CIGARETTE SMOKING AND LUNG DISEASE

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Tobacco is a dirty weed. I like it.
It satisfies no normal need. I like it.
It makes you thin, it makes you lean,
It takes the hair right off your bean.
It's the worst darn stuff I've ever seen.
I like it.

G.L. Hemminger
Penn State Froth
1915

"A custome Lothsome to the eye, hatefull to the Nose, harmefull to the braine, daungerous to the Lungs, and in the blacke stinking fume thereof, neerest resembling the horrible Stigian smoke of the pit that is bottomelesse."

King James I
Counterblaste to Tobacco
1604

CONTENTS

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Introduction

In November 1492, Christopher Columbus dispatched two of his men on an expedition through the jungles of Cuba to meet the Great Khan of China. Needless to say, they did not find him. What they did find was a group of the native inhabitants rolling up a dried herb in leaves, lighting one end, and sucking smoke through the other. One of the two men, Rodrigo de Jerez, returned to Spain and became the first European to smoke tobacco on the Continent. He was subsequently imprisoned by the Inquisition for this indiscretion, but the habit caught on rapidly anyway. Half a century later, the French ambassador to Portugal, Jean Nicot, sent samples of the tobacco plant, along with glowing accounts of its medicinal properties, to the queen of France; his efforts helped to spread its use all over Europe. History rewarded his advertising efforts by making him the namesake for both the tobacco plant, Nicotiana tabacum, and its major alkaloid, nicotine. Tobacco has flourished in the ensuing four centuries, becoming the largest non-food cash crop in the world. The plant's history has been punctuated by intermittent efforts at limitations of its use, such as Rodrigo encountered; none has met with success. Today tobacco is under attack again, due to a combination of several factors: the realization that cigarette smoking is a major health hazard to the smoker; the emphasis on prevention of disease in the general population; the question of harmful effects of passive smoking; the growing militancy of nonsmokers in asserting their rights; and the growth of consumerism in the regulation of the tobacco industry. What I will do today is to review the scientific evidence underlying this latest assault on tobacco use, and evaluate the prospects for reducing its hazards, in relation to respiratory diseases. Since cigarette smoking is by far the most common and the most dangerous form of tobacco use in this country, my comments will be confined largely to it. Only pulmonary disease will be discussed. This is not to understate the importance of other harmful effects of smoking; a list of non-pulmonary diseases associated with cigarette smoking appears in Appendix I.

Tobacco and Cigarettes in the U.S.

Each year the United States produces about two billion pounds of Nicotiana tabacum, the bulk of which goes into the manufacture of some 600 billion cigarettes (1). Half of the national tobacco acreage is in North Carolina and Kentucky, with four other southern states containing another quarter. The cultivation of tobacco is a complicated and labor-intensive process, requiring careful harvesting followed by curing and aging. Because of these requirements, and also because the federal government restricts the amount of tobacco that can be grown, tobacco farming can be extremely profitable: an acre of tobacco may gross $3,000 to $4,000, compared to $150 for an acre of corn (2).

The average American cigarette contains about one gram of tobacco and miscellaneous additives, which are not subject to disclosure or governmental regulation (3). The constituents of the smoke resulting from combustion of a cigarette vary widely depending on the conditions under which the tobacco was grown, harvested, cured, and aged; the presence of additives; the use of a filter; the porosity of the wrapper; and the manner in which the cigarette is smoked. In

order to impart some uniformity to the descriptions of cigarette smoke, the Federal Trade Commission periodically evaluates cigarettes made in the United States. A smoking machine inhales at a standard puff frequency and duration until a fixed amount of the cigarette has burned. The collected smoke which passes through a specific type of glass filter comprises the gas phase of the smoke; the retained portion consists of an aerosol of particles 0.1-1 micron in diameter. The total weight of the retained particles, minus the water and nicotine, is the tar content of the cigarette. Nicotine, although technically in the particulate phase and hence part of the tar, is quantified separately. These tables show some of the gas phase and the particulate phase constituents of mainstream smoke, i.e., the smoke that is drawn through the butt end of the cigarette. All told there are an estimated 2,000-4,000 substances in cigarette smoke (3). A great deal of the difficulty in cigarette smoke toxicology is due to the sheer complexity of its composition.

