identify groups of people who may have a greater sensitivity to the carcinogenic effect of cigarette smoke. Interest has developed in the possibility that aryl hydrocarbon hydroxylase (AHH) may be a genetically determined enzyme that mediates such increased susceptibility to certain environmental carcinogens.

AHH is an enzyme system which metabolizes polycyclic aromatic hydrocarbons; some of the resulting metabolites are carcinogenic. It has been postulated that persons with high levels of this enzyme may be at greater risk of developing cancer from exposure to the polycyclic hydrocarbons in cigarette smoke than those with low levels.

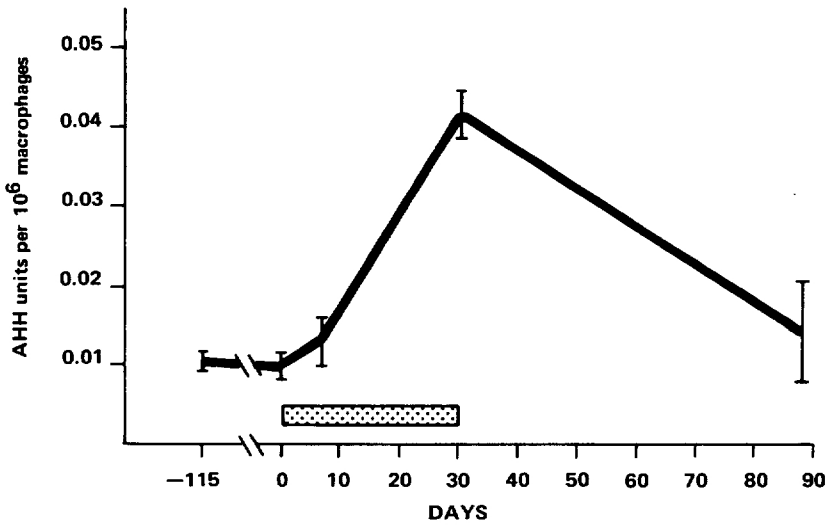
The amount of AHH produced in response to an inducing stimulus can be used to separate a population into three groups (those capable of being induced to produce high, medium, and low levels of AHH). Kellerman, et al. (*8*) studied the induction of AHH activity in 353 healthy subjects (67 families with 165 children). They felt that the enzyme was controlled by a single gene locus with two alleles (one able to be induced to produce high AHH levels with a gene frequency of .283 and one, to produce low levels with a gene frequency of .717). All six possible crossmatings were found in the families studied, and no deviations from the expected phenotypes were found in the children.

Cantrell, et al. (*2*), studied 19 healthy volunteers and found that cigarette smokers had higher levels of AHH in their pulmonary aveolar macrophages than nonsmokers. In one subject they showed an increase in AHH activity starting 1 week after he began to smoke 10 to 15 cigarettes per day (*2*, Fig. 1). Holt and Keast (*7*) also showed increased levels of AHH activity in homogenates of lung tissue from mice exposed to cigarette smoke.

Kellermann (*9*) also studied the inducibility of AHH in the lymphocytes of 50 patients with bronchogenic carcinoma and compared them to a healthy white population and to a group of patients with nonrespiratory malignancies (Table 3). They found that lung cancer patients had a statistically significant, higher percentage of persons homozygous for the high allele, i.e., able to be induced to high AHH levels, than either the healthy or tumor controls. They postulated that the reason for the greater frequency of persons homozygous for the high AHH inducibility allele in the lung cancer group was that this group was more susceptible to lung cancer due to their increased ability to convert polycyclic aromatic hydrocarbons into carcinogenic metabolites. The incidence of lung cancer,

however, does not show a markedly familial occurrence pattern; therefore, a single genetic locus can not be the major factor determining susceptibility. Persons with increased ability to metabolize polycyclic aromatic hydrocarbons may well be a group at increased risk of developing lung cancer if they smoke; however, prospective studies of random populations controlled for smoking and environmental factors will be necessary before this genetic susceptibility can be confirmed.

FIGURE 1.—Production of aryl hydrocarbon hydroxylase (AHH) in macrophages from one person in response to cigarette smoking



NOTE.—Shaded bar indicates duration of smoking; the vertical lines indicate the range of duplicate determinations at each time period.

