Subclinical Effects of Smoking*
Physiologic Comparison of Healthy Middle-aged Smokers and Nonsmokers and Interrelationships of Lung Function Measurements

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Measurements of ventilatory function, distribution of ventilation, diffusing capacity, and lung mechanics were made on healthy middle-aged smokers and nonsmokers drawn from a randomly selected population in order to assess the effects of cigarette smoking and the interrelationships of the several indices of lung function. Although very few subjects had abnormal function, there were significant differences in most indices of function between smokers and nonsmokers. For the total group studied, there were significant correlations between various indices of function. A significant proportion of the variance in diffusing capacity and in diffusing capacity per liter of lung volume can be accounted for by an index of lung recoil which may, in turn, be related to size of terminal air spaces.

It is generally acknowledged that cigarette smoking is the leading cause of chronic airflow obstruction. Nevertheless, only a minority of smokers develop clinically significant obstructive disease, and fewer still develop severe functional impairment. It has been suggested that a small number of smokers have "some special susceptibility to the effects of tobacco smoke on the lungs."

It does not necessarily follow, however, that the remainder of smokers are totally immune to the effects of smoking. Many studies have shown that smokers have altered lung function which may not reach clinical significance. Studies of patients with diagnosed diseases have characterized the abnormalities which describe the later stages of disease. Many of the studies which attempt to identify early stages of disease have involved subjects drawn from smoking cessation programs or emphysema screening centers, which may attract people who suspect they already have a respiratory problem and may have or be on the verge of developing clinical disease. Studies which have correlated lung function with morphologic evidence of disease have been based on autopsy data or on subjects undergoing pulmonary resection for lung tumor.

In the study described here, we measured a variety of indices of lung function in a group of current regular cigarette smokers of middle age who did not have respiratory disease together with an age/sex-matched group of subjects who had never smoked, all subjects drawn from a randomly selected community population. Smokers in this 40 to 60-year age group would be considered at risk of developing evidence of impaired lung function. The measurements employed were intended to assess ventilatory function, distribution of ventilation, gas exchange, and the elastic characteristics of the lung. The objective of the study was to determine which of the indices of lung function might be affected by cigarette smoking in essentially healthy subjects and to examine the interrelationships of the several indices of function.

METHODS

Candidates for these studies were drawn from the randomly selected population of Tucson, Arizona, enrolled in a prospective longitudinal study of respiratory health. This epidemiologic study was begun in 1972, and the population has continued to be followed up with sequential surveys. At each survey, health information is collected by self-administered questionnaires and spirometric/volume data are obtained. The fifth survey was completed in June 1979, and subject selection was based on information available as of that time.

Candidates were selected on the basis of age and smoking history; they were between the ages of 40 and 60 years and either had never smoked or were current regular cigarette smokers. In addition, based on questionnaire information, subjects were excluded from consideration if they had a history of heart trouble, chest surgery, physician-diagnosed asthma, chronic bronchitis, or emphysema. An attempt was made to match each smoker with a nonsmoker of the same age and sex.

Though eligibility for study was based on previous information collected through June 1979, the status of many candidates had changed by the time the present study was undertaken in 1981, reducing the total number of potential subjects. There were 11 female smokers eligible for study, of whom two refused to participate. Of the 24 male smokers considered eligible, satisfactory data were obtained on 13. Of the remaining 11, four were excused because they had quit smoking in the past year, four refused (one because of claustrophobia), one had had a recent myocardial infarction, and in

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two data could not be obtained for technical reasons.

Data were obtained on ten of 18 eligible nonsmoking women. Of the remaining women, five refused, one had developed symptomatic asthma, and in two technical problems occurred. There was a paucity of nonsmoking males in this age group, and data were obtained on nine of 19 thought to be eligible. Two men refused, one had a back problem which prevented plethysmographic studies, one had symptomatic asthma, one had recently been operated on for a carcinoma of the esophagus, three had had recent coronary bypass surgery, and technical difficulties were encountered in two. Thus, included in this study were 22 current regular smokers, mean age 54.14 (SD ± 4.69) years, and 19 nonsmokers, mean age 54.47 (SD ± 4.36) years.

For each smoker, cigarette consumption in pack-years was calculated as the product of number of packs of cigarettes (20 cigarettes/pack) smoked per day multiplied by the number of years the subject smoked. Consumption varied from 23 to 93 pack-years, with a mean of 45.4 (SD ± 18.1) for the smoking group.

The purpose of the study was explained and subjects gave informed, signed consent.