Table 1. Constituents of Mainstream Tobacco Smoke

Gas Phase

- Nitrogen
- Oxygen
- Carbon Dioxide
- Carbon Monoxide
- Nitric Oxide
- Ammonia
- N-Histamines
- Hydrogen Cyanide
- Acetonitrile
- Volatile Hydrocarbons
- Volatile Aldehydes and Ketones
  - Formaldehyde
  - Acetaldehyde
  - Acrolein

Table 2. Constituents of Mainstream Tobacco Smoke

Particulate Phase

- Water
- Nicotine
- "Tar"
  - N-Nitrosamines
  - Aromatic Amines
  - Alkanes and Alkenes
  - Isoprenoids
  - Benzenes and Naphthalenes
  - Polynuclear Aromatic Hydrocarbons
  - Aza-Arenes
  - Phenols

The overall pattern of cigarette consumption in the twentieth century in this country has consisted of a sharp rise in use during the first sixty years, followed by a slow decline. Figure 1 depicts per capita consumption of cigarettes in the United States since 1900 (4). Automation of cigarette manufacture, then mobilization of young men into the armed forces during World War I spurred the early surge in cigarette use. The Second World War gave further impetus to the trend, such that by the early 1960's over 200 packs of cigarettes per year were consumed for every adult in the nation. Per capita consumption peaked in 1963, the year before the first Surgeon General's report on the Health Consequences of Smoking, and has declined modestly since then. The actual percentage of Americans who smoke has fallen from about 45% of the adult population in 1958 to 32% in 1983; because of growth in the population, however, the absolute number of smokers has remained fairly constant, near 50 million (5).

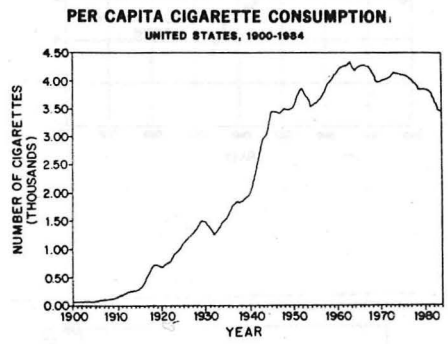

Figure 1. Per capita cigarette consumption in the U.S., 1900-1984. Value for 1984 is estimated. Data plotted from reference 4.

Analysis of smoking trends by sex reveals some interesting differences. Historically, the prevalence of smoking in women has lagged behind that of men by about 30 years. Figure 2 depicts the percentage of men and women smokers as ascertained by surveys in Milwaukee since the 1920's (6). Note the sharp rise in prevalence in both sexes, with a persistent male predominance through the 1950's. Since then, the discrepancy between the sexes has vanished as more men than women gave up smoking. Earlier in the century, female smokers tended to begin the habit later in life than did men. As is obvious from Figure 3, the age at initiation of smoking for women has gradually fallen in more recent birth cohorts to the mid-teens, the same as for men (7). Finally, the number of cigarettes smoked by women has increased, though not yet to the levels smoked by men. In short, women are becoming more like men in their smoking habits (7). All these

trends imply increases in the overall burden of exposure to cigarette smoking among the female population, and consequently, the overall burden of smoking-induced disease. As we will see, predictions of increasing disease incidence based on these trends in smoking behavior are well borne out.

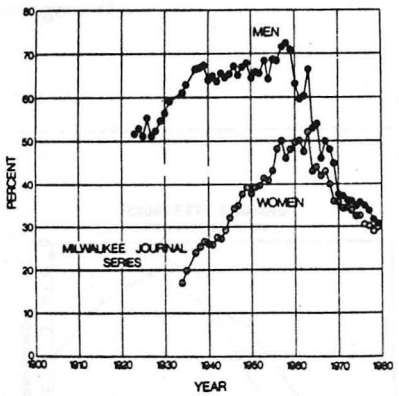

Figure 2. Percentage of general population which smokes, by sex, 1930-1980. Data were obtained by surveys in Milwaukee. From reference 6.