Source: Cantrell, E.T., et al. (*2*).

TABLE 3. – *Aryl hydrocarbon hydroxylase (AHH) inducibility in patients with lung cancer, with other tumors, and in healthy controls*

GROUP	NUMBER IN GROUP	DISTRIBUTION OF GENOTYPES (PERCENT)[1]			GENE FREQUENCIES OF A AND B ALLELES	
		AA	AB	BB	A	B
Healthy control	85	44.7	45.9	9.4	0.676	0.324
Tumor control	46	43.5	45.6	10.9	0.663	0.337
Lung cancer	50	4.0	66.0	30.0	0.370	0.630

[1] AA = low inducibility; AB = intermediate inducibility; BB = high inducibility

Source: Kellerman, G., et al. (9).

SUMMARY OF RECENT CANCER FINDINGS

1. Filter cigarette smokers have a lower risk of developing lung cancer than nonfilter cigarette smokers, but that risk is still greater than the risk to nonsmokers and increases with increasing number of filtered cigarettes smoked.

2. Cigarette smoking and exposure to radioactivity by uranium mining have been related to cytologic changes in the respiratory tract epithelium including carcinoma *in situ*. Cigarette smoking has been more strongly related to these changes than mining exposure.

3. Crysotile asbestos has been shown to contain traces of the carcinogen benzo(a)pyrene, and the combination of the two has been shown to be a more potent carcinogen in rats than either alone.

4. Heavy smoking prior to a first primary oral or respiratory cancer has been shown to be related to the development of a second primary in the respiratory tract or oral cavity.

5. Results from one study have shown a greater proportion of lung cancer patients having high levels of aryl hydrocarbon hydroxylase activity than among either healthy persons or persons with other cancers. Persons with high levels of AHH may be a group which has a genetically determined increased risk of lung cancer if they smoke, but no excess risk if they do not smoke.

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CHAPTER 3
Non-Neoplastic Bronchopulmonary Diseases

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INTRODUCTION

Chronic non-neoplastic lung diseases are major causes of permanent and temporary disability in the United States. Chronic obstructive pulmonary disease (COPD) is the largest subgroup of these diseases and in this report refers to chronic bronchitis and/or emphysema. Relationships between smoking and non-neoplastic lung diseases have been reviewed in previous reports on the health consequences of smoking (*36, 37, 38, 39, 40, 41, 42, 43*).

Cigarette smoking is the most important cause of COPD. Cigarette smokers have higher death rates from chronic bronchitis and emphysema, more frequently report symptoms of pulmonary disease, and have poorer performance on pulmonary function tests than do nonsmokers. These differences become even more marked as the number of cigarettes smoked increases. The relationship between cigarette smoking and COPD has been demonstrated in many different national and ethnic groups and is more striking in men than in women. Pipe and cigar smokers have higher morbidity and mortality rates from COPD than do nonsmokers but are at lower risk than cigarette smokers. Cessation of cigarette smoking often results in improved pulmonary function tests, decreased pulmonary symptoms, and reduced COPD mortality rates.

In addition to an increased risk of COPD, cigarette smokers are more frequently subject to and require longer convalescence from other respiratory infections than nonsmokers. Also, if they require surgery, they are more likely to develop postoperative respiratory complications.

The relative importance of air pollution in the development of COPD remains controversial, but it is clearly less significant under most circumstances than cigarette smoking. The combination of cigarette smoking and polluted air, however, may produce higher rates of COPD than either factor alone.

Several occupational exposure groups incur an increased risk of COPD, and cigarette smoking adds significantly to this risk. In particular, exposure to cotton fiber and coal dust appears to act in concert with cigarette smoking to promote the development of pulmonary disease.

Autopsy studies have demonstrated a dose-related effect of cigarette smoking on the severity of macroscopic emphysema. Increased goblet cell density, alveolar septal rupture, bronchial epithelial thickening, and mucous gland hypertrophy are more commonly found in the lungs of smokers than in those of nonsmokers.

