Emphysema in Lung Macrosections Correlated with Smoking Habits

Abstract. *The relationship between smoking and pulmonary emphysema was explored in 71 autopsies, by correlating Gough-Wentworth lung macrosections with smoking histories. An increasing percentage of smokers was found with each increment of emphysema. Particularly close relationship was observed between centrilobular emphysema and smoking. No definite association was found between smoking and panlobular emphysema.*

A number of reports have implicated smoking in the development of pulmonary emphysema. Most investigators have relied on tests of pulmonary function to quantitate the extent of disease (*1*). Such an approach is necessary and quite valuable in living subjects and comprehensive epidemiological studies. On the other hand, the frequent discrepancy between physiological criteria and anatomical changes has been stressed (*2*). A basic morphological concept of emphysema, where possible, has been generally considered more desirable.

In a more direct approach to the problem, others have investigated smoking in conjunction with structural lung defects. Thus, Auerbach and co-workers assessed various histological alterations and found rupturing of the alveolar septa and alveolar fibrosis to be highly associated with cigarette smoking (*3*). Both of these are characteristic of emphysema. Thurlbeck also observed a close connection between smoking and morphological severity of emphysema (*4*). Previously, we found abnormal proliferative bronchial epithelial changes occurring with emphysema (*5*), similar to those described by Auerbach and colleagues as following exposure to cigarettes (*6*). Despite such data, there remains uncertainty concerning the role of tobacco in the genesis of the affection. In the recent report on *Smoking and Health* from the office of the U.S. Surgeon General, it was concluded that "a relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal" (*7*).

The purpose of the investigation reported herein was to analyze smoking habits in relation to severity and type of emphysema in a series of necropsies selected at random. Single lungs from 71 routine autopsies on mature adults were used. Smoking histories, in varying degrees of completeness, were available in all instances. All subjects were Caucasians dying of a variety of causes in two private general hospitals (*8*) serving the community of Jacksonville, Florida. The age range was 40 to 97 years with a mean age of 67.2 years. Utilizing the technique of Gough and Wentworth (*9*) we prepared paper-mounted, sagittal whole-lung sections from each lung at three approximately equally spaced locations: (i) at the level of the hilus, (ii) midway between the hilus and the lateral aspect of the lung, and (iii) near the lateral margin of the lung. This resulted in a total of 213 sections for the 71 subjects. Each section was examined according to a method currently being used in our laboratory, whereby the section, without knowledge of the case identity, is matched against a panel of preselected standards. A scale of 0 to 6 was used.

A designation of 0 indicated no discernible emphysema, and grades of 1 through 6 steady increments in severity from slight to extreme disease. A grade of 3, for example, reflected about 50 percent parenchymal destruction in a particular sample and a grade of 6, practically "no" functionable lung. In each of the separate categories of severity, several examples of varying distribution and type were included. It was thus nearly always possible to match an unknown with a standard of comparable disease. The general severity of emphysema in the lung of an individual was then computed as the mean of the three separate, equally spaced, sagittal whole lung sections.

The mean grades were divided into categories. I, No emphysema—subjects with no grossly discernible emphysema in any of the three whole lung sections. II, Mild emphysema—subjects with a mean of 1.0 to 2.0 units of emphysema. III, Moderate emphysema—subjects with a mean of 2.0 to 4.0 units. IV, Severe emphysema—subjects with a mean of 4.1 to 6.0 units of emphysema.

The pathological type of emphysema was judged in every affected lung sample as panlobular (emphysematous changes distributed diffusely throughout the secondary pulmonary lobules), centrilobular (emphysematous changes located around the centers of the secondary lobules) or mixed (*10*). The mixed variety was subdivided into mainly panlobular and mainly centrilobular. For making statistical comparisons at the local tissue level, mainly panlobular was then combined with "pure" panlobular emphysema samples and mainly centrilobular with the centrilobular specimens. The mean grades were divided into categories: I, No emphysema—samples with grading of 0. II, Mild emphysema—grades of 1 and 2. III, Moderate emphysema—grades of 3 and 4. IV, Severe emphysema—grades 5 and 6.

Smoking histories were obtained from next-of-kin of each individual by means of a questionnaire technique. This was necessitated by the notorious unreliability and frequent omission of smoking data in clinical records of critically ill patients. Conceivably, relatives of people with specific smoking habits or diseases might have been more responsive to inquiry than others, thus introducing an element of bias into the sample. This apparently was not the case, however. A comparison of the frequency distribution with respect to emphysema severity in the 71 subjects in this study of smoking proved to be statistically comparable to that of a larger group of subjects from our hospital comprising an investigation on

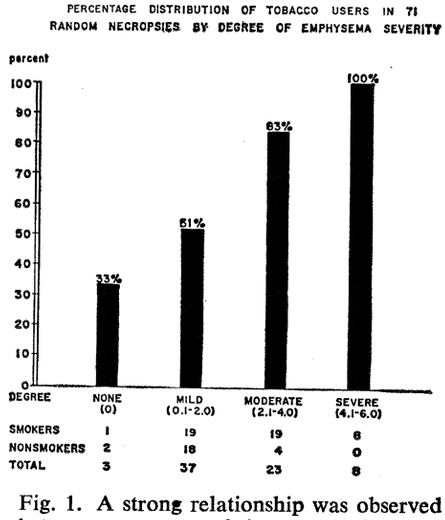

Fig. 1. A strong relationship was observed between percentage of cigarette smokers and increments of emphysema ($.005 > p > .001$ with Chi square test).

