptomatic individuals, all of whom were nonsmokers except for some black males. A computerized pneumotachygraph was used. The two studies (out of five) with the largest FEV_1 were averaged, provided values agreed within 10%. Subjects resided in rural Lebanon, Connecticut, urban Ansonia, Connecticut, and semirural Winnsboro, South Carolina. Between 54 and

75% of all residents ≥7 years of age were tested. Of the total, there were 455 white and 114 black females ≥20 years of age and 194 white and 120 black males ≥18 years of age. Since simple linear regressions overpredicted at each end of the age range and underpredicted in the middle range, more complex models (utilizing weight as a variable as well) were developed. The lower 95% confidence limits thus obtained were closer to predicted values.

C. *The Influence of Race*

It is now well accepted that blacks residing both in Africa and in the New World (26–30), East Indians (31, 32), yellow-skinned peoples (28, 33, 34), and Pacific Islanders (35, 36) have smaller regressions for lung volumes against height than whites. This knowledge has not consistently been applied in the clinical interpretation of pulmonary function tests or in the epidemiologic screening of populations. For blacks, most studies have shown the difference to be in the range of 10–15% and a 13% scaling factor has been proposed to adjust values measured in blacks to those predicted for whites (37). A similar factor (12.5%) "converted" the FEV_1 of East Indians (31).

D. *The Influence of Age*

It is well known that FVC, FEV_1, and flow rates in adults decline with age. The FVC increases up to age 24 and then remains stable to age 35 (25). Simple linear regressions against age, by using a single negative term for age over the range 20–70 years, overpredict values in young adults. The difference is not large in absolute terms (100–200 cc for FVC in white males, height 175 cm, age 20). Nevertheless, Schoenberg (25) suggests that there might be important consequences in determining occupational risk. When 18- to 20-year-old workers start jobs, preemployment tests may be considered below normal. If the worker is not refused employment, significant function loss shown on subsequent tests may be overlooked because the rate of decline appears no greater than expected for all adults.

It is less well recognized that FEV_1/FVC varies with age. Most cross-sectional surveys have shown a decline with age and then a slight increase in the elderly (11, 13, 24, 38). Schoenberg (25) demonstrated this increase at age 55 in both sexes. A recent longitudinal study of 259 elderly subjects conducted over a 5-year span (39) disclosed a greater absolute and relative decline in FVC than in FEV_1 with a consequent increase in FEV_1/FVC. These changes were greater in men than women, and in those 70–90 years of age than in those 62–69. The 42 men ≥70 years of age lost a yearly average of 125 cc FVC (4% of baseline) and 70 cc FEV_1 (3.1% of baseline). Since reduction in FEV_1/FVC is considered by many authors as a basic impairment which reflects symptomatic status, interpreters of spirometry must recognize that a single value for this ratio cannot be used as the lower limit of normal for all age groups. However, review of the literature shows that this practice continues.

Recently, mean transit time (or effective time) of forced expiration has been proposed as the single most sensitive test for obstruction, in both central and peripheral airways (40–43). This measurement can be applied over the full range

of growth and shows no difference between the sexes (41). However, age remains an important factor; mean transit time increases linearly with age (41, 43).

E. Other Factors Influencing Spirometric Results

VC, PFR, FEV_1, and airway conductance display circadian rhythm (44–46). Variations are small and probably negligible in interpreting individual values but introduce a small systematic error in comparing mean values of different groups or of the same group at various intervals.

The time of year may influence spirometric results, perhaps through differences in levels of pollutants or incidence of respiratory infections. In addition, FEV (47) and airway resistance (48) vary with the hours of daylight, the former with an amplitude of 100 cc.

Altitude may affect spirometric results. Schoenberg *et al.* (25) in reviewing their own and other workers' findings, concluded that FVC in young adults increases ca. 100 cc for every 300 m above sea level, up to an altitude of 4000 m.

Smoking immediately preceding spirometric testing is another variable which should be controlled. The acute effects of smoking even one cigarette include decreased flow rates (49).

The variability of spirometric results is greater when they are abnormal. When measurements were made at two and three weekly intervals in patients with stable irreversible chronic obstructive airway disease, the coefficients of variation were large (±11.1% for FVC and ±14.8% for FEV_1) (50). In the opinion of the investigators, this variation must be considered when assessing the effects of treatment. In an earlier study, Fletcher (51) found that 5% of apparently "normal" men showed a difference in FEV_1 ≥400 cc between two determinations at a 10- to 12-day interval. Variation was greater when values were abnormal.