As part of the regular survey, standard spirometric evaluation was performed, yielding values for forced vital capacity (FVC) and forced expired volume in the first second of expiration (FEV1), selecting the best of three successive measurements. Carbon monoxide diffusing capacity (DLCO) by the single-breath method was performed in duplicate and results expressed as the greatest DLCO per unit lung volume (DLCO/VA) for each subject. On most subjects, chest roentgenograms were obtained and revealed no abnormality.

Before undertaking the plethysmographic studies, each subject inhaled two breaths of isoproterenol sulphate administered from a metered-dose inhaler (Medihaler-Iso, Biker Laboratories). Subjects were then seated in an air-conditioned pressure-corrected, integrated flow, volume displacement body plethysmograph (J. H. Emerson Co), using techniques described in connection with similar previous studies. Air-conditioning was controlled for thermal stability throughout the studies. Flow at the mouth was measured with a 7.5-cm diameter, 400-screen pneumotachograph (F. E. Wiedeman) connected to a differential pressure transducer (Sanborn 270). During the studies breathing air, the dead space of the apparatus was reduced to that of the mouthpiece alone by a bias flow exiting near the mouthpiece which drew room air through the pneumotachograph at 0.5 Ls-1 and which was offset electrically. The pneumotachograph had been separately calibrated for air and for a mixture of 80 percent helium-20 percent oxygen (HeO2). The bias flow was not used when HeO2 flow was measured.

Exspiratory pressure was measured by the balloon catheter method of Milic-Emili et al. Each 10-cm long balloon (0.06 mm thickness, 3.5 cm perimeter) was mounted on a 110-cm long polyethylene tube (PE 200) and the optimum balloon volume determined by the water immersion technique of Lemen et al. The balloon catheter was passed transnasally to the point of maximum negative pressure with the least cardiac artifact. In anticipation of future repeat studies, the final balloon depth was recorded for each subject. The difference between esophageal pressure and mouth pressure, the transpulmonary pressure, was measured by a differential pressure transducer (Hewlett-Packard 2688B). All data were recorded on a multichannel oscillograph (Hewlett-Packard model 7788A).

Thoracic gas volume at functional residual capacity (FRC) was measured by the method of DuBois et al., after which the subject immediately inspired to total lung capacity (TLC) and maximally expired to residual volume (RV), permitting calculation of subdivisions of lung volume.

Maximum expiratory flow-volume (MEVF) curves were displayed as mouth flow vs plethysmographic volume on a cathode-ray storage oscilloscope (Tektronix 564B) from which they were traced onto centimeter graph paper using a beam-splitter. At least three curves were used to construct an MEVF envelope. The maneuvers were performed breathing air and following equilibration with HeO2. For the latter, equilibration was determined by monitoring expired nitrogen and was considered complete when expired N2 fell to 8 percent or less. For subsequent comparison, the outer envelope was used to define a single MEVF curve for air and HeO2.

The single breath nitrogen test was also performed in triplicate. After expiration to RV, the subject slowly inspired 100 percent O2 after which he slowly exhaled, controlling expiratory flow to less than 0.5 Ls-1 by watching a display of flow on a volt meter. Expired percent N2 concentration, measured with a nitrogen meter (Hewlett-Packard Vertek 47302A), was plotted against plethysmographic volume during the maneuver on an X-Y recorder. From these plots, the nitrogen slope of the alveolar plateau (phase 3) and the volume at the point of terminal inflection of N2 concentration, or closing volume (CV), were recorded. For each of the measurements, the mean of three trials was used for analysis.

Simultaneous measurements of transpulmonary pressure and plethysmographic volume were obtained under static conditions after full inspiration by interrupting expiratory flow with a gate valve during slow deflation from TLC to RV. To assure a constant volume history, each such maneuver was preceded by three maximal inspirations to TLC and following each maneuver TLC was verified by a final full inspiration. All data points from at least five such maneuvers were used to construct a final pressure-volume (P-V) curve, which was drawn as the best fit by eye to the data points. In addition, all volume and static transpulmonary pressure (Pst(VL)) values for all of the data points were recorded for subsequent exponential analysis.

