Thorax 1986;41:81–87

Editorial

Observations on the pathogenesis of chronic airflow obstruction in smokers: implications for the detection of "early" lung disease

Cigarette smoking causes various pathological changes in the lungs, some of which may lead to chronic airflow obstruction, which is an important cause of respiratory morbidity and mortality. The changes attributable to smoking include *large airway effects* (mucous gland enlargement and mucous hypersecretion, smooth muscle hypertrophy, atrophy of bronchial walls); *small airway changes* (bronchiolar inflammation, fibrosis, ulceration, and tortuousity, with diffuse narrowing of the airways); and *pulmonary emphysema*.[1-5] The relative roles of these pathological features in causing chronic airflow obstruction have been examined and two hypotheses for its pathogenesis in smokers have been proposed.

The most common condition associated with chronic airflow obstruction in smokers is emphysema, which is usually of the centrilobular type, although mixtures of centrilobular and panlobular changes are also found.[3,4] One current concept of the pathogenesis of emphysema is based on an imbalance between proteases and antiproteases in the lung parenchyma;[6-8] a relative excess of proteases, particularly elastases, is thought to occur in the lungs of many smokers, and this may promote the disruption of connective tissue fibres. Because the tissue fibre network is essential for the structural integrity of alveoli, proteolytic activity can lead to disruption of alveolar walls and alveolar enlargement.[9-11] Alveolar enlargement leads to decreased lung elasticity and decreased elastic support of the airway walls.[12,13] The resulting decrease in elastic driving pressure and increased likelihood of expiratory airway collapse is responsible, in turn, for decreased maximum expiratory airflow from the lungs and the characteristic spirometric pattern of chronic airflow obstruction.[14,15]* This hypothesis for the development of chronic airflow obstruction in smokers emphasises the parenchymal effects of smoking in producing emphysema and loss of lung elasticity.

An alternative view is that pathological changes in the "small airways" (defined as airways less than 2 mm in internal diameter, principally the terminal and respiratory bronchioles) are either the major sites of airflow obstruction[16-18] or an important intermediate step in the pathogenesis of emphysema, which is then responsible for chronic airflow obstruction.[18-22]

The relative merits of these two hypotheses have not been tested, but they can be assessed from the published data of Mitchell and coworkers,[3] who described the post mortem features of emphysema and "small airway" pathology in relation to cumulative smoking exposure (expressed as pack years), and in relation to the presence and severity of chronic airflow obstruction assessed shortly before death. Mitchell and colleagues observed that "pathologic changes in large and small airways in the absence of much emphysema were very seldom associated with chronic airflow obstruction," but nonetheless they considered that the data were "consistent with a growing consensus that loss of small airway support by surrounding lung tissue in emphysema may cause kinking, tortuousity, and collapse of the airways, with subsequent increased airflow resistance and clinical obstruction".[3]

If a causal relationship exists between small airway pathology and emphysema or if small airway pathology were responsible for chronic airflow obstruction in smokers, highly significant associations between small airway pathlogy and emphysema, or between small airway pathlogy and chronic airflow obstruction, should be present in the data of Mitchell and coworkers. Further examination of their findings, however, shows no strong association, after cumulative smoking has been allowed for, between small airway pathlogy and either emphysema or chronic airflow obstruction. The prevalence rates of emphysema, small airway pathlogy and emphysema plus small airway pathlogy are shown for the total group of lungs studied by Mitchell *et al* (table 1), and the findings have been stratified into three smoking

*Airflow obstruction[4] is defined typically as a decreased FEV_1 (that is, a value less than 80% of that predicted) in the presence of a proportionately smaller decrease in forced vital capacity. As we shall show below, a decreased FEV_1 has poor sensitivity for predicting the presence of emphysema.