Acute, self-limited, noninfluenzal viral upper respiratory infection (simple URI) has not generally been found to decrease spirometric measurements in adults (52, 53). However, obstruction in the small airways has been demonstrated in spontaneous and induced URI by the following techniques: frequency dependence of compliance (53, 54), increased closing volume in smokers (55), decreased flows at low lung volumes on breathing helium–oxygen (55), increased total respiratory resistance by forced oscillometry (56), and greater sensitivity to parasympathomimetic challenge (56). Changes persist up to 8 weeks (53, 56). Therefore, the decrease in flows at low lung volumes (FEF_{25-75}, FEF_{75-85}, FEF_{75}, etc.) described in small airway obstruction would not be unexpected during an URI. In longitudinal studies on children under 7 years of age (57), FVC, FEV_1, and PFR as well as FEF_{25-75} and FEF_{50} were noted to decrease during coincidental URIs. Effects may be greater in young children because small airway conductance is lower in early childhood than in later years (58).

F. Normal Values for Instantaneous Maximum Flow Rates ($\dot{V}_{max}$)

Like FEF_{25-75} and FEF_{75-85}, these flows are inherently more variable than FVC and FEV_1. A pneumotachygraph or low-resistance spirometer, with expired volume measured at the mouth, is generally used in the field to obtain these flows and generate MEFV curves. Values for instantaneous flow rates using expired volume have been published by Cherniack and Raber based on 899 subjects (15) and Bass

based on 247 (18). In the latter paper, normal was partly defined by spirometric results, criteria for which were not indicated.

In two other investigations, volume was measured in the body plethysmograph. Black *et al.* used a composite of two curves showing the higher flow (19) and more recently, Knudson *et al.* (17) reported flows from a composite MEFV curve representing the subject's best performance at each decile of volume. Use of such an "outer envelope" curve to derive optimal flows has been reported to reduce variability (59). Values may differ from those derived from a single "best curve." Whether for this reason or for reasons relating to selection of subjects, the flows in Knudson's series are higher than those in others. Although the body plethysmograph and composite curves were used by these investigators in the field, this approach is less applicable to surveys in which the time available for testing a large number of subjects is limited. Stanescu *et al.* (60) have recently written that "concerning variability within an individual, values for $\dot{V}_{max}$ measured in relation to the expired volume are as good as (and more simple to measure than) $\dot{V}_{max}$ recorded with a body plethysmograph."

Values for $\dot{V}_{max}$ have been standardized for volume to achieve greater comparability between subjects of different size. Although TLC is preferable, it is not generally available in the field. As early as 1967, Lapp and Hyatt (61) published values for FEF_{50}/FVC and FEF_{75}/FVC; means in 34 normals were 0.98 and 0.45, respectively. We have found similar values in normal subjects (62). Knudson *et al.* (17) showed little change in the FEF_{50}/FVC and FEF_{75}/FVC with age, although Cherniack and Raber (15) found that FEF_{75} had a large negative correlation with age.

III. COMPARISON POPULATIONS

A comparison population should be equivalent to the surveyed population in all respects except exposure. Such a group is difficult to find and, if found, to motivate to undergo testing.

In the absence of a comparison population, it would seem advisable to compare the results in all subgroups of the surveyed population with the normal values in wide use in order to uncover impairment common to all in the study population. This has not always been the practice. Results for subjects in different exposure categories have been analyzed only relative to each other. Some investigators have used as a *comparison* population those in the group at risk who have had the least burden and/or duration of exposure or who are asymptomatic (63). Since values in this group are set at 100%, any impairment resulting from their level of exposure would be inapparent. Flows at different lung volumes were related to smoking and bronchitis in coal miners (64). Mean values were compared for smoking and nonsmoking, bronchitic and nonbronchitic groups matched by age and height. Compared to predicted values, the results for FEF_{75} seem low in *all* the groups, including the "comparison" set of nonsmokers without bronchitis.

IV. LOWER LIMITS OF NORMAL (lln's)

In the use of spirometry, the question "Who is abnormal?" becomes "*What value should be considered abnormal?*" Many surveys have not been concerned with this question and, therefore, cannot be used to obtain the prevalence of

spirometric impairment, even when prevalence rates of various symptoms (including "chronic bronchitis") are reported. The investigators have shown mean values and regression equations of spirometric measurements for the groups at various risk. These permit them to find statistically significant differences related to risk factors, but do not provide any information on prevalence of abnormality.