Many pathophysiologic mechanisms by which smoking may cause COPD have been proposed. Decreased overall pulmonary clearance, reduced ciliary motion, and impaired alveolar macrophage functions have all been related to cigarette smoking and probably play a role in the development of COPD. The exact mechanisms whereby cigarette smoking contributes to the development of COPD, however, remain only partially understood.

SMOKING AND RESPIRATORY MORBIDITY

An increased prevalence of respiratory symptoms in smokers from early teens to those past the age of 80 has been well established. Bewley, et al. (*5*), in a study in Derbyshire County, England, extended these findings to include younger children. In a questionnaire study of 7,115 schoolchildren ages 10 to 11½ years, he found that 6.9 percent of the boys and 2.6 percent of the girls smoked more than one cigarette per day. The boys who smoked reported more morning cough (21.5% to 6.1%), cough during the day or night (48.0% to 20%), and cough of 3-months duration (18.0% to 4.1%) than their nonsmoking schoolmates. The percentages for the girls were similar although based on smaller numbers of smokers. As in many studies of this type, it was impossible to control for air pollution, social class, or smoking habits of the parents; nevertheless, the results suggest that cigarette smoking even in this young age group produces respiratory symptoms.

Fridy, et al. (*12*), in a somewhat older population (average age 25 years), examined the effect of smoking on airway function during mild viral illness. They measured closing volumes for 22 subjects (9 cigarette smokers – average age 29.1, and 13 nonsmokers – average age 25.7) before onset and at weekly intervals from the beginning of a mild respiratory illness until all symptoms had subsided. The closing volumes for smokers prior to illness were higher than those for nonsmokers, but the difference was not statistically significant. In the tests done during the illness, the smokers had a statistically significant increase in the closing volumes (from 37.0 to 45.8 percent of their total lung capacity, while nonsmokers had no change, 32.7

and 31.7 percent). Smokers remained symptomatic more than twice as long as nonsmokers (35.7 and 16.5 days, respectively), and the mean duration of pulmonary function abnormalities in smokers was 29.7 days. Nonsmokers had no change in pulmonary function tests during illness.

SMOKING AND AIR POLLUTION

The relationships among air pollution, smoking, and COPD remain controversial. Reasons for this controversy include difficulties in controlling such variables as socioeconomic class, degree of crowding, ethnic differences, and age distribution as well as determining the exact type and amount of individual pollution exposure. Measuring individual pollution exposure even within a small area is difficult since both amount and type can vary dramatically from street to street (e.g., proximity of a street to a heavily traveled expressway).

In an effort to control as many of these variables as possible, two basic approaches in study design have been tried. The first approach is to find areas where pollution levels have been well measured and then to select study populations that are as similar as possible in areas with different pollution levels. Thus, effects on a population in a low pollution area can be compared to those on a similar population in a high pollution area. The second approach is to select a population that is as uniform as possible, for example, twins, and then measure individual responses to different pollution exposures. Both approaches have drawbacks as will be evident from the following studies.

Using the first approach, the Community Health and Environmental Surveillance System of the Environmental Protection Agency (*6, 11*), has conducted surveys in areas with different types and levels of pollution in four different parts of the United States (Chicago, New York City, the Salt Lake Basin, and the Rocky Mountain area). Within each part of the country, the researchers identified communities of similar socioeconomic status but different pollution levels. They then administered a questionnaire through the school systems to determine the frequency of lower respiratory tract infection in the children and their families. They reported an increased incidence of lower respiratory tract illness in children in high pollution communities compared to children in low pollution communities. This difference was demonstrable only in children whose families had lived in the high pollution communities for more than 3 years. They also reported an increased prevalence of chronic bronchitis in parents

who lived in high pollution communities compared to parents from low pollution communities. They calculated the excess risk of chronic bronchitis produced by air pollution to be one-third of that produced by smoking but to be additive with smoking.

