the nonsmoking controls. No relationship of this increased prevalence could be demonstrated to alpha$_1$-antitrypsin deficiency (see below). In addition, nonsmoking relatives and smoking controls were observed to show approximately the same prevalence of abnormalities. However, due to the large proportion of females in the nonsmoking relative group and to the clustering of two-thirds of the affected relatives in 10 families, firm conclusions cannot at present be drawn from this study concerning the relative contributions of smoking and of heredity to the pathogenesis of COPD.

In order to determine the relative significance of smoking and heredity in the pathogenesis of COPD, Cederlof, et al. (*45, 46*) have used the twin-study methods on registries in both Sweden and the USA. The specific details of this method are described in the section on Coronary Heart Disease. As may be noted from a summary of their work at the end of table A2, the authors compared the symptom prevalence among monozygotic and dizygotic twins who were both discordant and concordant for smoking habits. They observed that the hypermorbidity for COPD symptoms related to smoking persisted even after controlling for zygosity and concluded that a causal relationship of smoking and COPD symptoms was supported. However, genetic factors were still found to have an appreciable influence. Lundmann (*159*) has applied this method to the study of pulmonary function. He studied 37 monozygotic and 62 dizygotic twin pairs, measuring forced expiratory volumes and nitrogen washout gradients, and matched the various pairs for smoking discordancy. He observed that both of these parameters were adversely affected in twins who smoked and that these changes were correlated with cigarette consumption. The results are outlined at the end of table A3.

Alpha$_1$-antitrypsin (A_1AT)—Of more recent note and discussion has been the discovery of an association between a hereditary predisposition to COPD and the relative or absolute absence of alpha$_1$-antitrypsin, a serum glycoprotein enzyme. Eriksson (*78*) was the first investigator to observe a relationship between the presence of markedly decreased serum trypsin inhibitory capacity and panlobular emphysema. Since Eriksson's paper, much added research has been published concerning many facets of this intriguing area.

It appears that A_1AT deficiency is inherited as an autosomal recessive trait (*78, 216*) although Kueppers (*143*) considers the transmission to be by an autosomal codominant allele. It has been estimated that up to 5 percent of the general population may be heterozygous for this gene (*154*) although full cross-sectional studies of the population remain to be done.

Homozygous or severe deficiency of this enzyme has been asso-

ciated with a particular type of pulmonary emphysema. While the majority of lungs of emphysematous patients reveal bullous or centrilobular deformities, particularly of the upper lobes, this hereditary disorder reveals a panacinar change, most severe in the lower lobes (*101, 215, 226*). Patients with emphysema who are found to have the homozygous deficiency have been observed to include a greater percentage of female patients than is usually observed in the general emphysema population. Their disease begins earlier, is more severe, is characterized by dyspnea rather than cough, and frequently is unassociated with a history of preceding bronchitis (*101, 215, 226*). Radiographic studies of A_1AT-deficient patients have revealed decreased vascularization of the lower lobes and increased vascularization of the upper lobes (*101, 213*). It is estimated that between 1 and 2 percent of patients with COPD have this homozygous deficiency (*78, 216*). In family studies, it has been found that almost all the homozygous individuals are symptomatic by the age of 40 and that those who are not usually show alterations in pulmonary function studies. Guenter, et al. (*98*) studied 7 persons with homozygous deficiency. Of the five symptomatic individuals, 4 smoked and all had abnormal timed vital capacity. Neither of the two asymptomatic individuals smoked or had this change in vital capacity. All 7, however, were noted to be hypoxemic at rest and to have decreased pulmonary diffusing capacity.

It has been suggested (*154*) that the lack of this proteinase inhibitor in the serum of homozygous patients predisposes them to emphysema in the following manner: Leukocytes present in the blood contain significant amounts of proteinase enzymes as part of the overall defense mechanism against infection; the breakdown of these cells during acute infection releases proteinases into the pulmonary tissues and these, without the presence of a normal inhibitor, may contribute to the breakdown of the structural proteins of lung tissue.

Heterozygous individuals have been defined as those who show levels of A_1AT intermediate between those of normals and those with homozygous deficiency. At the present time, there is much debate about whether or not heterozygotes for A_1AT are at a greater risk of developing COPD than are A_1AT normals. A major difficulty is the lack of a precise definition of heterozygosity. At present, the best method for the determination of the level of A_1AT appears to be that of crossed serum immunoelectrophoresis because levels of trypsin inhibitory capacity (TIC) have been shown to rise acutely with infections.

Welch, et al. (*226*) feel that heterozygotes do not show an increased susceptibility to COPD. The heterozygotes which they studied showed symptoms of bronchitis and did not present the

lower lobe perfusion defects frequently noted in homozygotes. They also found no difference in the number of COPD patients among the heterozygotic and the general population. Other investigators, notably Lieberman, et al. (*154, 155*), Kueppers, et al. (*144*), and Larson, et al. (*148*) found significantly increased percentages of COPD patients among those with heterozygous deficiency as compared with the general population. Lieberman, et al. (*155*) observed that the percentage of heterozygotes among a group of healthy industrial workers was 4.7 percent while that among a group of patients with emphysema was 18.1 percent. In a recent review, Falk and Briscoe (*79*) considered that the available evidence points to an increased prevalence of COPD among heterozygotes.

Of more central interest to this discussion, however, is the possible relationship of smoking to the predisposition of disease among the heterozygote population. Kueppers, et al. (*144*) studied three populations: younger controls, older controls, and a group of COPD patients. They observed that of the 25 heterozygotes with COPD, only 2 were over 70 years of age, both were female and nonsmokers. The remaining 23 were cigarette smokers. Nevertheless, studies which adequately sort out the factors of genetic susceptibility and cigarette smoke exposure have yet to be reported.

An important question is to what extent the relationship between smoking and COPD is influenced by identifiable genetic factors. At present, it is possible to identify what appears to be only a very small group of susceptibles for whom genetic factors may be paramount in the pathogenesis of their ailment. Of greater public health import is whether lesser degrees of genetically identifiable susceptibility interact with cigarette smoking to account for a significant proportion of the problem.