A. Percentage of Predicted

Until recently, the conventional criteria for abnormality in clinical use have been carried over to epidemiologic screening. Although less than 80% of the predicted value has generally been considered abnormal, this guideline has not been *uniformly followed*. Particular confusion centers on a value of "80% of predicted," which most laboratories interpret as "within normal limits." However, the handbook "Chronic Obstructive Pulmonary Disease" of the American Lung Association (3) shows 80% as abnormal for FVC and FEV_1 (normal is *greater than* 80%) and 75% of predicted as abnormal for FEF_{25-75} and FEF_{75-85} (after Morris (65); normal is greater than 75%). On the other hand, McFadden *et al.* (66), in assessing various tests for small airway disease, defined an abnormal FEF_{25-75} as less than 80% of predicted (80% was normal), although they used Morris' predicted values.

B. Ratios to FVC

1. FEV_1/FVC. Although 0.75 had been widely used as the lln, recent practice tends to 0.70. Since FEV_1/FVC falls with increasing age and height (13, 25, 38), use of a constant value for all subjects is invalid. Using Morris' means and standard deviations (38) and mean − 1.64 SD (see below) as the lln, the cutoff value for a man 69 in. in height ranges from 0.69 at age 20 years to 0.59 at age 60. (These values are systematically low because of the Kory method used to calculate FEV_1; see above.) The result of using a constant value for FEV_1/FVC is that prevalence of impairment appears to increase as a population ages. This may falsely be attributed to duration of occupational exposure, total burden of occupational exposure, or pack years of cigarette smoking, since all of these correlate with age.

There is evidence that certain athletes (67) and others whose work activities develop the pectoral muscles (including the accessory muscles of respiration (68, 69)) have a relatively greater than normal FVC compared to FEV_1, with a resultingly lower FEV_1/FVC. This might be true of many industrial workers.

2. FEF_{25-75}/FVC. This ratio has been used to classify patients as to restrictive or obstructive impairment (70); a lln of 0.65 has been proposed (2, 71). Since FEF_{25-75} = FVC/2 midexpiratory time (MET), the ratio to FVC = ½MET. It would be simpler to use the MET as a flow-related measurement which is independent of volume with an upper limit of normal of 0.77.

C. The 95% Confidence Lower Limit

A rational statistical basis for the conventional "80% of predicted" does not exist. For the FVC and FEV_1 of some investigators (11), 80% of predicted has a confidence approximating 95% at the mean age and height of the normal popula-

tion they measured. This is not true for different ages and heights. The matter has been lucidly discussed by Sobol (72): "Applying the 80 percent rule to those functions defined by a regression equation adds another dimension to the error . . . percent of predicted will deviate from the regression line less for small values than it will for large values. Therefore, small predicted values, such as occur in the short and aged, will result in a higher incidence of abnormal findings. The use of a fixed percentage can be more or less stringent than the statistical limits depending upon the magnitude of the variance around the regression, but it will always result in a disproportion between the number of abnormal findings among small versus large values."

Thus, use of 80% of predicted as the lln, especially for flow rates, will lead to the identification as abnormal of many subjects whose values are within 95% confidence limits, particularly when they are shorter or older. On the other hand, the values for FVC and FEV_1 of taller or younger subjects may erroneously be considered "normal" because they are ≥80% predicted when in fact they are below the 95% confidence limits. This is illustrated by Fig. 4, which shows the relationship between the regression line for predicted FVC, the line for 80% of predicted, and the line for the 95% confidence limit.

A useful approach to statistically meaningful lln's is to consider as "normal" 95% of the normal population whose measurements are above a specified value. For such a one-sided test, the lln = mean (in liter/sec, etc.) − 1.64 SEE (standard error of the estimate (72, 73)). The lln may also be expressed as a percentage of predicted, i.e.: Below what percentage predicted can we consider, with 95% confidence, a subject's value to be abnormal? As shown for FVC in Fig. 5 for a man 70 in. in height, this ranges from 81% at age 20 to 76% at age 70. We have drawn up simple tables showing the lower 95% confidence limit cutoff values based on Morris' data for percentage predicted FVC, FEV_1, and FEF_{25-75} and for FEV_1/FVC for individuals of different ages and heights (74).