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Table 1 *Presence of emphysema and of "small airway" pathology (SAP) in postmortem lungs grouped according to lifetime cigarette consumption (data from Mitchell et al[3])*

Smoking (pack y)			*Emphysema*	
			Present	*Absent*
< 10	SAP	Present	1	11
		Absent	4	28
10–39	SAP	Present	5	7
		Absent	10	14
⩾ 40	SAP	Present	52	6
		Absent	38	20
Total group	SAP	Present	58	24
		Absent	52	62

groups: those who had smoked less than 10, 10–39, and 40 or more pack years. Mitchell and coworkers used a 100 point grading system to assess the extent of emphysema, and they considered mainly moderate to severe emphysema (grades ⩾30). Small airway pathology was classified according to the presence and severity of chronic inflammation, goblet cell metaplasia, and mural fibrosis in the peripheral airways. As cumulative smoking increased, the prevalence of emphysema increased from 11% to 41% to 78%, and the prevalence of small airway pathology also increased—from 25% to 33% to 50% (table 1). These findings show an exposure-response relationship for both emphysema and small airway pathology with cumulative smoking. Since the likelihood of either emphysema or small airway pathology increases with the amount smoked, it follows that the chance association of the two conditions also increases with smoking, because the expected occurrence by chance of emphysema plus small airway pathology is equal to the product of the probabilities (prevalences) of emphysema and of small airway pathology. In this case the expected prevalence of emphysema plus small airway pathology for increasing cigarette consumption is 3%, 14%, and 39%, compared with the observed rates of 2%, 14%, and 45% respectively.

An important conclusion from these findings is that the cumulative smoking history is a very strong determinant of the prevalence both of emphysema and of small airway pathology, and therefore of the association between emphysema and small airway pathology. In other words, quite apart from any causal relationship between small airway pathology and emphysema, cumulative smoking has a major influence on the chance association between the two conditions. Failure to account for the confounding effect of cumulative smoking may therefore bias tests of association between small airway pathology and emphysema so that a spurious association may be found.

These calculations of the observed and expected rates for emphysema plus small airway pathology in the various smoking categories show that only in the highest smoking group (⩾40 pack years) is there an excess of people with both emphysema and small airway pathology. A major proportion (59%) of the total observations, however, lies in this open ended high exposure category. This raises the possibility of inadequate control for confounding by smoking in this group, which could have resulted in a spurious excess of people with both emphysema and small airway pathology in this category. Such a spurious result would be amenable to testing in the original data by further stratifying the high smoking group, but unfortunately the data are no longer in an analysable form (RS Mitchell, personal communication).

Further features of Mitchell's data suggest that the above interpretation is probably correct. When the findings are analysed according to either the absence or the presence of severe chronic airflow obstruction that was thought to cause death (table 2), the prevalence of emphysema was 17% and 99% and the prevalence of small airway pathology was 29% and 59%. The resulting expected rates for emphysema plus small airway pathology were very similar to the observed values (5% and 59% versus 7% and 59% respectively).

Among Mitchell's subjects who died from chronic airflow obstruction, emphysema was found in the lungs of all but one, whereas small airway pathology occurred in only 59% of the same group (table 2), emphasising the greater importance of emphysema in determining chronic airflow obstruction in this study population. The distribution of emphysema grades for those dying with or without evidence of chronic airflow obstruction is shown in figure 1. On a scale of zero to 100 all of those dying from chronic airflow obstruction had emphysema grades of 35 or higher, while only 11 of 87 (12%) of those without chronic airflow obstruction had similar high grades of emphysema. Those who were classified as having "disabling" or "suspect mild" chronic airflow obstruction had proportions of high grade

Table 2 *Presence of emphysema and of "small airway" pathology (SAP) in postmortem lung specimens with respect to the presence or absence of severe chronic airflow obstruction (CAO) thought to have caused death (data from Mitchell et al[3])*

CAO			*Emphysema*	
			Present	*Absent*
No CAO	SAP	Present	6	19
		Absent	9	53
CAO caused death	SAP	Present	38	1
		Absent	26	0