Air Pollution

Numerous epidemiological studies have been conducted in order to examine the effect of air pollution on human nonneoplastic respiratory disease. Three major types of studies have been utilized: observation of the mortality and morbidity due to an acute episode of increased air pollution, observation of the day-to-day variation in mortality and its relation to air pollution levels, and geographical comparisons. The majority of studies fall into the third category, and these are detailed in table A6.

A number of studies did not show an association among air pollution, respiratory symptoms, and pulmonary dysfunction (*81, 204*). More recent studies which evaluated the factors of smoking, social class, and air pollution separately noted a greater prevalence of

COPD symptoms, pulmonary dysfunction, and COPD mortality in areas of high pollution (*12, 122, 146, 233*). Lambert and Reid (*146*) observed that in the absence of cigarette smoking the correlation between COPD symptoms and air pollution was slight and suggested that the two factors may interact to produce higher rates of disease.

The evidence which has accumulated in the past 7 years gives further support to the conclusion of the Surgeon General's Advisory Committee on Smoking and Health as stated in its 1964 Report that: "For the bulk of the population of the United States, the relative importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than atmospheric pollution or occupational exposures."

Occupational Hazards

Exposure to various dusty occupational environments has been shown in many studies to be associated with the development of various forms of nonneoplastic lung disease. Lowe (*158*), in a review of the relationship of occupational exposure and chronic bronchitis, noted that among workers exposed to dust significant increases in COPD mortality were observed. These occupations included coal mining, tinning, galvanizing, riveting, and caulking. Commenting on a previously unreported study of more than 20,000 steel workers, he observed that the relationship between mean dust exposure levels and COPD prevalence was much stronger among smokers than among nonsmokers.

More recently, Bouhuys and Peters (*37*) reviewed those specific industrial exposures related to lung disease. COPD was found to be associated with exposure to coal dust, asbestos, bagasse dust, isocyanates, various irritant gases, and textile dusts (cotton, flax, or hemp).

Studies which have investigated the interrelationship between smoking, industrial exposure, and COPD are listed in table A7. Additional compounds, not listed in the table, but which also appear to be related to COPD, are chlorine (*49*) and washing powder dust (*97*). Cigarette smoking and harmful dust exposures appear to act in a combined manner in the production of COPD.

Although an increased prevalence of COPD is found with certain occupational exposures, in none is the relationship as strong as that between COPD and cigarette smoking. To demonstrate an increased occupational risk, careful analysis of smoking habits is required. The relative importance of cigarette smoking appears to be much greater than occupational exposure as an etiologic factor in COPD.

Cadmium—Chronic industrial exposure to cadmium in man has been found to induce pulmonary emphysema without significant accompanying chronic bronchitis (*34, 35, 210*).

Nandi, et al. (*177*) recently investigated the contribution of the cadmium in cigarette smoke to the pathogenesis of emphysema. Analyzing whole cigarettes, ash, and filters, they found that an average of 69 percent of the cadmium present in the cigarette (approximately 16 micrograms 20 cigarettes) is inhaled in the smoke. In a related study (*153*), these investigators showed that the level of cadmium in water-soluble liver protein on autopsy was three times greater in those patients with a history of chronic bronchitis/emphysema than that found in those without such a history. Unfortunately, no smoking histories were available.

PATHOLOGICAL STUDIES

The relationship between smoking habits and pathological changes in the bronchial tree and pulmonary parenchyma has been investigated by several groups of workers. Metaplastic changes, although found in nonsmokers, are much more common in smokers (table 10, Cancer Chapter), and a dose-relationship of increasing metaplasia with increased smoking has been evident in many of the studies.

Pathological studies which deal primarily with pulmonary parenchymal and non-metaplastic bronchial changes are presented in table 8. Goblet cell distention, alveolar septal rupture, thickened bronchial epithelium, and mucous gland hypertrophy have been found to be more frequent in smokers than in nonsmokers. Auerbach, et al. (*17*) noted a dose-response relationship between the amount of smoking and the degree of septal rupture.

Anderson, et al. (*4, 5*) studied the difference in the type of emphysema shown by smokers and nonsmokers. In their study, listed in table 8, they noted that the group of patients with panlobular emphysema was comprised of equal numbers of smokers and nonsmokers while of patients with centrilobular emphysema, 98 percent were smokers. More recently, the same authors studied lung macrosections from 80 nonsmokers. While most were normal, 24 demonstrated parenchymal dilatation and disruption consistent with panlobular emphysema. Thurlbeck, et al. (*217*) have also observed that centrilobular emphysema rarely occurs in nonsmokers.

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking*[1]

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results	Comments
Chang, 1957, U.S.A., Korea (47).	62 males and 43 females autopsied within 5 hours of death (no data available on case selection).	*Distention of goblet cells (by percent of smoking group)* *None* / *Few* / *⅓ of surface* / *½ of surface* / *Most of surface* / *Whole surface* NS(22) . 13.6 / 22.7 / 31.8 / 22.7 / 9.1 / .. SM(49) . 12.2 / 10.2 / 10.2 / 18.4 / 26.5 / 22.5	The authors also noted that smokers' lungs showed shorter cilia and thicker epithelium (20 percent nonsmokers and 36 percent smokers had respiratory disease.)
Ide et al., 1959, U.S.A. (*123*).	93 males autopsied within 6 hours of death. No cases of pneumonia or lung disease included.	*Mean thickness of tracheal and bronchial epithelium (μ) in cigarette smokers and nonsmokers* / *Mean ciliary height in trachea and bronchus on cigarette smokers and nonsmokers* *Trachea* / *Bronchus* / *Trachea* / *Bronchus* NS(23) ..... 52.8 / 47.7 / (23) 6.39 / 5.95 Light(31) ..... 62.0 / 57.5 / (29) 5.62 / 5.40 Heavy(10) ..... 66.2 / 61.9 / (10) 4.89 / 4.66	No cigar or pipe smokers were included.
Auerbach et al., 1963, U.S.A. (*17*).	654 males over 60 years of age autopsied at East Orange VA Hospital.	*Age-standardized percentage distribution of subjects according to degree of rupture of the alveolar septums* *Degree of rupture* / *0–0.25* / *0.5–0.75* / *1.0–1.25* / *1.5–1.75* / *2.0–2.25* / *2.5–3.00* Never smoked ..... 19.4 / 50.5 / 24.0 / 3.6 / 1.6 / .. Current cigarette .... / .4 / 5.1 / 16.2 / 39.2 / 39.1 †Current cigar .... / 24.6 / 45.4 / 26.2 / 3.8 / .. †Current pipe ..... 5.4 / 23.0 / 53.5 / 15.9 / 2.2 / .. Current pipe, cigar ..... 4.8 / 7.6 / 46.5 / 33.6 / 7.5 / ..	The authors also noted a dose-response relationship between smoking and degree of rupture. †None had ever smoked cigarettes regularly.