Another way to express statistically valid lln's while retaining the percentage

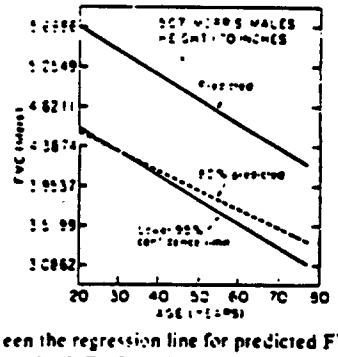

FIG. 4. The relationship between the regression line for predicted FVC at a height of 70 in. (slightly modified from Morris (111)), the line for 80% of predicted, and the line for 95% confidence. The last was so minimally curved that it is drawn as a straight line. Note that 80% of predicted is increasingly above the 95% confidence limit from age 30 on. For the decade 20–30 years of age, on the other hand (an age range of many industrial workers), the 95% confidence limit is above the line for 80% of predicted.

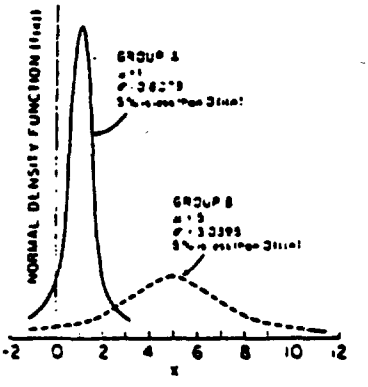

FIG. 5. The distribution of values for two groups with an identical prevalence (5%) below the lower limit of normal, yet with distributions (and means) which show important differences. Reproduced, with permission, from A. Miller, J. C. Thornton, H. Smith, Jr., and J. F. Morris (1980). *Amer. J. Ind. Med.* 1, No. 1, published by Liss, New York.

predicted and 80% rules of thumb has recently been proposed by Sobol (75). This involves "normalizing" all subjects by determining the value of the mean when mean − 2 SD (1.64 would be preferable for a one-sided distribution) represents 80% of the mean. Using this procedure, 1 SD below the mean would be 90% of predicted.

The statistical lln for flow rates such as the FEF_{25-75} may be as low as 20% of predicted in older, shorter subjects. The greater variance of such tests, however, is more or less offset by their greater decrements with disease (77). Values this low are frequently encountered in clinical practice. While use of such a lln for patients with overt disease may present no difficulty, it may be less applicable to early disease. Thus, while McFadden (66) joined Morris (76) in concluding that percentage of predicted flow rates is highly sensitive in detecting small airway obstruction, Marcq and Minette (78) using predicted −1.64 SEE found that these tests did not improve the ability of conventional indices (FEV_1 and FEV_1/FVC) to detect abnormality in smokers.

"Statistical" definitions of the lln (based on the SEE) have been inconsistent. Most investigators use 1.64 SEE below the mean; some use 2.00 SEE or 1.00 SEE and others use half the mean (79). The National Institute of Occupational Safety and Health Laboratory in Cincinnati defines "abnormal" as the value above which 99% of their normal population fall (mean −2.33 SEE) and classifies those in between the 1st and 5th percentiles as "borderline."

D. Limitations of a Lower Limit of Normal Based on a "Normal" Population: Does "Not Likely to Be Normal" Mean "Abnormal?"

The values used to define the lln were obtained from studies of normal populations. The limits were selected to provide 95% of the subjects with a classification of "normal" and 5% with a classification of "abnormal." It is important to realize that *some normal subjects will be classified as "abnormal."*

Studying large numbers of normal subjects does not define an abnormal (in the sense of *diseased*) group. It allows us to classify an individual as abnormal only in the sense of *not belonging in the normal group*. Such a classification does not state the probability that a subject is *in a diseased group* (e.g., patients with obstructive airway disease, or patients with interstitial lung disease). To do so requires defining and analyzing the distribution of values for the diseased group, and comparing it with the normal population. As an example of this approach, we applied conventional and statistical lln's to 100 randomly selected patients referred to our clinical pulmonary laboratory with the diagnosis of "COPD," "chronic bronchitis," and/or "emphysema" made by a Pulmonary Division physician. (We were aware that some patients are referred to the laboratory with a tentative clinical diagnosis which may be disproven, and that airflow obstruction need not be present in all patients with chronic bronchitis.) Using conventional criteria, we found 89% abnormal for FEV_1 percentage predicted (<80), 90% for FEV_1/FVC (<0.70) and 95% for FEF_{25-75} percentage predicted (<75). Using 1.64 SEE below the predicted mean as the lln, 85% were abnormal for FEV_1, 73% for FEV_1/FVC, and 60% for FEF_{25-75}.

This groups of patients with clinically defined disease was limited and is referred to for purposes of illustration. Tashkin *et al.* (80) defined an abnormal group to provide an estimate of test sensitivity. Two respiratory specialists made a diagnosis "based on their own professional judgment and experience, as to the presence or absence of chronic obstructive respiratory disease, taking into consideration the results of all the lung function tests, responses to the respiratory questionnaire and reported findings on physical examination." This "clinical" definition is based to an unknown extent on the results of the tests under consideration.