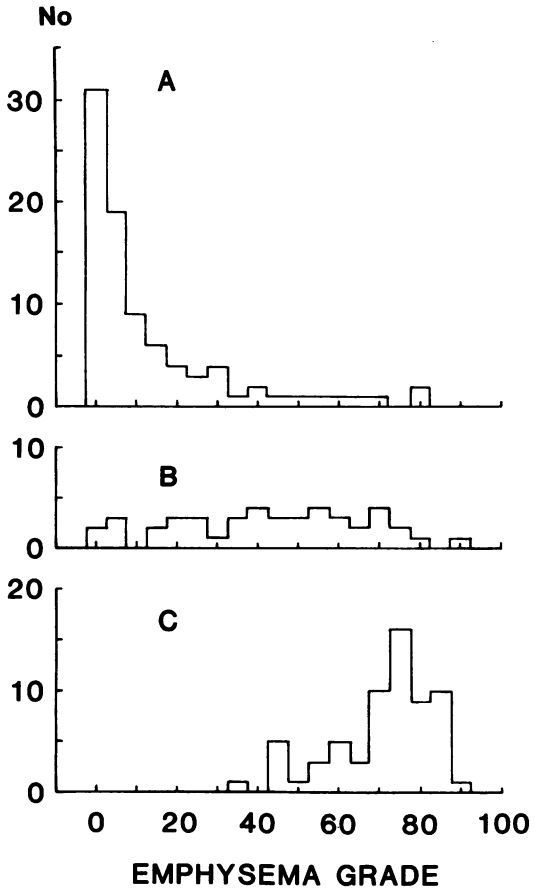

Fig 1 *Frequency histogram of emphysema grades redrawn from the data of Mitchell et al.*[3] *(A) Subjects without clinical chronic airflow obstruction (n = 87). (B) Subjects with chronic airflow obstruction of a degree that did not cause death (n = 44). (C) Subjects with chronic airflow obstruction that caused their death (n = 65).*

emphysema that were intermediate between the proportions in those without chronic airflow obstruction and those dying from it (fig 1).

This is not to say that small airway pathology, or for that matter large airway disease, is irrelevant to airflow obstruction in a proportion of smokers. Indeed, there is experimental evidence that small airway pathology in the presence of emphysema has a greater than additive effect in producing airflow obstruction,[23] and postmortem studies in man show that intrinsic airway narrowing contributes to limitation of expiratory airflow in emphysematous lungs.[24] "Pure" intrinsic airway narrowing causing severe chronic airflow obstruction is an unusual finding in smokers. Patients with severe chronic airflow obstruction due to "primary bronchial disease"[25] are found occasionally, but the usual physiological findings in subjects with disabling chronic airflow obstruction suggest a combination of emphysema and intrinsic airway narrowing. This observation may simply reflect the fact that the two conditions together produce greater airflow limitation than either alone, and that more severely disabled individuals are more likely to come to a physician's attention.

Partly to address this issue of end stage chronic airflow obstruction versus less disabling disease, Hale and coworkers[26] recently compared the relative contributions of emphysema and small airway pathology in smokers with severe airflow obstruction and in a group of non-smokers and a group of smokers without severe pulmonary disease who died outside hospital. Two thirds of smokers dying with severe chronic airflow obstruction had emphysema of 30 or more units, compared with 12% of smokers without severe lung disease and 7% of non-smokers. Premortem FEV_1 measurements correlated more closely with the severity of emphysema (determined by inspection of lung slices) than with the severity of small airway pathology (determined histologically). The authors concluded that among smokers with chronic airflow obstruction "no morphologic or pathologic feature of the small airways was an independent predictor of ventilatory function beyond that of emphysema alone."[26] The findings confirm those of Mitchell *et al*[3] and earlier workers,[1 2] but in the absence of quantitative information on smoking we cannot determine whether the data of Hale and colleagues show independent contributions or interactions between emphysema and small airway pathology in producing chronic airflow obstruction.

Additional support for the independent occurrence of small airway pathology and emphysema comes from morphological studies showing that the distribution of small airway pathology in the upper and lower lung lobes does not parallel the distribution of emphysema in the same lungs.[27 28] The lack of a morphological association between small airway pathology and emphysema suggests that the two either are determined by different host responses to a common agent or are responses to different components of cigarette smoke. In either case the pathological findings suggest that small airway pathology and emphysema are not causally related.

The studies of lung pathology are pertinent to the development of chronic airflow obstruction and the question of how "early" (subclinical) changes in lung function might be recognised. As a general principle, it seems desirable to have some means whereby affected individuals may be identified at a stage when the changes in their lungs might be reversible, or at least limited at the earliest possible stage, even if

attempts to persuade smokers to quit smoking have been largely unrewarding.[18 29] Moreover, greater understanding of "early" smoking effects would possibly help to define a subgroup of the general population who are particularly susceptible to chronic airflow obstruction from smoking and other agents. One candidate for such "early" change would be an asymptomatic increase in lung distensibility, indicative of mild emphysema (see below), with an increased risk of chronic airflow obstruction due either to progression of emphysema or to development of intrinsic airway narrowing in addition. Furthermore, knowledge of the "early" effects of smoking may help to distinguish changes attributable to smoking from those caused by exposure to other air contaminants, such as those occurring in the workplace.