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking* (cont.)

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results	Comments
Anderson et al., 1964, U.S.A. (5).	39 males and 32 females (Caucasians) undergoing routine autopsy (40-97 years of age.)	*Severity of emphysema (mean degree)* *Males*: NS(4) 1.5; SM(35) 2.8 (not significant) *Females*: (20) 1.0; (12) 1.9 ($p<0.05$)	The authors also noted that: Every person showing severe disease was a smoker. Among those with panlobular emphysema, there was an equal distribution of smokers and nonsmokers while among those with centrilobular emphysema 98 percent were smokers and only 2 percent were nonsmokers.
Anderson et al., 1966, U.S.A. (6).	107 males and 58 females autopsied for whom smoking data was available.	*Percentage distribution of tobacco users in 165 necropsies by degree of emphysema severity* None 36 (12/33) Mild 69 (58/84) Moderate 91 (30/33) Severe 93 (14/15) *Mean severity of emphysema* SM(114) 2.3; NS(51) 0.9 ($p<0.001$) Male(107) 2.2; Female(58) 1.2 ($p<0.001$) Never smoked 0.9 <20 cigarettes/day 1.9 20-40 cigarettes/day 2.4 >40 cigarettes/day 2.3	
Megahed et al., 1967, Egypt (165).	50 male patients with chronic bronchitis undergoing bronchial biopsy and lavage.	*Mucous gland hypertrophy* *Percent* NS 29 (2/7) SM 77 (33/43) ($p<0.02$)	

TABLE 8.—*Studies concerning the relation of human pulmonary histology and smoking* (cont.)

(Actual number of deaths shown in parentheses)

SM = Smokers. NS = Nonsmokers

Author, year, country, reference	Number and type of population	Results						Comments
			Degree of tracheal and bronchial arteriolar thickening (by percentage of smokers)					
			0.0–0.4	*0.5–0.9*	*1.0–1.4*	*1.5–1.9*	*2.0+*	
Auerbach et al., 1968, U.S.A. (*14*).	562 males autopsied at East Orange VA Hospital.	Never smoked (122)	46.1	39.3	13.3	1.3	..	
		<20 cigarettes/day (120)	11.7	22.0	33.6	28.4	4.4	
		20–40 cigarettes/day (254)	5.0	8.6	37.4	40.9	8.1	
		>40 cigarettes/day (66)	1.3	1.4	31.5	45.3	20.5	

[1] Numerous experiments detailing changes in bronchial epithelium are detailed tabularly in the Cancer chapter.

EXPERIMENTAL STUDIES

ANIMAL STUDIES

A number of investigators have studied the effect of the inhalation of cigarette smoke on the macroscopic and microscopic structure of the tracheobronchial tree and pulmonary parenchyma of animals. Studies dealing with metaplasia and cellular atypism of the trachea and bronchi are listed in table A16 of the cancer chapter. Studies more directly concerned with the pathology of COPD are listed in table 9. They show that cigarette smoke exposure is associated with changes similar to those found in humans with COPD, i.e., bronchitis, parenchymal disruption, alveolar septal rupture, alveolar space dilatation, and the loss of cilia and ciliated cells in the bronchial mucosa.

The investigations of Auerbach and his coworkers (*15, 16, 88*) have demonstrated by the use of both light and electron microscopy that dogs who inhale cigarette smoke through tracheostomas develop progressively more severe lesions of the bronchi and parenchyma with increased exposure to cigarette smoke. In electron microscopic studies of specimens taken from the lungs of dogs thus exposed to cigarette smoke, the following changes were observed: In 5 dogs sacrificed after only 44 days of smoking exposure, there was a proliferation of goblet cells as well as a partial loss of cilia in the lining cells, and in 5 dogs sacrificed after 420 days or more of exposure, the number of cell layers in the bronchial epithelium was found to be twice that of the nonsmoking dogs. Goblet cells and ciliated columnar cells were no longer present; instead, the surface was lined with columnar and cuboidal cells with stubby projections in place of cilia. Mitotic figures were frequently observed in the basal cells. These findings may be relevant to carcinogenesis as well as to the development of COPD.

In a long-term experiment, carried out by the same group, dogs were exposed to varying doses of cigarette smoke. Details of the experimental procedure have been outlined in the section on Pulmonary Carcinogenesis. The animals were separated into nonsmoker, filter-tip cigarette, nonfilter-light, and nonfilter-heavy exposure groups. The dogs were "smoked" for 875 days, or approximately 29 months. The animals which died during the experiment and the animals sacrificed after day 875 were examined for pulmonary parenchymal changes as well as for bronchial epithelial alterations. As seen in figures 1 and 2, dose-related pathological changes, including fibrosis and emphysema, were found in the lung parenchyma of the exposed dogs. These changes were similar to those seen in the lungs of humans with COPD.