V. HOW TO COMPARE GROUPS: THE DISTRIBUTION OF OBSERVED VALUES

The distribution function of a random variable describes the probability that the random variable assumes a value in any given interval. Therefore, the probability that a random variable satisfies any specified condition can be calculated from a knowledge of the distribution function. An estimate of the distribution function can be obtained from the collection of individual observations which result from a random sampling of the population. For a Gaussian distribution, knowledge of the mean and variance (standard deviation) allows calculation of probabilities.

If two or more groups are to be tested for differences in their pulmonary function related to an environmental exposure, the comparison should be based on their distribution of observed values, not their prevalence of abnormality. Information is lost when each subject's response is replaced by a classification of normal or abnormal. For example, the percentage of individuals in each of two groups with values below the lln may be identical, yet the two groups are truly different. This is seen in Fig. 5. In group A, the majority of observations are only slightly above the lln while in group B, the majority of observations are far above the lln. Although the prevalence of abnormality is identical, the two groups have very different distributions. On the other hand, there may be a considerable dif-

ference in prevalence (of 25%, as shown in Fig. 6) with no meaningful difference in distributions. The latter situation is often seen in epidemiologic studies. Two groups (Group A thought to be at risk because of its exposure to a toxic agent and Group B, similar in other respects but lacking this exposure) are compared to a third group (C), a standard population. Both test groups (A and B) have meaningfully different distributions from the standard group (C) even though differences between A and B are minimal.

In both situations illustrated above, looking only at prevalence rates can be misleading. Therefore, to establish that a certain group is different (in this discussion, different in its spirometric measurements) and that this difference is related to a quantifiable variable (e.g., environmental exposure), one should analyze the distribution of observations. Small differences in the distributions can point to a significant effect of the exposure. When the distributions of large groups are compared, even tests with greater inherent variability whose clinical interpretation remains unclear (such as $\dot{V}_{max}$) may provide useful information. That differences are "statistically significant" does not mean that they are "clinically important."

VI. PREVALENCE RATES FOR SPIROMETRIC ABNORMALITY

A. Why Look at Prevalence Rates?

1. Prevalence rates are based on the identification of "abnormal" individuals. Identifying who is abnormal individualizes the problem on the one hand and demonstrates its social impact on the other. The uses of prevalence data depend on the definition of abnormality. Identifying early lung disease allows intervention at a more remediable stage, either by the individual to stop smoking or by society to ameliorate occupational exposure. It is generally based on tests which show greater variation in normal individuals. Overt disease is generally manifest by symptoms and other clinical findings. However, dyspnea is a very subjective complaint and airway obstruction does not correlate well with the symptoms of cough or expectoration (81, 82), or with radiographic changes. Demonstrating (and

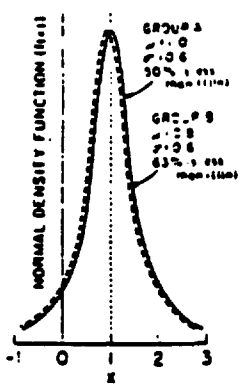

FIG. 6. The distribution of values for two groups with a 25% difference in prevalence, yet with no practical difference in distribution of values (or means).

quantitating) disease identifies subjects who may require clinical care or disability compensation, and allows society to allocate medical or financial resources.

2. Once abnormality is identified and quantitated, trends can be followed, and correlations made to changes in work practices, atmospheric pollution, smoking habit, etc.

3. Several large, carefully done studies have demonstrated the prognostic value of abnormal spirometric findings. Those at greater risk of progressive disease and death can be identified. Petty *et al.* (83) studied residents of a small Colorado city 7 years after an initial survey, and found that those who had had an $FEV_1/FVC \leq 0.59$ had a greater decline in FVC and FEV_1 and a threefold greater mortality. Those with a normal FEV_1 initially remained normal. Bates (84) followed 216 men with chronic bronchitis over a 10-year interval, and noted a significant decline in FEV_1 and FEF_{25-75} in 10% (whom he termed as having "malignant bronchitis"). He suggested a fall in $FEF_{25-75} \geq 0.6$ liters/sec in 1 year with no improvement the following year as an indicator of progressive disease. Fletcher's monumental studies of patients with chronic bronchitis (81, 82) have demonstrated that cough and sputum production do not point to a poor prognosis, which is indicated by a greater decline in FEV_1 with age. Cessation of smoking not only decreases mucus hypersecretion but returns the slope of decline in FEV_1 to normal.