Static compliance was calculated as the 0.5-L volume change above FRC divided by the corresponding pressure change on the P-V curve. Subjects also breathed in time to a metronome at a frequency of 20 breaths per minute and data were obtained for calculation of pulmonary resistance (Rpullm) by the method of Frank et al.9

From MEVF curves for air and HeO2, maximum expiratory flow (Vmax) was measured at percent increments of vital capacity (VC) and TLC and, by comparing P-V curves, at volumes corresponding to 1 cm H2O increments of Pst(VL) from 1 to 13 cm H2O. Density dependence of Vmax at these volume increments was expressed as the ratio of Vmax breathing HeO2 to Vmax breathing air (Vmax). At increments of Pst(VL) corresponding to volumes between peak flow and closing volume, density dependence is independent of lung volume.10 Although there was no systematic change in Vmax/Vm within this volume range, there was within-subject variability in values. Consequently, for each subject, a mean value for Vmax/Vm was calculated by averaging the values at 1 cm H2O increments of Pst(VL) in this volume range in order to correct for the variability inherent in Vmax/Vm measured at one selected volume. The calculated mean Vmax/Vm often differed slightly from the Vmax/Vm measured at 50%VC in a given individual. However, in all 41 subjects, the average of the mean Vmax/Vm (1.389 SD ± .197) did not differ significantly from the average Vmax/Vm at 50%VC (1.360 SD ± .264). For subsequent analysis, the mean Vmax/Vm was used.

Static deflation P-V curves were evaluated by exponential analysis which provided a numerical expression for curve shape.11 For each subject, all values for volume and corresponding Pst(VL) between FRC and TLC were fitted to the equation:

\[ V = V_{max} - Ae^{-\beta V} \]  

(1)

where V and P are volume and pressure respectively, Vmax is volume extrapolated to infinite pressure, and A is the difference between Vmax and volume extrapolated to P = 0. The exponential curve fitting was performed on the University of Arizona Computer Center system (DEC 10/45 CYBER 175). The computer program was provided by R. C. Schreter and B. K. Oxenham, Imperial College of Science and Technology, London, and incorporates an iterative least mean square regression and statistical tests for quality of fit as described by Gibson et al.11 Data analyses were also performed on the University of Arizona.
### Table 1—Lung Function Measurements for Individual Smokers and Nonsmokers*  

<table>
<thead>
<tr>
<th>Age, Ht, yr cm Pack-yr FEV₁ %pFEV₁ TLC RV RV/TLC DL/Vₐ k ln k CV/C 3 Vₐ/Vₐ Rpulm</th>
<th>Smokers</th>
<th>N14</th>
<th>Ni0</th>
<th>N8</th>
<th>Ni</th>
<th>S12</th>
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<td>173</td>
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<td>3.00</td>
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<td>6.65</td>
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<tr>
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<td>175</td>
<td>38</td>
<td>3.74</td>
<td>106</td>
<td>7.47</td>
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</table>

| Values considered to be abnormal (%pFEV₁, DVₐ/Vₐ, Rpulm) |

| Values for ln k outside normal 95% confidence interval |

Computer System utilizing the SPSS routines. Statistical procedures included analysis of variance (ANOVA), Pearson product-moment correlation and regression analysis.

**Results**

In Table 1 are listed, by smoking category, lung function measurements for all subjects tested, together with sex, age, height, and, for smokers, pack-years of smoking. In Table 2 are shown the mean and standard deviation (SD) of lung function variables by smoking group and p values (by ANOVA).

**Smokers vs Nonsmokers**

Because of the criteria used for subject selection, there was no difference in age between smokers and nonsmokers. There were more male smokers than male nonsmokers. Because of this, smokers as a group were slightly taller than nonsmokers and, perhaps as a consequence, the mean vital capacity (VC) and forced expiratory vital capacity (FVC) were also slightly higher, but these differences were not significant. Though the mean FEV₁ for nonsmokers was slightly greater than that for smokers, this difference was also not significant. Because the average FEV₁ was slightly lower and the FVC slightly higher in smokers, the FEV₁/FVC ratio was significantly lower in the smoking group (p = .019).

Subclinical Effects of Smoking (Kudrow et al)
Table 2—Lung Function Measurements By Smoking Category