Several major problems in these surveys make it difficult to evaluate the results. The authors describe the areas as having different kinds of pollution. The Salt Lake Basin and Rocky Mountain areas were felt to be high in sulfur dioxide (SO_2) and low in total suspended particles (TSP), while New York and Chicago were high in both these pollutants. As a result, in the Salt Lake Basin and Rocky Mountain areas, communities were separated into low and high pollution communities only on the basis of their SO_2 levels. Many communities classified as low pollution communities on the basis of their SO_2 levels had higher levels of total suspended particles than the communities classified as high pollution communities by SO_2 level (Table 1). In fact, the average total suspended particles level for the low pollution communities in the Salt Lake Basin was higher than that for the high pollution communities (Table 2) in the Salt Lake Basin. These differences exemplify the difficulties of using only one pollutant as a marker of total pollution exposure.

Additional problems with these studies were the differences in socioeconomic class measurements between low and high pollution communities in some of the regions. In the Rocky Mountain area, the percentage of fathers who completed high school varied from 91 percent in one of the low communities to 58 percent in one of the high pollution communities. There were also major differences between high and low pollution communities in the percentage of families with more than one person per room in the Salt Lake Basin (59.6% to 51.2%), Rocky Mountain area (87.0% to 68.0%), and New York (85.0% to 72.0%). Residential stability (percentage of families living in the community for more than 3 years) was different in the high and low pollution communities in New York (58.0% to 36.0%) and Chicago (56.0% to 46.0%). The percentage of parents who currently smoke also differed for high and low pollution communities in New York (53% to 45% for the fathers and 47% to 37% for the mothers). These differences raise questions as to whether the high and low pollution communities were really similar enough populations to justify the claim that differences in incidence of respiratory tract illness could be attributable to differences in air pollution.

TABLE 1. – *Levels of sulfur dioxide (SO_2) and total suspended particulates (TSP) in four Utah communities, 1971, and in five Rocky Mountain communities, 1970*

Area	Community Pollution Classification	Pollution levels in $\mu g/m^3$	
		SO_2	TSP
Utah (Salt Lake Basin)	Low	8	78
	Intermediate 1	15	81
	Intermediate 2	22	45
	High	62	66
Rocky Mountain Area	Low 1	10	50
	Low 2	26	68
	Low 3	46	110
	High 1	109	43
	High 2	186	102

Source: Chapman. R.S., et al. (6).

TABLE 2. – *Mean annual levels of sulfur dioxide (SO_2) and total suspended particulates (TSP) in four areas*

Area	Pollution levels in $\mu g/m^3$							
	SO_2				TSP			
	During Study		Decade Preceding Study		During Study		Decade Preceding Study	
	Low	High	Low	High	Low	High	Low	High
Five Rocky Mountain Areas	10	275	10	263	45	110	50	101
Salt Lake Basin	9	65	< 20	144	78	66	82	62
New York	23	63	< 30	431	34	104	40	201
Chicago	57	106	109	250	111	151	121	165

NOTE. – Area includes highest- and lowest-polluted communities.
Source: French, J.G., et al. (*11*).

Increased prevalence of COPD has also been demonstrated in areas of high pollution in the Netherlands (*44*), Yokkaichi, Japan (*25*), and Cracow, Poland (*30*). Again, however, these studies were poorly controlled for socioeconomic status.

Several recently published studies have used the second major method of investigating the relationship between smoking, air pollution, and COPD, i.e., to select a uniform population and then to measure individual differences to pollution exposure. Comstock, et al. (*8*), in an attempt to control for occupational exposure and socioeconomic class, studied three separate, uniform populations of telephone workers and used as a measure of pollution the location of the place of work and residence. The populations studied were telephone installers and repairmen in Baltimore, New York City, Washington, D.C., and rural Westchester County in 1962 (survey 1) and in 1967 (survey 2); and telephone installers and repairmen in Tokyo in 1967 (survey 3). They were unable to find any relation between pulmonary symptoms and degree of urbanization of place of work or place of residence (either current or past). They were, however, able to establish a strong correlation between smoking habits and pulmonary symptoms. Given the crude estimation of pollution exposure used in this study (all workers in each city were treated as though they received the same exposure), a small difference in symptoms due to air pollution could have been missed, whereas the difference due to smoking could be detected both because it was larger and because it was possible to determine individual exposure more exactly.