(iv) Most diseases, especially those of environmental origin, are multifactorial. Reporting findings as prevalence, by identifying the affected individuals, may uncover other casual mechanisms, e.g., smoking, other exposures, ethnicity, genetic influences, etc. (See Fletcher on this matter, below.)

B. Use of Multiple Measurements to Define Abnormality

Since no test will detect 100% of abnormals, and we are often interested in finding early disease, for which no single simple measurement is available, many authors have used multiple tests to define abnormality. When this approach is used, the results are very different when a subject is classified as abnormal because *any one* test is abnormal or because *more than one* test is abnormal. This is illustrated in Table 1. Each of three tests classifies a normal individual as "abnormal" with a probability of 0.05. If an individual is to be considered abnormal when *one or more* of the three tests are positive (i.e., one, two, or three tests are positive), the probability of classifying a normal subject as abnormal rises to 0.1426 (if the tests are independent; somewhat less if they are not). An investigator who wishes to define abnormality with 95% confidence by using any one of three tests may do so by setting each test at the 0.017 rather than 0.05 level.

TABLE 1
PROBABILITY OF A FALSE POSITIVE USING THREE INDEPENDENT TESTS TO DETECT ABNORMALITY

Number of positive tests	Probability
1 (of 3)	0.1354
2 (of 3)	0.0071
(All) 3	0.0001

On the other hand, if *two or more positive results* are required to classify a subject as abnormal, the corresponding probability is 0.0072, i.e., the probability of a false positive is much less than when one test is used. Requiring all three to be positive reduces the probability to 0.0001.

Many authors have defined their abnormal group by abnormality of one or more of a large number of tests, e.g., FEV_1/FVC, $\dot{V}_{max_{50}}$, $\dot{V}_{max_{75}}$, FEF_{25-75}, and closing volume (85). In the past we defined air flow obstruction as a decrease in any one of these three tests, FEF_{25-75}, $\dot{V}_{max_{75}}/FVC$, or FEV_1/FVC (86). Whatever limits of normal are used for the individual tests, such a definition will increase the prevalence of impairment, perhaps obscuring differences between groups.

The artifact introduced by defining abnormality on the basis of one or more abnormal tests has been discussed. Sobol (72) concluded that: "One final source of trouble caused by multiple tests is that the likelihood that one of them will be abnormal in a group of normal subjects increases as the number of tests used increases." Knudson *et al.* (87) examined this problem, using mean − 1.64 SEE as their definition of abnormality. When impairment was defined as abnormality of any one of three tests (FEV_1, FEV_1/FVC, and FEF_{25-75}), 10.8% of the normal subjects, from whose values "normal" was defined, were now abnormal. This is not far from the 14.3% expected from Table 1, especially when one considers that the three measurements are not independent.

C. *Prevalence Rates in General Populations*

Prevalence rates of impaired spirometry in the general population are not readily available. Investigations have been characterized by inconsistencies in test procedures, source of predicted values, and definitions of abnormality. In addition, many investigators have presented mean values without indicating what percentage of the population was abnormal. As Fletcher has pointed out (88), "Most epidemiologists have avoided this problem (where . . . the lower limits of normal are to be set) by simply recording differences in mean test values between groups of subjects. One objection to this custom, in relation to causative factors such as smoking, is that only a minority of smokers appear to be sufficiently susceptible to smoking to develop significant airflow obstruction. Thus, with aging, the distribution of FEV levels or of severity of emphysema at autopsy becomes skewed as a majority of subjects remain normal, but there develops a "tail" of clinically significant abnormalities. The mean value of a group or population with such a distribution is not the best index for comparing the effects of smoking or any other agent; for the effect on the susceptible minority tends to be overwhelmed by the unaffected majority."

Even though many papers present prevalence of respiratory symptoms or of chronic bronchitis in various populations, few have reported prevalence of spirometric impairment. Bouhuys (89) compared Spanish hemp workers with a control population of farm and marble workers for whom he found FEV_1 values <80% of predicted in 12% of those 20–69 years of age, 15.6% of those 40–69 years of age, and 31% of those 50–69 years of age. The survey of Chilliwack (90), an unpolluted town in Canada, found 12.6% of men to have severe obstructive lung disease; about 70% of these had an $FEV_1/FVC \leq 0.60$. The FEV_1/FVC was be-

low 0.75 in 26.4% of 18,403 British male civil servants 40–64 years of age (91). The prevalence of this "abnormality" increased from 19.5% in the age group 40–49 years to 28.8% at ages 50–59, and 40.8% at ages 60–64. Kuperman and Riker (71) noted that 21 of 119 subjects (18%) in a community survey who were "normal by clinical criteria" had FEV_1/FVC values below 0.75. Bower (79) reported that FEF_{25-75} was "less than half" the predicted value in 19% of U.S. male bank employees ≥40 years of age.