<table>
<thead>
<tr>
<th></th>
<th>Smokers Mean</th>
<th>Smokers SD</th>
<th>Nonsmokers Mean</th>
<th>Nonsmokers SD</th>
<th>p</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>54.14</td>
<td>4.69</td>
<td>54.47</td>
<td>4.36</td>
<td>.814 (NS)</td>
</tr>
<tr>
<td>Ht, cm</td>
<td>172</td>
<td>10.10</td>
<td>169</td>
<td>8.87</td>
<td>.322 (NS)</td>
</tr>
<tr>
<td>Pack-yr</td>
<td>45.36</td>
<td>10.10</td>
<td>0</td>
<td>0</td>
<td>---</td>
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<tr>
<td>FEV1</td>
<td>3.04</td>
<td>0.73</td>
<td>3.22</td>
<td>0.71</td>
<td>.460 (NS)</td>
</tr>
<tr>
<td>%pFEV1</td>
<td>94.39</td>
<td>16.31</td>
<td>105.97</td>
<td>15.31</td>
<td>.042</td>
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<tr>
<td>TLC</td>
<td>6.08</td>
<td>1.20</td>
<td>5.32</td>
<td>0.92</td>
<td>.029</td>
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<tr>
<td>RV</td>
<td>2.05</td>
<td>0.33</td>
<td>1.52</td>
<td>0.32</td>
<td>&lt;.0001</td>
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<tr>
<td>RV/TLC%</td>
<td>34.21</td>
<td>4.50</td>
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<tr>
<td>DL</td>
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<td>29.46</td>
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<td>.010</td>
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<td>DL/Va</td>
<td>4.41</td>
<td>0.82</td>
<td>5.17</td>
<td>0.61</td>
<td>.002</td>
</tr>
<tr>
<td>ln k</td>
<td>1.717</td>
<td>0.035</td>
<td>1.41</td>
<td>0.033</td>
<td>.002</td>
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<tr>
<td>ln k</td>
<td>2.734</td>
<td>.324</td>
<td>1.982</td>
<td>.232</td>
<td>.002</td>
</tr>
<tr>
<td>CV/NC</td>
<td>27.67</td>
<td>10.99</td>
<td>26.17</td>
<td>5.71</td>
<td>.006</td>
</tr>
<tr>
<td>Slope 3</td>
<td>2.10</td>
<td>1.56</td>
<td>0.88</td>
<td>1.02</td>
<td>.012</td>
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<td>Vw/Va</td>
<td>1.31</td>
<td>0.16</td>
<td>1.48</td>
<td>0.20</td>
<td>.003</td>
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<td>Rpulm</td>
<td>2.47</td>
<td>0.68</td>
<td>1.92</td>
<td>0.65</td>
<td>.031</td>
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</table>

To correct for sex, age, and height, FVC, and FEV1 were expressed as percent predicted using regression equations derived from data obtained on asymptomatic nonsmokers in the Tucson population. Again, there were no significant differences in percent predicted FVC. However, the mean percent predicted FEV1 (%pFEV1) for smokers was significantly lower than the mean value for nonsmokers (p = .025). Using the lower 95th percentile as defined by Knudson et al as the lower limit of normal, one of the 19 nonsmokers and two of the 22 smokers would be considered to have an abnormal value for FEV1. If a %pFEV1 of 65% or less is considered clinically important, only one smoker would fit this category. Thus, with these few exceptions, the subjects in this study would be considered healthy by standard spirometric criteria.

There is some evidence from the Vmax values to suggest that the MEFV curve of smokers is more concave in the direction of the volume axis; ie, Vmax is lower at lower lung volumes. The maximum expiratory flows after 50 percent and 75 percent of the vital capacity had been expired (Vmax50% and Vmax75%, respectively) in smokers was not significantly different from the mean flows in nonsmokers. However, when size compensated by expressing flow in TLCs per sec (ie, Vmax/TLC), both Vmax50% (p = .004) and Vmax75% (p = .011) were significantly lower in smokers.

Density dependence of Vmax, defined as the \( \frac{V_{w}}{V_{a}} \) ratio, varied from 1.05 to 1.85. If a normal response is defined as \( \frac{V_{w}}{V_{a}} \) of at least 1.20, then seven smokers and one nonsmoker would be classified as nonresponders. The mean \( \frac{V_{w}}{V_{a}} \) of smokers was significantly lower than the ratio for nonsmokers (p = .003).

The alveolar volume (V\(_{a}\)) or total lung capacity derived from the single-breath diffusing capacity, as expected, differed slightly from the TLC measured plethysmographically, but the differences were not statistically significant for the 41 subjects tested. Differences between smokers and nonsmokers for V\(_{a}\) did not achieve significance. However, plethysmographically determined TLC of smokers was slightly but significantly larger (p = .029) than that of nonsmokers, probably because there were more males in the smoking group than in the nonsmoking group. Of greater significance were the larger FRC (p < .001) and RV (p < .001) of the smokers. Although very few subjects had RV/TLC ratios which would be considered abnormal, the mean RV/TLC for smokers was significantly greater than for nonsmokers (p = .004).