Hrubec, et al. (*15*), in a study of twins from the U.S. Veterans Registry, were unable to show a difference in respiratory symptoms either between individuals with different exposure to air pollution or between members of twin pairs with different air pollution exposures. However, they too used a crude measure of air pollution exposure (by each zip code area), and so could have missed a small difference due to air pollution despite being able to relate respiratory symptoms to smoking, socioeconomic status, and alcohol intake.

Colley, et al. (*7*), in a study of 3,899 persons (20-year-olds born during the last week of March 1946 in the United Kingdom), were also unable to show a relation between COPD and air pollution. They used as their estimates of air pollution exposure the domestic coal consumption in the towns where the subjects lived. This method of estimating air pollution exposure is subject to the same limitation cited for the previous two studies – limited sensitivity to small risks due to air pollution.

In summary, if an increased risk of COPD due to air pollution exists, it is small compared to that due to cigarette smoking under conditions of air pollution to which the average person is exposed. The possibility remains that the two different kinds of exposure may interact to increase the total effect beyond that contributed by each exposure.

SMOKING AND OCCUPATIONAL DISEASE

Friedman, et al. (*13*), in a study of 70,289 men and women who had had Kaiser-Permanente multiphasic health checkups, noted that smokers were more likely to report occupational exposure on a questionnaire (Table 3) than nonsmokers. The differences are small but statistically significant and need to be considered when investigating the relationship of smoking to occupational diseases. They were not able to determine whether smokers' responses reflect actual differences in exposure or an increased awareness of and sensitivity to occupational exposure.

Exposure to coal and granite dust and cotton fiber carries an increased risk of COPD. This risk is further increased by cigarette smoking. Other new data have been published which clarify the risk in certain occupational groups.

Mill Workers – Byssinosis

Berry, et al. (*4*), in a study of 595 workers in the Lancashire cotton mills over a 3-year period, found that the decline in forced expiratory volume in one second (FEV_1) was 19 ml/year greater in smokers than in nonsmokers (59 ml/year compared to 40 ml/year, $P > .02$) but they could not demonstrate a dose-response relationship.

Firemen

Sidor and Peters (*32, 33*), in a cross-sectional study of 1,768 Boston firemen, were unable to show a significant relationship between severity of fire exposure and impairment of pulmonary function tests or prevalence of COPD; there was a clear harmful effect of cigarette smoking on both. They postulate that they were unable to show an increased prevalence of COPD in this cross-sectional study because firemen who developed COPD were no longer capable of meeting the physical demands of the job and had retired, thus removing them from the study population. They were able, however, to show a higher incidence of COPD in men under the age of 35 years who had been on the force more than 6 months when compared to persons of the same age who had just been hired.

TABLE 3. – *Age-adjusted percentage of cigarette smokers and nonsmokers in each race-sex group responding positively to exposure to chemicals, fumes, sprays, and dusts*

Exposure	Time period[1]	Smoking status	Whites		Blacks		Yellows	
			% Men	% Women	% Men	% Women	% Men	% Women
Chemicals, cleaning fluids or solvents (or chemical sprays)[2]	Before 1 year ago	Smokers	24.0	6.4	26.0	11.8	16.7	4.1
		Nonsmokers	18.9	5.1	19.2	6.7	12.9	5.1
	In the past year	Smokers	12.1	3.0	14.2	5.1	13.1	3.5
		Nonsmokers	9.7	2.6	11.6	4.5	9.4	3.8
Insect or plant sprays	Before 1 year ago	Smokers	4.0	1.0	6.6	2.1	3.8	0.3
		Nonsmokers	3.5	0.9	5.1	1.9	2.5	1.0
	In the past year	Smokers	2.9	2.1	4.8	2.9	3.0	1.3
		Nonsmokers	2.9	1.8	4.8	3.0	3.6	1.8
Ammonia, chlorine, ozone or nitrous gases (nitrous oxides or other irritating gases)[2]	Before 1 year ago	Smokers	7.9	2.3	10.3	4.8	6.2	0.9
		Nonsmokers	6.2	1.9	7.0	3.2	4.5	1.7
	In the past year	Smokers	5.4	1.9	7.6	3.9	8.0	0.5
		Nonsmokers	3.7	1.5	5.8	3.1	3.5	1.7
Engine or exhaust fumes (more than 2 hours a day)[2]	Before 1 year ago	Smokers	11.8	1.0	17.6	1.9	4.0	0.0
		Nonsmokers	6.9	0.5	13.1	0.6	3.6	0.1
	In the past year	Smokers	8.7	0.7	17.6	1.0	4.3	0.5
		Nonsmokers	5.2	0.5	13.3	1.2	3.9	0.2