Spirometry was performed on a representative sample comprising one-fifth of the adult population of a small Colorado city (92). Of the 281 men tested in the age range 20–69, 37 (13%) had an $FEV_1/FVC \leq 0.59$. Of those 49–69 years of age, the prevalence of this impairment was 17% and of those 60–69, 32%. Only 2% of the 328 women aged 20–69 had this abnormality.

In Tucson, Knudson and associates (87) found that 24.4% of asyptomatic male smokers and 35.3% of symptomatic males had an abnormal FEF_{25}. Corresponding rates of abnormality for the entire survey population can be estimated, since the authors' criteria for abnormal were the fifth percentile values for nonsmoking asymptomatic subjects, who comprised ca. 25% of the total. In a stratified sample of 206 residents of unpolluted Manitoba, Nelson and Cherniack (93) defined abnormality in a similar way: more than 2 SD beyond the mean value for the asymptomatic nonsmokers. As in Knudson's investigation, 13–18% of male smokers had an abnormal FEV_1/FVC.

If one is interested in prevalence of spirometric impairment as it is conventionally defined in a "normal" population, the population from which the normal values in general use are derived (11) is an obvious group to analyze. As seen in Table 2, when conventional lln's are applied to the values for FVC and FEV_1, 5.5 and 5.9%, respectively, of all men have abnormal values (74). These frequencies are in agreement with a statistical definition of abnormality at the 0.05 level. However, 10.2% of subjects ≥50 years of age have a decreased FEV_1. Indeed, a decreased FEV_1 (or FVC) is here defined as ≤79% of predicted,[1] as is the common practice. If the American Lung Association (3) criteria (≤80% of predicted) are used, the prevalence of abnormality would be greater.

Prevalence rates for airflow obstruction are much higher. Using FEV_1/FVC as the test and 0.70 as the lln, 18.1% of all the subjects are abnormal. At age 50 and above, 37% are abnormal. Using FEF_{25-75} as the test and 75% of predicted as the lln, 17.8% of all subjects are "abnormal": for those ≥40 years of age, 20.6% are abnormal. Again, use of the lln recommended by the American Lung Association (76% of predicted) would result in a slightly higher prevalence of abnormality, as shown in Table 2.

The prevalence of airflow "abnormality" in this selected nonsmoking, healthy population is compared in Table 3 with rates reported in populations which included smokers and those with symptoms and overt disease. The prevalence in the "normal" population is less than in most but not all of the comparison populations.

[1] Normal was defined as any value which would round off at the fourth decimal to 80% of predicted or greater, i.e., 79.5000 was normal, 79.4999 was decreased.

TABLE 2
PREVALENCE OF ABNORMAL[a] SPIROMETRY IN MORRIS' NONSMOKING MEN (74)

Age group (years)	Number	FVC ≤79% predicted	FEV_1 ≤79% predicted	FEV_1/FVC ≤0.74	FEV_1/FVC ≤0.69	FEF_{25-75} ≤74% predicted	FEF_{25-75} ≤75% predicted
≤39	308	17 (5.5%)	13 (4.2%)	88 (28.6%)	38 (12.3%)	49 (15.9%)	53 (17.2%)
40–49	91	3 (3.3%)	6 (6.6%)	37 (40.7%)	13 (14.3%)	16 (17.6%)	16 (17.6%)
50–59	66	5 (7.8%)	6 (9.1%)	41 (62.1%)	23 (34.8%)	13 (19.7%)	13 (19.7%)
≥40	199	11 (5.5%)	17 (8.5%)	107 (53.8%)	54 (27.2%)	41 (20.6%)	41 (20.6%)
≥50	108	8 (7.4%)	11 (10.2%)	70 (64.8%)	41 (37.0%)	25 (23.2%)	25 (23.2%)
≥60	42	3 (7.1%)	5 (11.9%)	29 (69.0%)	18 (42.9%)	12 (28.6%)	12 (28.6%)
All ages	507[b]	28 (5.5%)	30 (5.9%)	195 (38.5%)	92 (18.1%)	90 (17.8%)	94 (18.5%)

[a] Conventional criteria; see text.
[b] 10 subjects deleted because of inconsistent data or transcriptional errors.