Of the measurements derived from the single-breath nitrogen test, the closing volume/vital capacity ratio (CV/VC%) did not distinguish between groups (p = .50). However, the closing capacity/total lung capacity ratio (CC/TLC%) was significantly greater in the smokers (p = .011). Inasmuch as CC is the sum of CV and RV, and the RV/TLC was significantly greater in smokers, this is not surprising. The nitrogen slope of phase 3 was abnormal in five of 21 smokers but in only one of 19 nonsmokers, and the mean for smokers was significantly greater (p = .012).

Measurements of single-breath diffusing capacity (DL) also revealed significant differences. The DL of smokers was significantly lower than the mean value for nonsmokers (p = .010). Diffusing capacity per liter lung volume (DL/Va) was also significantly lower in smokers (p = .002). However, using the prediction equations and normal limits for nonsmokers recently described by Miller et al only one smoker would be identified as having abnormal values for DL and DL/Va. Even that subject would not be classified as abnormal if the smoking-specific prediction equations of Miller et al were used.

The mean pulmonary resistance (Rpulm) of the smokers, while not abnormal, was significantly greater than the mean for nonsmokers (p = .031). Only one subject, a smoker, had an abnormally high Rpulm based on the criteria of Frank et al.

Static deflation P-V data were fitted to the exponential equation described above (Eq 1) for 40 subjects. For only one subject, a nonsmoker, were the P-V data not satisfactory. The shape constant k, derived from exponential analysis of P-V data, was significantly greater in smokers than nonsmokers (p = .002). In a previous study of asymptomatic nonsmokers, the natural logarithm of k (ln k) rather than k showed a normal Gaussian distribution. This suggested that normal limits are better expressed using ln k rather than k itself. Thus, in Figure 1 we have plotted ln k for smokers and nonsmokers together with the age regression and 95 percent confidence limits based on the previous study of normal subjects. Three subjects,
including one nonsmoker, have ln k values above the 95 percent confidence interval, suggesting diminished lung elastic recoil and one subject, also a smoker, has a low value suggesting increased lung recoil. None of the values, however, fall far outside these 95 percent confidence limits. Static compliance (Cst), which correlates well with k, was also significantly greater in smokers (p = .036).

In the 22 smokers, pack-years of smoking showed a significant inverse correlation with FEV/FVC ratio (r = −.435, p = .022) and percent predicted FEV1 (r = −.483, p = .011). However, there was not a significant correlation of pack-years of smoking with measurements derived from the single-breath nitrogen test (CVNC or slope of phase 3), measurements of diffusing capacity (DL or DL/VA) or indices of lung elastic recoil (k, ln k, or Cst).

Relationships Between Measurements

As would be anticipated, measurements of similar phenomena correlated well with one another. Thus, there was significant correlation between %pFEV1 and Rpulm (r = −.428, p = .003) and between ln k and Cst (r = −.509, p < .001). A low %pFEV1 and increased RV/TLC are recognized indices of abnormality. Even though few subjects had abnormal values for these measurements, the two correlated (r = −.391, p = .006). The nitrogen slope of phase 3 correlated with %pFEV1 (r = −.560, p < .001) and Rpulm (r = .554, p < .001).

In neither smokers nor nonsmokers was a significant relationship found between FEV1 or Vmax measurements and k or ln k. Indeed, in the total group, there was no correlation found between indices of lung recoil and any of the MEFV or spirometric measurements. In addition, no significant correlation was found between indices of lung recoil and density dependence of Vmax or any measurement from the single-breath nitrogen test. Of all the measurements, only diffusing capacity correlated with indices of lung recoil. The correlation of DL with k was significant (r = −.326, p = .020), but the best correlation was the inverse relationship of DL/VA to k (r = −.518, p < .001). This is illustrated in Figure 2.

There were significant correlations of diffusing capacity to other measurements as well. The DL correlated with RV/TLC (r = −.516, p < .001), with the nitrogen slope of phase 3 (r = −.413, p = .004), and with Rpulm (r = −.318, p = .022). However, there were no significant correlations of DL/VA with these measurements.

Discussion

The objective of this study was to examine the effect of cigarette smoking in a randomly selected group of middle-aged subjects who had not developed overt disease. Subjects with physician-diagnosed respiratory disease were excluded from this study. In particular, we sought to exclude subjects with bronchoplastic disease whose lung function may vary from day to day. As a result, although respiratory symptoms were not considered in subject selection, all of the subjects regarded themselves as healthy.

As shown in Table 1, very few measurements of lung function or properties obtained in this sample of 41 subjects would be considered abnormal. Although four subjects had values for ln k which fell outside the normal 95 percent confidence interval, the deviation from the normal range was not remarkable. The one

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21422/ on 06/21/2017)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21422/ on 06/21/2017)
subject with a low value for ln k had an abnormal slope of phase 3, but the remaining three with high values for ln k had no other abnormalities of function.  