TABLE 3. – *Age-adjusted percentage of cigarette smokers and nonsmokers in each race-sex group responding positively to exposure to chemical, fumes, sprays, and dusts – Continued*

Exposure	Time period[1]	Smoking Status	Whites		Blacks		Yellows	
			% Men	% Women	% Men	% Women	% Men	% Women
Plastic or resin fumes	Before 1 year ago	Smokers	5.1	1.1	3.3	1.2	3.1	0.1
		Nonsmokers	3.5	0.8	3.0	0.6	2.2	0.3
	In the past year	Smokers	3.3	0.8	3.9	0.9	3.0	0.1
		Nonsmokers	2.5	0.6	4.3	0.6	1.3	0.3
Lead fumes or metal fumes (leaded sprays or paint sprays)[2]	Before 1 year ago	Smokers	8.2	0.9	9.1	1.5	4.1	0.1
		Nonsmokers	4.3	0.5	5.8	0.6	2.6	0.1
	In the past year	Smokers	5.5	0.7	7.7	1.3	3.3	0.5
		Nonsmokers	3.1	0.5	6.8	0.8	2.4	0.4
Asbestos, cement or grain (or flour) dusts[2]	Before 1 year ago	Smokers	7.1	0.6	11.5	1.2	2.7	0.0
		Nonsmokers	4.4	0.3	8.8	0.8	1.6	0.1
	In the past year	Smokers	2.8	0.4	7.5	1.0	2.7	0.1
		Nonsmokers	1.8	0.3	6.2	0.8	0.3	0.8
Silica, sandblasting, grinding or rock drilling dust (sand or coal)[2]	Before 1 year ago	Smokers	6.9	0.6	10.5	1.3	3.5	0.3
		Nonsmokers	4.0	0.5	6.8	0.7	2.9	0.0
	In the past year	Smokers	3.9	0.5	8.0	1.0	3.3	0.4
		Nonsmokers	2.3	0.4	6.6	0.9	3.5	0.4
Total number of subjects		Smokers	14,485	16,059	2,609	2.869	654	446
		Nonsmokers	8,282	18,526	1,116	3,218	712	1,313

[1]With a few slight variations, the questions were worded as follows:
Before 1 year ago: "Before 1 year ago have you ever worked in a place where you were often or daily around _____?"
In the past year: "In the past year have you worked in a place where you were often or daily around _____?"
[2]Material in parentheses appears in "past year" question but not in "before 1 year ago" question.

SMOKING AND PULMONARY FUNCTION TESTS

It is recognized that smokers as a group have poorer pulmonary function tests than nonsmokers. The standard pulmonary function tests generally only become abnormal late in the pathologic process of COPD and usually only after irreversible changes in the lungs have occurred. As a result, tests are needed that will identify persons at risk of developing COPD before they have irreversible loss of lung function. Standard tests of pulmonary resistance are inadequate for this purpose because they measure predominately resistance in the large airways while the first changes of COPD occur in bronchioles that are 2 mm and smaller. Small airway resistance may be measured through evaluating frequency dependent compliance, but this is often cumbersome to perform. Closing volume and maximum expiratory flow rates at 25 and 50 percent of vital capacity have the advantage of being relatively easy to perform, yet are still able to measure changes in the small airways. Closing volume is the lung volume at which the alveoli in the dependent portions of the lung begin to close, and it is usually expressed as a percent of vital capacity. Elevated closing volume is considered evidence of small airway dysfunction. Maximum expiratory flow rates at 25 and 50 percent of vital capacity measure air flow at low lung volumes where the resistance of the small airways makes up a much larger proportion of the measured resistance.