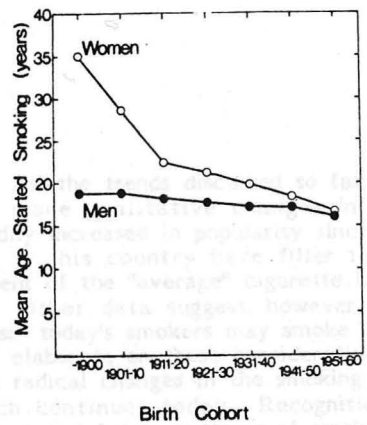

Figure 3. Age at initiation of smoking by decade of birth for men and women. From reference 7.

The prevalence of smoking among teenagers carries particular interest, since it reflects the rate of introduction of new smokers into the population. A study published by the National Institute for Education in 1979 caused a great deal of concern, because it suggested that the prevalence of smoking was not declining among young women, as it was among men. Figure 4 shows recent trends in teenage smoking, as ascertained by survey of high school seniors. These more recent data suggest that smoking prevalence among teenagers of both sexes is declining, but the rate of change is low, and the data may be unrepresentative of all teenagers (8).

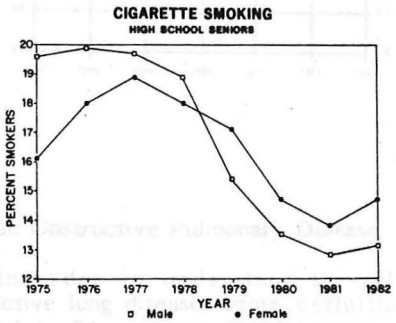

Figure 4. Frequency of cigarette smoking in high school seniors, 1975-1982. Data for male and female smokers. From reference 8.

All the trends discussed so far have been quantitative, but Americans have also made qualitative changes in their smoking habits. Filter tip cigarettes have steadily increased in popularity since the 1950's; over 90% of the cigarettes now sold in this country have filter tips. Concomitant with this, the tar and nicotine content of the "average" cigarette has consistently declined, as shown in Figure 5 (9). Other data suggest, however, that current smoking behavior may offset these gains: today's smokers may smoke more cigarettes, and in a different fashion. I will elaborate on these considerations later in the hour. The twentieth century has seen radical changes in the smoking habits of Americans, an evolutionary process which continues today. Recognition of these changes is essential to understanding present and future patterns of smoking-induced lung disease.

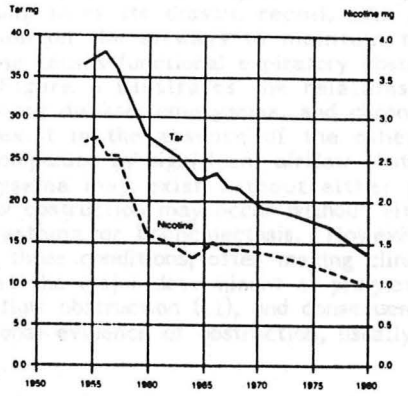

Figure 5. Tar and nicotine content of "average" (sales-weighted) U.S. cigarette, 1954-1980. From reference 9.

Chronic Obstructive Pulmonary Disease

In order to understand the relationship between cigarette smoking and obstructive lung disease, some definition of terms is necessary. Emphysema is defined as "an abnormal enlargement of the air spaces distal to the terminal nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls (10)." The diagnostic criterion is therefore a pathologic one, confirmable only at autopsy. Chronic bronchitis is defined as "a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucous hypersecretion and certain structural alterations in the bronchi. Anatomic changes may include hypertrophy of the mucous secreting apparatus and epithelial metaplasia, as well as more classic evidences of inflammation. In epidemiologic studies, the presence of cough or sputum production on most days for at least three months of the year has sometimes been accepted as a criterion for the diagnosis (10)." The diagnostic criterion is sometimes further expanded to include such sputum production for two consecutive years. The diagnosis of chronic bronchitis is therefore a clinical one, based entirely on the patient's history. Chronic obstructive pulmonary disease (COPD) "refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration (10)." The most widely used measure of expiratory airflow is the forced expiratory volume in the first second, the FEV_1. Airflow obstruction is said to be present when the FEV_1 is reduced below the range predicted by the subject's age, height, sex, and race and when the ratio of FEV_1 to forced vital capacity (FVC) is reduced. COPD can occur as a result of either chronic bronchitis or emphysema (as well as asthma and bronchiectasis, which will not be discussed today). In the

case of chronic bronchitis, the obstruction may result from intrinsic airway changes such as goblet cell and submucosal glandular hypertrophy, edema, inflammation, secretions, and bronchospasm. In emphysema, airflow obstruction occurs because the lung loses its elastic recoil. As a consequence there is no longer radial traction on the airways to maintain their patency during expiration, and their collapse causes functional expiratory obstruction.