Only three subjects had measurements of FEV₁ below the normal limit.¹⁰ One of these, a nonsmoker, also had an increased slope of phase 3 as the only other abnormality. Another of these, a smoker, also had an increased slope of phase 3 and abnormal Vₑ/Vₑ⁰, while the third, also a smoker, had no other abnormality. The only subject, a smoker, with the low DLₑ had no other abnormality.

With only these isolated and seemingly unrelated examples of abnormality, we could not conclude that measurements other than standard spirometric tests were capable of identifying individuals with incipient airflow obstructive disease. Nevertheless, although there were very few examples of discernible abnormality in function among these subjects, there were significant differences between smokers and nonsmokers when group mean values were compared.

The relationship between cigarette smoking and impaired ventilatory function is clearly recognized. Our earlier analysis of data from the Tucson population³⁸ demonstrated the relationship of pack-years of smoking to ventilatory function. Even in the 22 smokers selected for this study, this relationship was noted.

Although the CV/VC from the single breath nitrogen test has been said to distinguish between smokers and nonsmokers,³⁹ we could not confirm this in our general population or in the present study. The slope of phase 3, however, appears to be the more sensitive measurement and was significantly greater in the smokers than in nonsmokers. There is poor concordance between flow-volume and closing volume variables, however, and the significance of an abnormal slope of phase 3 is uncertain.³⁸

Dosman et al⁴⁰ found that the test of density dependence of Vₘₐₓ distinguished between smokers and nonsmokers, a finding confirmed in the present study. Although a failure to increase Vₘₐₓ by breathing HeO₂ has been described as a test of small airways dysfunction, interpretation of the test is more complex than first thought,³⁹,⁴⁰ and we are uncertain of the significance of our results.

Loss of lung elastic recoil has been considered a pathophysiologic hallmark of emphysema. To deal with the nonlinearity of the relationship of transpulmonary pressure to volume, the variability in absolute lung volumes, and potential differences in measurement techniques, mathematical expressions of curve shape have been employed. The exponential analysis used in this study yields the constant k (in units of cm H₂O⁻¹), an index of curve shape which is independent of sex and lung size and, unlike measurement of absolute Pₑ(L), is insensitive to differences in measurement technique.³⁴ Increased values for k have been associated with emphysema diagnosed clinically or determined by morphometric examination of the lung.¹²,¹⁸,⁴⁰ Other mathematical expressions of curve shape have been employed with similar results.¹³,²³ In the present study, only three subjects had values for k (or ln k) above the normal range, and none of these was sufficiently abnormal to be clearly indicative of emphysema. Nevertheless, there was a clear and significant trend for smokers to have higher values for k than nonsmokers.

Michaels et al⁴⁴ observed a decrease in lung elastic recoil in smokers after the administration of an aerosol bronchodilator. They postulated that cigarette smoke may result in increased smooth muscle tone at the level of peripheral airways or alveolar ducts resulting in an increase in Pₑ(L). By relieving this peripheral constriction, administration of bronchodilator may unmask loss of recoil in smokers. With this possibility in mind, all plethysmographic measurements of lung mechanics were performed after the administration of a bronchodilator aerosol in the present study.

In several studies, the relationship between altered lung function and morphologic changes have been examined, a subject recently summarized by Pare et al.²⁵ Park et al³⁵ assessed the extent of emphysema at autopsy in 26 patients with obstructive lung disease and found it best related to an elasticity coefficient and to the steady-state diffusing capacity. Zamel et al³⁶ found loss of lung recoil and reduced DLₑ/Vₑ in patients with morphologic evidence of emphysema in surgically resected lung. Berend et al³⁷ found that abnormalities of diffusing capacity correlated best with the presence of emphysema, whereas in some patients emphysema appeared to be present without detectable loss of recoil assessed by the half-inflation pressure analysis of Salazar and Knowles.³⁸ In their well-designed study of 55 subjects, Pare et al³⁸ performed extensive lung function studies within a week before lung resection for peripheral coin lesions. Their P-V data were analyzed by exponential curve fitting using the same method we employed. The resected lung specimens were graded for emphysema by the method of Thurlbeck and subjects grouped according to severity of emphysema. Measurements of diffusing capacity and the P-V shape constant k were significantly different in those with moderate-to-severe emphysema compared with the other groups. These authors found that k was the best predictor of emphysema in their subjects.