Several recently published studies contain data on small airway dysfunction in smokers. Lim (*20*) studied 50 smoking and 50 nonsmoking high school students and found in smokers a statistically significant reduction in the forced expiratory volume in one second when the test was started at normal end expiration (i.e , low lung volumes). Stanescu, et al. (*34*) noted elevated closing volumes in 16 healthy asymptomatic smokers when compared to 16 nonsmokers, but were unable to show any difference in maximum expiratory flow rates at 25 and 50 percent vital capacity. Ruff, et al. (*28*) studied 50 subjects ages 18 to 82 and showed increasing closing volumes with age and smoking. Martin, et al. (*21*), in a study of 50 subjects ages 12 to 68, found that 25 percent of the smokers had abnormal closing volumes, and Oxhoj, et al. (*26*) noted elevated closing volumes for 50-year-old smokers compared to nonsmokers. Dirksen, et al. (*10*) reported higher closing volumes in smokers and noted no change with cessation of smoking. Hoeppner, et al. (*14*) also showed elevated closing volumes in healthy smokers ages 16 to 61, but found these to be closely related to decreases in the static transpulmonary pressure. They postulate that the elevated closing volumes may be related to decreased elastic recoil rather than changes in small airway resistance.

The data have established the fact that a greater percentage of smokers than nonsmokers have elevated closing volumes, but the number of smokers with elevated closing volumes who will develop COPD remains to be determined.

Stebbings (*35*), in a further analysis of Densen's data (*9*) on the changes in pulmonary function test values in male postal workers and transit workers in New York City, noted significantly less decline in FEV_1 among Black smokers when compared to White smokers. This difference persisted even when corrections were made for differences in amount smoked, age at which smoking began, inhalation patterns, and smaller initial lung volumes in Blacks. Black and White nonsmokers did not differ in the rate of decline in FEV_1. By age 60 years, Blacks who smoked one pack per day had a .34 liter smaller cumulative decrease in FEV_1 than Whites who smoked the same amount.

α_1-ANTITRYPSIN

It would be useful to identify the populations at excessive risk of developing COPD from smoking. They then might be made aware of the hazard before they develop symptomatic lung disease. Persons with α_1-antitrypsin deficiency may be such a population.

α_1-antitrypsin deficiency is a rare homozygous recessive genetic defect which occurs in approximately one out of every 3,600 people and results in an increased susceptibility to and premature development of COPD. There is some evidence that smoking hastens the development of COPD in these people. The heterozygous state (producing intermediate levels of the α_1-antitrypsin in serum) is far more common than the homozygous state and is found in approximately 10 percent of the population. It is uncertain whether the heterozygous deficiency state predisposes to COPD.

α_1-antitrypsin inheritance patterns suggest multiple codominant alleles at one gene locus, some of which (most notably the S and Z alleles) produce lower serum protease levels than the normal M-allele (Table 4). The pathophysiologic mechanism of the deficiency state is felt to be the inability to inhibit the proteases found in the granulocytes and pulmonary macrophages which go on to damage essential constituents of lung tissue. Several recent reviews of the enzyme and the clinical syndrome produced by its deficiency have been published (*16, 17, 18*).

TABLE 4. – *The α_1-antitrypsin levels and frequency of protease inhibitor (Pi) phenotypes in healthy populations*

Protease inhibitor (Pi) type	Healthy populations	
	α_1-antitrypsin concentration (% normal)	Expected frequency of Pi types (per 1,000 people)
MM	100	898
(FM,FF,IM,MV,MX)	100	28
MW	80	–[a]
MP	80	1
MS	80	41
(FS,IS)	80	1
MZ	60	29
(FZ)	60	1
SS	55	1
SZ	40	1
ZZ	15	<1

[a] Seen rarely in Spanish populations.
Source: Mittman, C., Lieberman, J. (*22*).

In most studies of patients with COPD, investigators have found an increased prevalence of the partially deficient heterozygote phenotypes when compared to healthy control populations. In the few studies not finding this relationship, only α_1-antitrypsin levels were measured. Because α_1-antitrypsin is an acute phase protein and increases with infection, it is difficult to separate out the partially deficient heterozygote phenotypes by measuring only α_1-antitrypsin levels. It is necessary to identify the products of each allele electrophoretically in order to identify the deficient phenotypes.