Table 1. Comparison of mean severity of emphysema in 71 male and female smokers and nonsmokers.

Men		Women	
Smokers	Non-smokers	Smokers	Non-smokers
Number			
35	4	12	20
Mean degree of emphysema			
2.8	1.5	1.9	1.0
t-Test			
1.6049		2.1951	
Probability			
$.20 > p > .10$		$.05 > p > .02$	

lung morphology ($.75 > p > .50$ with Chi square test).

In this analysis of 71 subjects, there were 47 individuals who smoked regularly during their lifetimes. They had a mean of 2.6 units of emphysema in comparison to a mean of 1.1 units for the 24 nonsmokers, well over a twofold difference ($.001 > p$ with t-test). If smoking was associated with the development of emphysema in this study, as these figures suggested, an increasing percentage of smokers might be expected in each increment of emphysema severity. The outcome of this type of analysis is demonstrated in Fig. 1. It is noteworthy that only a third of the individuals with no grossly discernible emphysema were smokers, half with mild emphysema were smokers, most with moderate emphysema smoked, and every one of the subjects with severe disease were smokers ($.005 > p > .001$ with Chi square test).

The males of this investigation showed a mean of 2.7 units per subject; whereas the females had a mean of 1.4 units. In view of this sex difference, the observed differential between the smokers and nonsmokers conceivably might have been overstated with respect to emphysema. On the other hand, the sex difference might well have been, at least in part, a smoking difference. To elucidate this phase of the problem, the mean grades of emphysema of smokers and nonsmokers for men and women were computed (Table 1). Here, the female smokers had about twice as much emphysema as the female nonsmokers ($.05 > p > .02$ with t-test). A similar trend was observed for the men, although the difference was somewhat above an acceptable probability level ($.20 > p > .10$ with t-test).

An effort to correlate specific smoking habits with emphysema was made. In general, the separate categories of smokers were too small to permit statistical comparisons but certain items deserve brief comment. Of nine subjects who were either current or former pipe or cigar smokers, five had mild emphysema, four showed moderate disease and none had severe emphysema, suggesting a weaker association between pipes and cigars and emphysema than with cigarettes and emphysema. Half of the eight subjects with severe emphysema had smoked cigarettes for at least 10 years, but gave them up a year or more prior to the terminal illness. Only 50 percent of these individuals with severe disease continued to smoke up until the last illness. In contrast, individuals with mild and moderate emphysema usually smoked up until the time of their terminal sickness. The patients with advanced disease may have discontinued smoking on their physicians' advice or they may have been too sick to smoke. In any event, such circumstances are compatible with the view that parenchymal lung damage from smoking is largely irreversible.

Table 2. Relation between smoking and pathological type of emphysema in the affected whole lung samples. Percentages are shown in parentheses. Three equally spaced sagittal sections were taken from each subject. $.001 > p$, based on Chi-square comparison of panlobular and centrilobular variants.

Tobacco use	Pathological type of emphysema		Total samples
	Panlobular*	Centrilobular†	
Smokers	62 (53)	54 (98)	116 (68)
Nonsmokers	54 (47)	1 (2)	55 (32)
Total samples	116 (100)	55 (100)	171 (100)

* Panlobular and mainly panlobular. † Centrilobular and mainly centrilobular.

The association between smoking and lobular localization in individual lung samples is demonstrated in Table 2. To further test the intrinsic relationship between smoking and the two morphological variants, the frequency distribution by severity of the pathological types of emphysema in the 116 affected whole lung samples from smokers was determined. The majority of the mildly affected samples were of the panlobular or mainly panlobular type. Most of the severe samples of emphysema were centrilobular and mainly centrilobular ($.001 > p$). Hence, centrilobular emphysema appeared to be primarily a disease of smokers and became increasingly prevalent in the more severe examples of disease.

Finally, the pathological type of emphysema was related to severity in the subjects who did not smoke. In nonsmokers, there were 55 whole-lung sections with emphysema; 44 of these were judged to be mild and panlobular or mainly panlobular emphysema, and 10 were moderate in degree and consisted only of panlobular or mainly panlobular disease. There was only one specimen with centrilobular emphysema in the nonsmoking group and this was mild ($.001 > p$ with Chi square test).

Our findings support the notation in *Smoking and Health* (*7*) that "a relationship exists between pulmonary emphysema and cigarette smoking." In this study, there is strong indication that smoking is related in particular to the development of centrilobular emphysema. No strong relationship was noted between panlobular emphysema and smoking. Certainly there are other causative factors for emphysema besides cigarette smoking, but this study indicates such smoking to be a major factor in the development of a large proportion of cases of emphysema.

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