In the present study, only three subjects have elevated values for k and none of these has an abnormal DLₑ. Whether these subjects have lungs with emphysematous changes would be mere conjecture. Indeed, few of our subjects exhibit abnormalities in any of the measurements. The common association of various
measurements in the studies noted above led us to explore further these associations in the present study of essentially healthy subjects.

In theory, loss of lung elastic recoil should result in decrease in maximum expiratory flow. While it is true that the mean shape constant \( k \) was significantly higher in smokers and \%pFEV, and \( V_{\text{max}} \) were significantly lower, there was not a significant correlation of \( k \) with measurements of flow in the total group. In analysis of all data on all subjects, significant correlations included \( k, D_L, D_L/V_A \), and few other variables.

As noted, \( D \) correlated with several other measurements of lung function. To analyze these relationships further, we first examined a multiple regression of \( D_l \) on the slope of phase 3, shape constant \( k \), and measurements of ventilatory function. Because of the very limited range of age employed in this study, age was not included as an independent variable. The \( R^2 \) values revealed that the slope of phase 3 accounted for 17.5 percent of the variability of \( D_l \), \( k \) accounted for an additional 5 percent, and \%pFEV, and \( R_{\text{pulm}} \) added 2 percent and 3 percent, respectively. The various sources of inhomogeneity which can affect the single-breath nitrogen test have been examined and quantified, and the role of nonuniform ventilation in the measurement of \( D_L \) is recognized. Thus, it appeared that the slope of phase 3 as an index of gas distribution explained a significant proportion of the variance in \( D_L \). However, height, and, therefore, vital capacity, affect both the slope of phase 3 and \( D_L \) as shown by the significant height coefficients in the prediction equations for slope of phase 3 and \( D_L \). In the present study, the slope of phase 3 correlated with VC (\( r = -.484, p < .001 \)). It has also been shown that the measurement of \( D_L \) can vary with volume of gas inspired during the test maneuver. Therefore, we examined a multiple regression of \( D_L \) in which the inspired vital capacity was included as an independent variable and age was also added. From this analysis, the \( R^2 \) values revealed that the inspired VC explained 47 percent of the variance in \( D_L \) and \( \ln k \) entered next, adding 12.4 percent. Age did not enter significantly and the slope of phase 3 now contributed almost nothing. Thus, when VC is taken into account, the shape constant \( k \) explains a significant proportion of the remaining variance in \( D_L \). The relationship first noted between slope of phase 3 and \( D_L \) appeared only because both measurements were dependent on VC.

To compensate for volume, \( D_L \) can be expressed as \( D_L/V_A \). In the total group studied, there was a significant correlation of \( D_L/V_A \) with indices of lung recoil (Fig 2). When a multiple regression analysis was applied to \( D_L/V_A \), the shape constant \( k \) (expressed as \( \ln k \) ) was found to account for 28.8 percent of the variability of \( D_L/V_A \), with FEV/FVC adding 12.6 percent. Measurements from the single-breath nitrogen test explained only an additional 3 percent of the variance of \( D_L/V_A \). Because \( D_L \) was already divided by lung volume, the addition of inspired VC added almost nothing, and the effect of age was negligible, although, as noted, the age range was limited.

There are several observations, many based on structure-function correlations, which may assist in construction of a hypothesis to explain this inverse correlation of \( k \) to \( D_L/V_A \). In a study of normal and emphysematous human lungs obtained at autopsy, Greaves and Colebatch found that \( k \) derived from exponential analysis of \( P-V \) data was linearly related to morphometric measurement of mean linear intercepts (\( L_m \)) determined by the method described by Thurlbeck. This appeared to confirm the observation that an elevated value for \( k \) was an index of the presence of emphysema. However, the same relationship of \( k \) to \( L_m \) was demonstrated in a similar study of lungs from three different mammalian species, a study which did not involve a disease process. In this study of normal mammalian lungs, it was found that \( L_m \) explained 86 percent of the variance in \( k \) within and between species and that \( k \) related to the size of air spaces. Thus, if \( L_m \) is inversely related to the surface-volume ratio, then \( k \) is also so related.

In 1964, Vincent et al described enlargement of respiratory bronchioles and alveolar ducts, which they called duct ectasia, as a normal asymptomatic change associated with aging. Thurlbeck subsequently confirmed this phenomenon in a larger study of non-emphysematous lungs. He pointed out that the average interalveolar wall distance, \( L_m \), increased with advancing age. Other studies have shown that the shape constant \( k \) increases with age in the adult, an increase which is very likely related to this enlargement of terminal airspaces with age. To these observations one may add the additional observation that \( D_L \) and \( D_L/V_A \) decline with advancing age in the human adult. Thus, it may be possible to explain the relationship of \( D_L/V_A \) to \( k \) on the basis of enlargement of terminal airspaces.