Two recent studies using this technique showed an increased prevalence of deficient phenotypes in patients with COPD but not among control populations. Mittman, et al. (*23*) studied 240 patients with COPD admitted to LaVina Hospital in Altadena, California, and found that 19.1 percent had deficient phenotypes compared to only 7.1 percent of a control Scandinavian population. Keuppers and Donhardt (*19*) found prevalence rates for deficient phenotypes of 3.5 percent in healthy controls, 12.9 percent in persons retired from work because of COPD, and 15.7 percent in patients hospitalized for COPD.

Additional population studies have been done to determine the effect of the heterozygous state on the development of COPD. Webb, et al. (*47*) studied 500 persons visiting a multiphasic screening clinic in Monroe County, New York, and found that 11.6 percent had deficient phenotypes. He was unable to show differences in symptoms or in pulmonary function test values between persons with normal and deficient phenotypes. In a study of 451 randomly selected adults from the same county (*31*), pulmonary function studies were done on 40 deficient heterozygote phenotypes (20 MS and 20 MZ) and on normal phenotype (MM) controls matched for age, sex, and smoking habits. When total pulmonary resistance was measured by a forced oscillometric technique, the nonsmoking MZ subjects had significant impairment compared to their normal phenotype controls. All cigarette smokers, regardless of phenotype, had abnormal values.

Although the data are still inconclusive, it may well be that heterozygous deficient persons are a group at excessive risk of developing COPD especially if they smoke.

AUTOPSY AND PATHOPHYSIOLOGIC STUDIES

Autopsy Studies

Auerbach, et al. (*3*) have previously shown dose-related macroscopic emphysematous changes in the lungs of smokers. Now in an autopsy study (*2*) of 1,582 men and 388 women, they have examined microscopic lung parenchymal changes in relation to cigarette smoking. They were able to show that rupture of alveolar septa (emphysema) and fibrosis and thickening of the small arteries and arterioles are far greater in smokers than nonsmokers and increase with increasing amount smoked (Tables 5 and 6).

When these researchers examined former cigarette smokers, they found that those who had stopped more than 10 years prior to death had fewer pathologic changes than those who had stopped less than 10 years before death. But even in those who had stopped for more than 10 years, there was a greater degree of pathologic change in those who had been smoking more than one pack per day than in those who had been smoking less than one pack per day (Table 7).

Niewoehner, et al. (*24*), in an autopsy study of 39 men who died suddenly from various causes and who were below 40 years of age (20 nonsmokers and 19 smokers), observed a respiratory

TABLE 5. – *Means of the numerical values given lung sections at autopsy of male current smokers and nonsmokers, standardized for age*

	Subjects Who Never Smoked Regularly	Current Pipe or Cigar Smokers	Current Cigarette Smokers			
			<.5 Pk.	.5–1 Pk.	1–2 Pk.	>2 Pk.
Number of Subjects	175	141	66	115	440	216
Emphysema	0.09	0.90	1.43	1.92	2.17	2.27
Fibrosis	0.40	1.88	2.78	3.73	4.06	4.28
Thickening of arterioles	0.10	1.11	1.35	1.66	1.82	1.89
Thickening of arteries	0.02	0.23	0.42	0.68	0.83	0.90

NOTE. – Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

Source: Auerbach, O., et al. (*2*).

TABLE 6. – *Means of the numerical values given lung sections at autopsy of female current smokers and nonsmokers, standardized for age*

	Subjects Who Never Smoked Regularly	Current Cigarette Smokers	
		<1 Pk.	≥1 Pk.
Number of Subjects	252	33	64
Emphysema	0.05	1.37	1.70
Fibrosis	0.37	2.89	3.46
Thickening of arterioles	0.06	1.26	1.57
Thickening of arteries	0.01	0.40	0.64

NOTE. – Numerical values were determined by rating each lung section on scales of 0–4 for emphysema and thickening of the arterioles, 0–7 for fibrosis, and 0–3 for thickening of the arteries.

Source: Auerbach, O., et al. (*2*).