Because small airway pathology is a poor predictor of which smokers may have emphysema and possibly progress to disabling chronic airflow obstruction, attention should be directed more to tests that indicate the presence of mild or "early" emphysema. Measures of lung function in individuals before lung resection[20 30 31] and in postmortem lungs[12 32-35] have shown that elastic recoil changes correlate better than other lung function tests with the presence and severity of emphysema. Decreased elastic recoil pressures and increased lung distensibility, with an accompanying increase in total lung capacity (TLC) and functional residual capacity (FRC), have been found even in mildly emphysematous lungs.[11 24-26 31-35]

An exponential function of the general form $V = A - Be^{-KP}$ (where V is lung volume, P is static recoil pressure, and A, B, and K are constants) has been found useful in describing the static deflation pressure-volume (PF) curve.[12 13 25 36-38] The constant K in this expression has important biological significance: it is an index of lung distensibility that describes the shape of the pressure-volume curve over the upper half of lung volume, and it is inversely related to the bulk elastic modulus of the lungs;[13] it is influenced mainly by the density of surface tension forces within the lungs and these, in turn, are directly related to the alveolar surface to volume ratio, which is determined by the mean size of peripheral air spaces.[12 13] Because the distinguishing feature of emphysema is alveolar enlargement accompanied by disruption of the parenchymal fibre network, it is not surprising that an increase in K correlates closely with the presence and severity of readily ventilated emphysematous regions.[12 31]

That the constant K is the single best predictor of emphysema has been reported by Paré and coworkers,[31] whose data also provide estimates for the sensitivity, specificity, and predictive values[39] of various standard lung function tests (maximum expiratory flow-volume curves, lung volumes, gas transfer factor, and *PV* curves) that are used to determine the nature and severity of chronic airflow obstruction (table 3). In this study lung function measurements were obtained from patients shortly before lung resections were performed for cancer; the morphological features of the resected specimens were then compared with the preoperative lung function findings. As pointed out by Paré *et al*, there is a possibility of sampling error in the assessment of structural changes on the basis of small specimens, but the effects of sampling error are probably small when emphysema grades are classified as either 15 or less or greater than 15. The overall prevalence of emphysema grades greater than 15 was 16 out of 55 cases (29%). Tests showing high sensitivity for emphysema were an increased value for the exponential constant K and an increased TLC or FRC. Tests having a high specificity included an increased value of K, a decreased gas transfer factor (single breath diffusing capacity for carbon monoxide), a decreased maximum inspiratory pressure, and a decreased FEV_1.

Table 3 *Sensitivities, specificities, and predictive values for selected lung function tests in predicting the presence of emphysema (grades over 15) in resected lung specimens.* (values calculated from the results of Paré* et al[31]*)*

Abnormal result	*Sensitivity (%)*	*Specificity (%)*	*Predictive value positive (%)*	*Predictive value negative (%)*
Increased K	69	87	69	87
Decreased PLmi	0	92	0	69
Decreased PL90	38	82	46	76
Decreased PL60	19	80	27	71
Decreased TLCO	38	95	75	79
Decreased FEV_1	13	90	33	71
Decreased FEF_{50}	44	80	47	78
Increased TLC	56	67	41	79
Increased FRC	75	56	41	85

*For definitions of sensitivity, specificity, and predictive values see ref 39.
K—the exponential constant in $V = A - Be^{-KP}$ (see text); PLmi, PL90, PL60—static recoil pressures at maximal inflation, 90%, and 60% of total lung capacity; TLCO—gas transfer factor (single breath diffusing capacity for carbon monoxide); FEF_{50}—the maximum expiratory flow at 50% of forced vital capacity; TLC—total lung capacity; FRC—functional residual capacity.

Overall, the tests having the highest predictive values were found for an increased K and a decreased gas transfer factor (table 3). This result is perhaps to be expected because it can be shown on theoretical grounds that the exponential constant K and the gas transfer factor are inversely related through the dependence of each test on the alveolar surface to volume ratio (mean size of alveoli); studies on human subjects have shown a relationship between 1/K and gas transfer factor.[40] The findings of Pereira and coworkers[41] and earlier studies confirm that substantial changes in lung distensibility and gas transfer factor occur in subjects with emphysema, but not in those with exclusively airway disease.