TABLE 9.—*Experiments concerning the effect of the inhalation of cigarette smoke upon the tracheo-bronchial tree and pulmonary parenchyma of animals*[1]

(Actual number of animals shown in parentheses)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results
Leuchtenberger, et al., 1960, U.S.A. (*152*).	603 CF_1 female mice.	A. Inhalation. B. Up to 8 cigarettes/day for up to 2 years. C. Cigarette smoke.	*Number of mice showing specified changes* *Months exposure* / *Number of cigarettes* / *Number of mice* / *No change* / *Mild bronchitis* / *Severe bronchitis with atypism* 0 / 0 / 150 / 146 / 2 / 2 (no atypism) 1–3 / 100–200 / 36 / 20 / 9 / 7 4–8 / 250–500 / 36 / 19 / 10 / 7 9–23 / 600–1600 / 34 / 19 / 7 / 8 1–23 / 25–1526 / 151 / 88 / 33 / 30
Holland et al., 1963. (*123*).	60 rabbits.	A. Inhalation. B. Up to 20 cigarettes/day for 2–5. C. "Normal cigarette smoke".	*Cytology of tracheobronchial mucosa* *Normal* / *Focal hyperplasia* / *Generalized hyperplasia* / *Generalized emphysema* Controls ..... (30) 21/30 / 6/30 / 3/30 / 1/30 Exposed ..... (30) 7/30 / 10/30 / 9/30 / 11/30
Hernandez et al., 1966 U.S.A. (*111*).	Adult Greyhound dogs.	A. Inhalation. B. Twice daily/5 per week. C. Cigarette smoke.	*Number of sections* / *Mean number of months* / *Mean parenchymal disruption/dog* / *Groups compared* / *P-value* I. Controls ..... (8) 112 / .. / 0.7150 / I–III / insignificant II. All exposed ..... (15) 205 / 10.50 / 0.9383 / II–I / insignificant III. Exposed <1 year ..... (7) 98 / 4.60 / 0.6421 / III–IV / $p < 0.05$ IV. Exposed >1 year ..... (8) 107 / 14.74 / 1.2350 / IV–I / $p < 0.02$

TABLE 9.—*Experiments concerning the effect of the inhalation of cigarette smoke upon the tracheo-bronchial tree and pulmonary parenchyma of animals*[1] *(cont.)*

(Actual number of animals shown in parentheses)

Author, year, country, reference	Animal and strain	A. Type of exposure B. Duration C. Material	Results
Auerbach et al., 1967, U.S.A. (*15, 16*).	Beagle dogs.	A. Active inhalation via tracheostomy. B. Up to 12 cigarettes per day for up to 423 days. C. Cigarette smoke.	Controls ....(10)—No evidence of pulmonary fibrosis or septal rupture. Exposed ....(10)—*Early (sacrificed)*: 1. Alveolar space dilatation. 2. Pad-like attachments to alveolar septa. *Medium exposure*: Septal wall thickening. *Latest exposure*: 1. Focal subpleural pulmonary fibrosis. 2. Ruptured alveolar septa. 3. Granulomata.
Frasca et al., 1968, U.S.A. (*88*).	Beagle dogs.	A. Active inhalation via tracheostomy. B. Up to 12 cigarettes per day for up to 423 days. C. Cigarette smoke.	Electron microscopic results: After 44 days — Increased number of goblet cells. Decreased number of cilia on surface lining cells. After 420 days— Increased number of epithelial cell layers. Loss of ciliated columnar cells. Frequent interruptions in basement membrane.

[1] Numerous experiments detailing changes in bronchial epithelium are detailed tabularly in the Cancer Chapter.

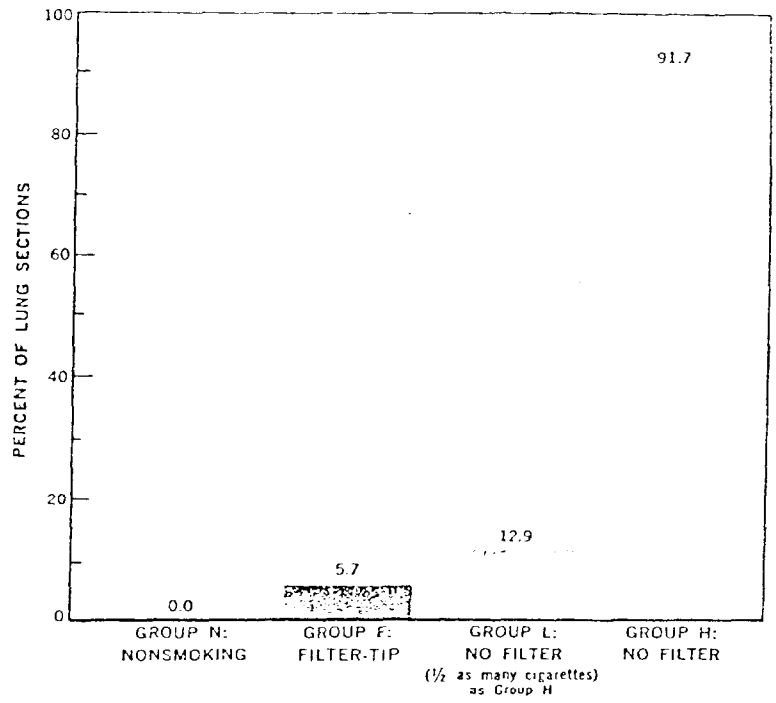

FIGURE 1.—Percent of lung sections with grade IV or V fibrosis.
SOURCES: Hammond, et al. (*104*).

Several investigative groups have exposed rodents to various ambient concentrations of nitrogen dioxide over prolonged periods of time. This gas is found in cigarette smoke and in some industrially polluted air. The results of these studies are outlined in table A10. It is clear that chronic exposure to low levels of NO_2 is capable of inducing lesions in the bronchial tree although the relationship between these changes, cigarette smoking, and the development of COPD remains to be determined.

Rosenkrantz, et al. (*196, 197*) have recently undertaken experiments dealing with pulmonary cellular metabolism. They exposed Swiss albino mice to cigarette smoke or its vapor phase for varying lengths of time. On autopsy, animals exposed to cigarette smoke showed elevations in the levels of lung DNA, lactate, and glycogen which the authors conclude reflect hyperplasia and macrophage infiltration. Similarly, a dose-related increase in lung hydroxyproline was observed. This was considered to be due to increased fibroblastic collagen synthesis.