If diffusing capacity is a function of the available gas exchanging surface, then a decrease in the surface-volume ratio may be followed by a decrease in the diffusing capacity/volume ratio. This implies that the available absolute surface area is decreased, a destructive phenomenon often associated with emphysema. This would be compatible with an elevated \( k \) and an abnormally low \( D_L/V_A \) in human subjects with emphysema. Silvers et al, in a study of excised lungs, found that the half inflation pressure of Salazar and Knowles distinguished even mild emphysema from non-emphysematous lungs. However, Thurlbeck found that in mild emphysema, surface area was not decreased, even though interalveolar wall distance was increased. On the other hand, together with the enlargement of...
terminal air spaces, Thurlbeck has found a loss of alveolar parenchyma with advancing age. Inasmuch as the number of alveoli per unit volume is unchanged, this implies a loss of tissue per alveolus. It has been postulated, though not proved, that this may also represent a loss of capillary bed. If enlargement of terminal air spaces is accompanied by loss of capillary bed, this could account for the inverse association of $k$ with $DLVA$. In their morphometric study of post-mortem lungs, however, Butler and Kleinerman reported a clear trend of increasing alveolar diameter with age but noted only a slight suggestion of decreasing capillary density. They believed that the very slight decrease in capillary density was only the relative effect of air space enlargement on their measurements and did not represent actual loss of vessels. They postulated that the decrease in $DL$ with age may result from a diminishing capillary density/alveolar diameter ratio.

If $k$ is an index of size of air spaces, as suggested by the data of Haber et al., then the inverse relationship of $k$ to $DLVA$ may be the result of decreased gas phase conductance associated with larger air spaces. At some point beyond terminal bronchioles, convective transfer of inspired gas becomes less effective than gaseous diffusion as the dominant transport mechanism for moving gas molecules. In effect, this creates a gas-phase diffusion barrier between gas moved by convective flow and the gas in contact with the alveolar surface. Diffusion equilibrium requires a finite time and depends on the distance to be traversed and thus on the volume of the terminal air space itself. In the normal lung, the average distance to be traversed by gas diffusion is only about 2 mm. However, from measurements of resin casts of lung units, it has been shown that the mean diffusion distances may be increased to 7 mm in centrilobular emphysema and to more than 10 mm in panacinar emphysema. This distance to be traversed by gas diffusion constitutes a resistance to gas exchange which is added to the resistances presented by the alveolar membrane and blood phases, all of which are included in the measurement of $D_L$, the reciprocal of the summed resistances. Thus $DLVA$, the equivalent of Krogh's diffusion constant, might be inversely related to the size of terminal air spaces. Insofar as the exponential constant $k$ is an index of the size of these spaces, this may explain the significant inverse correlation observed between $k$ and $DLVA$ in the present study.

As a group, the smokers in this study had higher values for $k$ and lower values for $DLVA$ than the nonsmokers. This may represent only an accelerated effect of aging in the smokers. Although, in the absence of morphologic data, very mild emphysema cannot be ruled out, few, if any, of our subjects could be said to have clinical or physiologic evidence of emphysema. The smokers may simply have greater enlargement of terminal air spaces than the nonsmokers, which may be reflected by their $k$ and $DLVA$ values. At least, we would propose this as a hypothesis which may merit further investigation.

Pulmonary emphysema has been defined in anatomic rather than clinical terms. The 1958 Ciba Symposium defined emphysema as increase in "size of airspaces distal to the terminal bronchiolus either from dilatation or from destruction of their walls." The 1962 American Thoracic Society Statement defined it as enlargement of air spaces "accompanied by destructive changes of the alveolar wall," thus including both processes. If tissue destruction is a necessary criterion of emphysema, it may be possible that excessive enlargement of airspaces may occur first, before actual alveolar wall destruction with reduction of surface area occurs. This early change may be present in our smokers.

In view of the interest in detection of early disease, we should point out that the measurements which reveal these changes in smokers are not sufficiently sensitive in themselves and are not practical to employ for such a purpose. Moreover, we cannot state with certainty, based on the evidence, that these smokers are indeed developing emphysema and, even if they do, they may not exhibit clinical manifestations in the future. Based on these data, however, we would postulate that, even in this group of generally healthy subjects, subtle changes in many parameters of lung function can be detected which can be attributed to the cumulative effects of cigarette smoking.

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