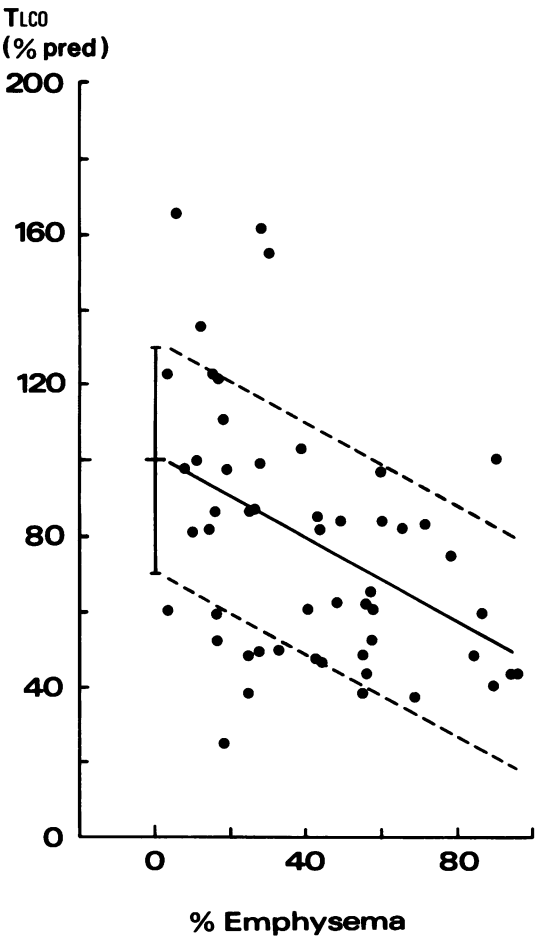

Fig 2 *Regression of steady state gas transfer factor (TLCO), expressed as a percentage of the predicted normal value, on emphysema grade ($r^2 = 0.19$). Bars indicate one standard deviation. Data from Thurlbeck et al.*[42]

In an earlier study by Thurlbeck and colleagues[42] steady state diffusing capacity (transfer factor) measurements showed a significant decrease with increasing emphysema grades, but there was considerable variability (fig 2). Among subjects with "mild" emphysema (grades 5–20), transfer factor was less than 80% of the predicted normal in four of 16 cases (25%), while for "moderate" (grades 20–60) and "severe" (grades > 60) disease the corresponding proportions of abnormal transfer factor measurements were 15 out of 26 (58%) and seven out of 10 (70%) cases. The sensitivity of gas transfer factor in predicting the presence of mild to moderate emphysema was less in this study than in that of Paré *et al*,[31] but the use of a steady state rather than a single breath method may have been responsible for this difference.

Although reduction in single breath gas transfer factor is related to the presence of emphysema and correlates with the more complex measurement K, there are limitations to the use of transfer factor in determining which smokers may have emphysema. Gas transfer factor is influenced by diseases other than emphysema, and, more importantly, it is systematically decreased in most "healthy" smokers (being about 10–20% less on average than that of non-smokers).[43-47] The reason for this general decrease in transfer factor is unknown; but it appears to be a "step" effect, occurring even in young smokers within a year or two of starting smoking, and it may be partly reversible on stopping smoking.[43-47] Although an asymptomatic increase in alveolar size might explain some of this abnormality in transfer factor, the generalised finding is inconsistent with the relatively small proportion of "healthy" smokers (perhaps 20%) who have abnormally increased lung distensibility.[48] If gas transfer factor is to be used as a screening test for emphysema in smokers, the systematic difference from non-smokers should be allowed for and comparisons should be made with values obtained from "healthy" smokers rather than a non-smoking population.[43]

The exponential constant K is at present the optimum lung function test for detecting emphysema during life, and the development of an on line computerised measurement system[49] has made this approach simpler and more generally applicable than previously. Although pressure-volume curves have been used in several epidemiological studies,[48 50-52] this complex test, which requires the swallowing of an oesophageal balloon, is unlikely to gain general acceptance for screening purposes. As a diagnostic and research tool, however, it has great power to detect "early" emphysematous changes and to discriminate between loss of lung elasticity and increased airway resistance as the principal cause of airflow obstruction in a given individual.[25] Its wider applica-

tion might throw more light on the early stages of the development of chronic airflow obstruction.

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