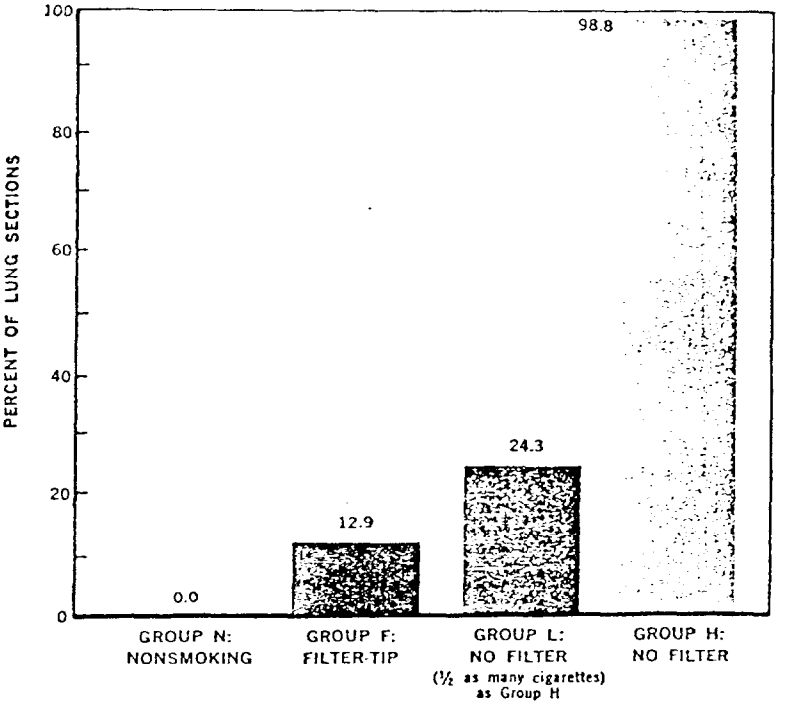

FIGURE 2.—Percent of lung sections with grade II or III emphysema.
SOURCES Hammond, et al. (*104*).

Aviado and coworkers have performed a series of experiments on live animals and in heart-lung preparations to study the effect of cigarette smoke on pulmonary physiology and structure (*18, 19, 20, 21, 22, 179, 180, 199, 200, 201, 202*). The authors observed that cigarette smoke causes acute bronchoconstriction both by the release of histamine and the stimulation of parasympathetic nerve pathways in the lung. Bronchial arterial injections of nicotine were found to cause reactions similar to those observed after cigarette smoke inhalation. The bronchoconstriction was usually followed by bronchodilatation which the authors attributed to sympathetic stimulation. As mentioned in the Chapter on Cardiovascular Diseases, nicotine has been shown to induce the release of catecholamines.

Experiments by Aviado and coworkers as well as other authors (*66, 99*) using guinea pigs showed that exposure to cigarette smoke was associated with increased bronchopulmonary resistance and decreased pulmonary compliance. The authors related these changes to the bronchoconstriction of terminal ventilatory units.

Similar experiments in dogs showed that the increase in resistance following either cigarette smoke exposure or intravenous nicotine could be blocked by pretreatment with atropine. As a parasympathetic blocker, atropine would decrease the acute bronchoconstrictive phase.

Most recently, Aviado and his colleagues (*20, 130*) have attempted to induce physiologic and anatomic changes similar to those found in the lungs of patients with emphysema. They exposed male rats to cigarette smoke, the introduction of the enzyme papain, as well as to partial tracheal ligation. In 10 rats exposed to cigarette smoke twice daily for 30 minutes over a period of 10 weeks, no changes in pulmonary compliance or resistance were noted. Also, no abnormal histological changes were observed in the group exposed only to cigarette smoke. However, animals who underwent tracheal ligation as well as smoke exposure showed increased numbers of enlarged air spaces and increased pulmonary resistance when compared with animals who underwent only tracheal ligation.

Studies in Humans

The acute effects of cigarette smoke inhalation on bronchopulmonary function in man have been investigated by a number of workers. The results of these studies are presented in table 11. The majority of studies, particularly the more recent ones, found that the inhalation of cigarette smoke is associated with an acute increase in pulmonary resistance and a decrease in pulmonary compliance. Chapman (*48*) also observed decreases in pulmonary diffusing capacity and arterial O_2 tension. Chiang and Wang (*51*) noted changes in nitrogen washout time and alveolar dilution factor, alterations which reflect impaired alveolar ventilation and gas mixing.

James (*131*) examined the effect of prior smoking on the multiple breath nitrogen washout test in 41 pneumoconiotic miners and 5 normal young males. Prior smoking of a cigarette in the subject's normal manner was found to adversely affect the indices of distribution in 20 percent of the miners and in all of the 5 normals who smoked within one hour of testing. The author suggests that smoking be prohibited prior to any series of pulmonary function studies.

Anderson and Williams (*9*) studied the acute effect of cigarette smoke inhalation upon the ventilation-perfusion (V/Q) measurements in the lung in normals and in patients with COPD. Cigarette smoking was observed to cause acute changes in the V/Q measurements, and the COPD patients were found to be particularly liable to these changes.

Finally, Robertson, et al. (*194*) studied the effect of unfiltered and filtered cigarette smoke and cigar smoke upon bronchial reactivity in 19 of the most reactive persons in a group of 91 heavy smokers. They observed that bronchial reactivity was significantly reduced by increasing the retention efficiency of the filter and that reactivity to inhaled cigar tobacco was no less than that to cigarette smoke. They concluded that differences in inhalation account for the difference in COPD prevalence observed between cigarette and cigar smokers.

Studies Concerning Pulmonary Clearance

Overall Clearance

The ability of the lung to rid itself of inhaled particles that cannot be easily exhaled is dependent upon a number of physiologic mechanisms including ciliary activity, the mucous sheath, and the pulmonary alveolar macrophage. Studies concerning the effect of human cigarette smoking and the exposure of animals to cigarette smoke on this clearance system are presented in table A13. LaBelle, et al. (*145*) and Bair and Dilley (*23*) observed no change in clearance following the exposure of rats, rabbits, or dogs to cigarette smoke. The latter authors noted, however, that normal clearance rates obtained prior to smoking were too low to reflect any significant change except complete cessation.

Albert, et al. (*3*) exposed donkeys to cigarette smoke via nasal catheter and observed impairment of clearance times. Holma (*125*) obtained similar results in rabbits.