TABLE 3
PREVALENCE OF SPIROMETRIC ABNORMALITY IN VARIOUS COMPARISON POPULATIONS

Test	Definition of abnormality	Morris' normal population (11)		Comparison population		
		Age group (years)	Prevalence (percentage)	Age group (years)	Prevalence (percentage)	Composition
FEV_1	≤79% predicted*	All	5.9	20–69	12	Spanish male farm and marble workers (89)
		≥40	8.5	40–69	15.6	
		≥50	10.2	50–59	31	
FEV/FVC	≤0.74	>40	51.8	40–65	26.4	British male civil servants (91)
		40–49	40.7	40–49	19.5	
		50–59	62.1	50–59	28.8	
		>60	69.0	60–65	40.8	
FEF_{25-75}	≤49% predicted*	>40	5.6		19	U.S. male White collar workers (79)
FEV/FVC	≤0.59	all	2.8	all	13	Colorado males (92)
		>40	5.6	>40	17	
		≥60	11.9	>60	32	

* The predicted values used in the comparison and normal populations were not the same.

TABLE 4
MEAN VALUES OF SPIROMETRIC TESTS IN THE WHITE MALE POPULATION OF MICHIGAN, 1978 (BY SMOKING HISTORY)

	Nonsmokers (n = 154)	Ex-smokers (n = 157)	Current smokers (n = 186)
FVC percentage predicted (11)	99.22	97.32	94.74
FEV_1 percentage predicted	105.78	101.64	96.13
FEV_1/FVC	0.802 (0.756)*	0.770	0.773
FEF_{25-75} percentage predicted	97.58	88.16	80.48
Age (years)	42.08	48.80	38.47
Height (in.)	69.18	68.83	69.26

* Value of FEV_1/FVC in the Morris series (11) at the mean age and height of the nonsmokers in Michigan.

Additional data on the prevalence of abnormal spirometry (as conventionally defined) in the general population would be useful. Together with Dr. Irving J. Selikoff and his group at the Mount Sinai School of Medicine Environmental Sciences Laboratory, we have recently completed a clinical, radiographic and spirometric survey of a cross-sectional population of a large industrial state (Michigan) (94). Subjects were representative of the general population of the state for residence (urban versus rural), occupation and age. Spirometric data were obtained on 983 white adults (497 men) with known smoking histories.

Table 4 shows the distribution of spirometric values. Values for the 154 male nonsmokers were similar to those of Morris. Expressed as percentage of Morris' predicted values, the range was from 97.58% (for FEF_{25-75}) to 105.78% (for FEV_1). Values for FVC agreed most closely with Morris' values. The higher values for FEV_1 were expected since results were obtained by extrapolation whereas Morris used the Kory method which leads to lower values. The slightly lower values for FEF_{25-75} may relate to more complete expirations achieved when effort was monitored with the MEFV curve.

Frequencies of abnormal spirometric tests using conventional criteria (Table 5) were similar to those in Morris' population. (The considerations for FEV_1 and FEF_{25-75} in the preceding paragraph apply to the prevalence rates as well.) A recent study of Vermont male dairy farmers and nonmineral industrial workers

TABLE 5
PREVALENCE OF SPIROMETRIC ABNORMALITIES* IN THE WHITE MALE POPULATION OF MICHIGAN, 1978 (BY SMOKING HISTORY)

Cigarette smoking status	Number examined	Abnormal FVC	Abnormal FEV_1	Abnormal FEF_{25-75}
Never	154	9 (6%) [6%]†	2 (1%) [6%]†	24 (16%) [18%]†
Former	157	15 (10%)	17 (11%)	60 (38%)
Current	186	28 (15%)	24 (13%)	80 (43%)

* Conventional criteria: see text.
† Prevalence of "abnormality" using similar criteria in the Oregon Respiratory Association Survey (11).

(95) showed prevalence rates of abnormal FVC (also defined as <80% of Morris' predicted) remarkably similar to those in Table 5. Among nonsmokers, 6% (farmers) and 7% (industrial workers) were abnormal; among former smokers, 14 and 12%, and among current smokers, 13 and 10%, respectively. These studies give support to regarding the frequencies of spirometric abnormality shown in Table 5 as reference rates for a white population in the United States. When abnormality is conventionally defined, rates should exceed these before a group is thought to have an increased prevalence of spirometric impairment.

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