In a related study, Albert, et al. (*2*) studied the bronchial clearance times of 9 nonsmokers and 14 cigarette smokers in a total population of 36 subjects. The rates of bronchial clearance were slower on the average in the cigarette smokers when compared with the nonsmokers, although a wide variation was present in each group. In relation to their study mentioned above, they also noted that the shape of the whole lung clearance curves seen in smokers (with markedly prolonged 50 percent clearance times) was similar to that developed in the donkey following acute exposures to sulfur dioxide or cigarette smoke.

Ciliary Function

Numerous experiments have shown that cigarette smoke or certain constituents of cigarette smoke adversely affect and can even bring about a cessation of ciliary activity in respiratory epithelium *in vivo* and *in vitro* in cultures of ciliated microorganisms. The results of a number of these experiments are presented in table 12.

Ciliary activity has been shown to be affected by particulate matter as well as by the gas phase components of cigarette smoke. The relative importance of these two large classes of components of smoke in producing ciliastasis is presently a matter of some discussion. Dalhamn and Rylander (*63*, *64*) consider the particulate phase to be of greater importance while Battista and Kensler (*28*, *29*) conclude that gas phase components are more important in the induction of ciliastasis.

Studies investigating the effect of cigarette smoke on the morphology of the tracheobronchial tree in animals have noted a decrease or absence in the number of cilia in smoke-exposed animals. Recently, Kennedy and Elliot (*134*) studied the effect of the direct exposure of cigarette smoke upon the electron microscopic structure of protozoan mitochondria. After 42 minutes of exposure to mainstream smoke, they noted destruction of the internal membrane structure of the mitochondria.

Thus, cigarette smoke has been shown to be toxic to ciliary function by pathological (including electron microscopic) and physiological methods.

Phagocytosis

The effect of cigarette smoke upon pulmonary alveolar phagocytosis, one part of the clearance mechanism, has been studied by several authors. Masin and Masin (*162*) observed increased variation in the size of lipid inclusions in sputum macrophages obtained from smokers as compared to those obtained from nonsmokers. They attributed these differences to a combined effect of irritation of the alveolar lining, increased turnover of alveolar cells, and increased injury to the macrophages. Green and Carolin (*96*) noted that cigarette smoke inhibited the ability of rabbit alveolar macrophages to clear cultures of *S. aureus*. This effect was noticeably reduced by filtration. Similarly, Yeager (*239*) exposed rabbit alveolar macrophages which had been induced by *M. bovis* to cigarette smoke and observed a dose-dependent decrease in protein synthesis. This alteration occurred at smoke solution concentrations that did not affect cell viability. The alteration was only partly reversible and was due mainly to gas phase components. Myrvik and Evans (*175*) observed similar protein synthesis alterations in macrophages exposed to NO_2.

Roque and Pickren (*195*) obtained alveolar macrophages at thoracotomy from 17 smokers and 4 nonsmokers. They found a decrease in the activity of oxidoreductases and hydrolases in the macrophages of smokers. The reduction in the enzymatic activity was directly proportional to the amount of stored fluorescent material present in the macrophages. This material was thought to

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Bickerman and Barach, 1954, U.S.A. (*31*).	I. 66 male and 25 female patients with chronic nontuberculous respiratory diseases (average age 50). II. 20 male and 7 female normal subjects (average age 20).	A. Pulmonary function. B. 3 cigarettes. C. 30 minutes.	*Vital capacity (VC)* I. 10/91 decrease. II. No significant change.	*Maximal breathing capacity* 10/91 decrease. No significant change.	9/91 patients showed VC increase due to clearance of secretions. All mild or moderate smokers.
Elch, et al., 1957, U.S.A. (*76*).	I. 31 patients with obstructive pulmonary emphysema. II. 14 normal subjects. III. 5 patients with respiratory complaints. All habitual smokers.	A. Esophageal balloon technique to measure pulmonary compliance and resistance. B. 1 cigarette. C. Undefined.	*Mean airway resistance* I. Statistically significant increase. II. No change. III. No change.	*Mean airway compliance* No change. No change. No change.	

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Attinger et al., 1958, U.S.A. (*15*).	I. 20 normal subjects (10 Sm, 10 NS). II. 34 patients with various diseases; 9 rheumatic heart diseases, 8 pulmonary emphysema, 7 asthma, 5 pulmonary fibrosis, 5 undefined.	A. Esophagal balloon technique to measure pulmonary compliance and resistance. B. 1–4 cigarettes. C. 10 minute interval between cigarettes.	I. No change. II. Expiratory resistance rose significantly only among patients with emphysema.	No change. No change.	
Motley and Kuzman, 1958, U.S.A. (*174*).	125 males and 16 females (24–70 years of age—normals and patients).	A. Pulmonary function. B. 2 cigarettes. C. Undefined.	41 smokers (8 normals, 33 patients with cardiopulmonary disease).	*Pulmonary compliance* Significant decrease after smoking.	Various groups of normals and cardiopulmonary patients showed little or no change in arterial pO_2 during exercise and at rest following cigarette smoke inhalation.
Nadel and Comroe, 1961, U.S.A. (*176*).	I. 22 patients with cardiopulmonary disease—all smokers. II. 36 normals (21 smokers, 15 nonsmokers).	A. Body plethysmography. B. 15 puffs. C. 5 minutes.	*Airway conductance/thoracic gas volume* I. 18/22 significant decrease (inhibited by pretreatment with isoproterenol aerosol). II. 31/36 significant decrease (inhibited by pretreatment with isoproterenol aerosol).		Nicotine bitartrate aerosol evoked no change.

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results		Comments
Simonsson, 1962, Sweden, (207).	I. 9 male and 7 female normals (*most smokers*). II. 15 male and 1 female pulmonary disease patients (*most smokers*).	A. *Pulmonary* function. B. 1-2 cigarettes. C. 5-6 minutes per cigarette.	*Mean* $FEV_{1.0}$ (*immediately after*) I. Significant decrease. II. Significant decrease.	*Mean* $FEV_{1.0}$ (*45 minutes later*) No significant decrease. Significant decrease.	No significant changes observed in FEV/FVC.
Zamel et al., 1963, England, (240).	I. 6 male and 6 female nonsmokers. II. 6 male and 6 female smokers (18–32 years of age.)	A. Body plethysmography. B. 1 cigarette. C. Undefined.	*Airway resistance* I. Significant increase. II. Significant increase.		
Chapman, 1965, Ireland (48).	I. 12 normal volunteers (all smokers). II. 6 patients with chronic non-specific lung disease.	A. Pulmonary function Arterial blood studies. B. 1 cigarette. C. Undefined.	I. All showed a decrease in diffusing capacity. II. 4/6—significant decrease in arterial 0_2 tension. No change in vital capacity or FEV.		
McDermott and Collins, 1965, Wales (160).	I. 32 normals. II. 28 with chronic bronchitis (All cigarette smokers 35–60 years of age.)	A. Body plethysmography. B. Cigarette. C. Undefined.	*Mean airway resistance* I. Significant increase. II. Significant increase.		Light smokers showed greater changes than heavy smokers.

TABLE 11.—*Experiments concerning the acute effect of cigarette smoke inhalation on human pulmonary function (cont.)*

Author, year, country, reference	Number and type of population	A. Method [1] B. Material [1] C. Duration of smoking	Results			Comments
Miller and Sproule, 1966, U.S.A. (*166*).	10 normal cigarette smokers (40 years of age).	A. Esophageal balloon technique. B. 1 cigarette. C. One inhalation every 30–60 seconds.	$FEV_{0.5}$ No significant change	*Dynamic compliance* Significant decrease.	*Inspiratory and expiratory resistance* Significant increase	
Sterling, 1967, England (*213*).	11 normal adults (8 smokers, 3 nonsmokers).	A. Body plethysmography. B. 15 inhalations. C. 5 minutes.	*Airway resistance* Significant increase (Return to normal in 30 minutes).			
Chiang and Wang, 1970, Formosa (*51*).	7 male normal nonsmokers (18–43 years of age).	A. Pulmonary function Nitrogen washout. B. 2 cigarettes. C. Undefined.	*Nitrogen washout time* Significant increase.	*Lung clearance index* Significant increase.	*Alveolar dilution factor* Significant decrease.	All lung volumes, except for residual volume showed no significant change. No significant change in any of the flow rates.
Guyatt et al., 1970, England (*100*).	710 subjects; 508 smoked between measures 202 did not smoke.	A. Body plethysmography. B. 1 cigarette. C. Undefined.	*Bronchoconstriction* Significant increase with smoking.			On the average, nonsmokers and ex-smokers showed bronchodilation and smokers showed bronchoconstriction. The authors postulate that the result among nonsmokers is due to the release of adrenal hormones in these subjects.

[1] All the experiments listed concern studies of pulmonary function before and after smoking the epecified number of cigarettes (unless otherwise specified).

TABLE 12.—*Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance*

Author, year, country, reference	Subjects	Method	Results	Comments
Laurenzi et al., 1963, U.S.A. (*149*).	Swiss-Webster male mice.	Mice exposed to aerosol of *S. aureus* and sacrificed at intervals following exposure to various stimuli.	Significant increase in *S. aureus* retention in mice exposed to: (a) hypoxia—retention ratio 2.5 (10 percent 0_2). (b) cigarette smoke—retention ratio 4.5.	
LaBelle et al., 1966, U.S.A. (*145*).	Albino female rabbits.	Silver iodide or colloidal gold intratracheally.	17–30 hours of exposure to cigarette smoke caused no change in pulmonary clearance as compared with controls breathing room air.	
Bair and Dilley, 1967, U.S.A. (*23*).	Sprague-Dawley female rats, male beagle dogs.	Radioactive aerosol. Radioactive aerosol.	Acute exposure to cigarette smoke had no gross effect on clearance. Chronic exposure to cigarette smoke (up to 18–20 cigarettes/7 hour day/5 day week for up to 420 days) had no observable effects. The authors noted, however, that normal clearance rates were too low to reflect anything but complete cessation.	

Author, year, country, reference	Subjects	Method		*Number of subjects*	*Average age*	*50 percent clearance time (minutes)*	*90 percent clearance time (minutes)*	Comments
Albert et al., 1969, U.S.A. (*2*).	36 subjects undergoing 117 experiments.	Radioactive tagged $Fe0_2$ particles measured with Scintillation counter.	Nonsmokers	9	28	88	357	† Approximate values. None of 9 nonsmokers had 50 percent times over 200 minutes or 90 percent times over 600 minutes while 6/14 smokers exceeded both these limits.
			All smokers	14	33	172	†496	
			20–29 cigarettes/day	7	29	191	†519	
			30–40 cigarettes/day	7	36	153	†474	
			Uranium miners	3	52	310	580	
			Cigar and pipe smokers	4	46	87	376	
			Emphysema patients	2	66	330	575	

TABLE 12.—*Experiments concerning the effect of cigarette smoke on human and animal pulmonary clearance (cont.)*

Author, year, country, reference	Subjects	Method	Results						Comments
Albert et al., 1969, U.S.A. (*5*).	*Donkeys exposed* to cigarette smoke by nasal catheter.	Radioactive tagged $Fe0_2$ particles measured with Scintillation counter.	*Average number cigarettes in 2-hour period*	*Percent clearance*		*Halftime clearance*		*Tracheal transit time*		*Those donkeys exposed* to the greatest amount of smoke showed residual impairment of clearance for at least 2 months after acute exposure.
				Control	*Cigarette*	*Control*	*Cigarette*	*Control*	*Cigarette*	
			18–24	58	69	1.2	1.9	0.6	1.2	
			36	58	64	1.0	3.4	0.4	5.8	
Holma, 1969, U.S.A. (*125*).	Rabbits (anesthetized).	Cr^{51} monodisperse polystyrene aerosol.	Exposure to fresh cigarette smoke (1.5 cc. puffs, 40 puffs/8 minutes) caused a "significant" increase in lung retention 10 minutes following cessation of exposure.							

originate in tobacco smoke. The authors suggested that the tobacco smoke may have induced abnormalities in the mitochondria of the macrophage. In a study of pulmonary macrophages harvested by endobronchial lavage from smokers and nonsmokers, Pratt, et al. (*187*) observed that the macrophages of smokers contained an abnormal pigment.

These studies indicate that the function of pulmonary clearance carried on by the macrophage and ciliary systems is adversely affected by cigarette smoke.

Studies Concerning the Surfactant System

The surfactant system of the lung consists of various biologically active compounds such as phospholipids and mucopolysaccharides which are present in the alveolar lining. Normal pulmonary function is influenced and partly determined by the integrity of this system (*203*). The purpose of the surfactant system is to maintain the proper amount of surface tension in the alveoli so that the expansion and contraction of the alveoli are facilitated.

Studies concerning the effect of cigarette smoke upon the surfactant system and the surface tension of the pulmonary alveoli are presented in table A14. Exposure of rat and dog lung extracts to cigarette smoke has been found to induce a notable decrease in the maximal surface tension demonstrated by the extracts (*94, 165, 224*). Cook and Webb (*57*) observed that surfactant activity was diminished in smokers and in patients with pulmonary disease when compared with healthy nonsmokers.

Scarpelli (*203*) in a recent review, concluded that the lowering of maximal surface tension by cigarette smoke has been demonstrated reasonably well. The relationship of these findings to the pathogenesis of emphysema is unclear at this time.

OTHER RESPIRATORY DISORDERS

Infectious Respiratory Diseases

Several studies have examined the question of whether cigarette smokers are at an increased risk of developing infectious respiratory and bronchopulmonary disease. Table A15 presents a summary of these studies. Lowe (*157*) observed an excess of smokers among 705 tuberculosis patients, but Brown and Campbell (*43*) in a similar study found that the difference was not present when the cases and controls were matched for alcohol intake. More recent studies have been concerned with the frequency of upper respiratory infections among groups of smokers and nonsmokers. A number of investigators (*108, 181, 183*) have reported increased

rates of respiratory illnesses among smokers. Finklea, et al. (*83*) studied a male college population (prospectively) during the 1968–69 influenza epidemic. They found that smokers of all amounts experienced more clinical illness than did nonsmokers and that this relation was dose-dependent. Similarly, smokers required more bed rest than nonsmokers.

A survey conducted by the National Center for Health Statistics (*220*), involving approximately 134,000 persons, showed that male cigarette smokers reported 54 percent more cases of acute bronchitis than males who had never smoked cigarettes, while female smokers reported 74 percent more acute bronchitis than did females who had never smoked. Male cigarette smokers reported 22 percent more cases of influenza than did males who had never smoked cigarettes, while the female smokers reported an excess of 9 percent.

Experimental evidence in support of this relationship has been noted by Spurgash, et al. (*211*). Mice were challenged with *Klebsiella pneumoniae* or *Diplococcus pneumoniae* before or after a single exposure to cigarette smoke. They observed that those animals exposed to smoke exhibited a decrease in resistance to respiratory infection, as shown by an increase in mortality and a decrease in survival time. Preexposure to cigarette smoke was found to have no significant effect on resistance of mice to influenza infection initiated by aerosol exposure. However, exposure of infected mice to smoke resulted in significantly higher mortality, thus suggesting that cigarette smoke can aggravate an existing respiratory viral infection.

In the light of the experimental evidence presented above concerning the effect of cigarette smoke on pulmonary clearance, phagocytosis, and ciliary function, it seems reasonable to conclude that such changes in tracheobronchial physiologic function would predispose a person to respiratory infections or aggravate already existing ones.

Further evidence is derived from the work of Henry, et al. (*109*) and Ehrlich, et al. (*75*). These investigators exposed squirrel monkeys to atmospheres containing 10 and 5 p.p.m. of nitrogen dioxide. They observed that this exposure increased the susceptibility of the animals to airborne *Klebsiella pneumoniae* as demonstrated by increased mortality and reduced lung clearance of viable bacteria. Infectious challenge with influenza virus 24 hours before exposure to 10 p.p.m. was fatal to all monkeys within three days. Infected controls showed symptoms of viral infection but did not succumb to the infection. The extent to which the various oxides of nitrogen present in cigarette smoke contribute to the increased susceptibility to respiratory disease noted in smokers is presently undefined.

Postoperative Complications

Several studies have been published which examine the questions of whether smokers run an increased risk of developing postoperative pulmonary complications over nonsmokers undergoing similar operations.

Morton (*173*) reported on a study of more than 1,100 patients undergoing abdominal operations in which he found that cigarette and mixed smokers were significantly more likely to develop bronchitis, bronchopneumonia, or atelectasis during the postoperative period than nonsmokers (table A16).

Wiklander and Norlin (*229*) examined the incidence of postoperative complications in 200 patients undergoing laparotomy in the winter months when it was expected that pulmonary complications would be at their maximum. These authors found no significant differences between the frequency of complications in smokers and nonsmokers. No information about the definition of a smoker and no data on dosage of tobacco smoke were reported.

Piper (*186*) observed the prevalence of postoperative pulmonary complications in 150 patients undergoing laparotomy. Of the total sample, 66.7 percent developed pulmonary complications during the first postoperative week. All patients considered in the statistical analysis as having pulmonary complications had radiographic evidence of disease. Of the cigarette smokers, 73.5 percent had complications as compared to 55.5 percent of the nonsmokers. When the smokers were divided according to dosage, heavy smokers being those consuming more than 10 cigarettes per day for the previous six months, 55 percent of light smokers and 88 percent of heavy smokers were considered to have postoperative complications. Piper also reported that stopping smoking for up to four days preoperatively had no apparent effect on the incidence of complications.

Wightman (*228*) reported on the incidence of postoperative pulmonary complications in 455 patients undergoing abdominal operations and in 330 patients undergoing other operations. Of the cigarette smokers, 14.8 percent developed complications as compared to 6.3 percent of the nonsmokers. The substantial difference between these figures and those of Piper (*186*) is due to the latter's use of radiographic criteria alone. Wightman utilized only clinical criteria.

Morton (*172*) has recently reported a study of postoperative hypoxemia in 10 patients, 5 of whom were cigarette smokers. Four of the smokers had chronic bronchitis. He found that the smokers had a more pronounced decrease in arterial oxygen saturation, persisting into the second postoperative day (table A17).