Figure 6 illustrates the relationship among the entities chronic obstructive pulmonary disease, emphysema, and chronic bronchitis. Note that each condition may exist in the absence of the other, so that chronic bronchitis is commonly unaccompanied by significant airflow obstruction, so-called chronic simple bronchitis; emphysema may exist without either productive cough or airflow obstruction; airflow obstruction may occur without either chronic bronchitis or emphysema, as with asthma or bronchiectasis. However, most patients with COPD have elements of all three conditions, often making clinical differentiation difficult. What is clear is that the major determinant of prognosis in all patients with COPD is the degree of airflow obstruction (11), and consequently, most clinical attention has focused on functional evidence of obstruction, usually the FEV_1.

RELATIONSHIP OF COPD, EMPHYSEMA, AND CHRONIC BRONCHITIS

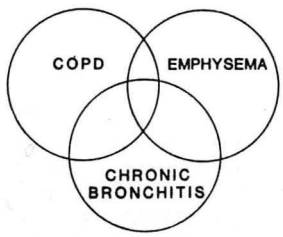

Figure 6. Relationship of COPD, emphysema, and chronic bronchitis. Figure is schematic and does not portray relative frequencies.

The natural history of COPD is depicted schematically in Figure 7, which shows the evolution of lung function (FEV_1) with age in a normal person and one with COPD. The upper line shows the course of evolution of the FEV_1 in a normal person. After age 25, the FEV_1 declines at a rate of 20-30 ml per year (12). By age 70, the FEV_1 is reduced to perhaps 60-80% of its value in youth, but still well above the level at which symptoms may appear. In contrast, the patient destined to develop COPD starts at a similar level of lung function, but declines more rapidly, at 50-80 ml per year or occasionally even faster (13). The result is that

in the fifth, sixth, or seventh decade such a person's FEV_1 falls below 1 liter, a level usually accompanied by severe dyspnea and disability. The presence of a FEV_1 of 1 liter in a patient with COPD implies a five-year survival of about 50% (11). The clinical course may vary depending on whether emphysema or chronic bronchitis predominates, but the level of lung function remains the major determinant of survival (14).

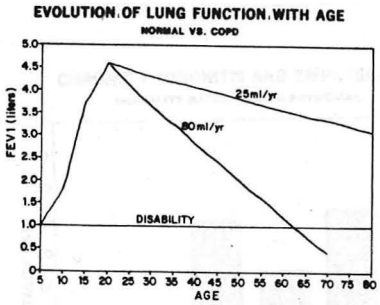

Figure 7. Evolution of FEV_1 with age in normal persons and those with COPD. After about age 20, the normal person loses about 25 ml per year. Plotted for comparison is the FEV_1 of a patient with COPD losing function at 80 ml per year, FEV_1 of about 1 liter is frequently disabling.

The data which relate cigarette smoking to COPD take several forms. Clinically, smokers are consistently found to have increased evidence of cough, sputum production, wheeze, dyspnea, and nonspecific chest illness; such symptoms have been shown to occur in a significant fraction of smokers as early as their teens (15). In large epidemiologic studies cigarette smokers consistently have lower FEV_1 than do nonsmokers (16). A longitudinal study of school children in Boston has shown that those teenagers who smoke show less growth in FEV_1 than nonsmoking children; the earlier and the heavier the smoking, the greater the blunting in lung functional development (17). Pathologic data show similar results, with the severity of emphysema at autopsy increasing with years of smoking and packs per day smoked (18). Autopsy studies of young, asymptomatic smokers who died of nonpulmonary causes have shown the presence of early inflammatory lesions in the small airways of the lung; the most prominent is a respiratory bronchiolitis, with clusters of pigmented alveolar macrophages surrounding respiratory bronchioles (19).

The most striking data relating cigarette smoking to COPD are derived from several large studies (20) which have compared mortality from various diseases between smokers and nonsmokers. Perhaps the best-known of such studies is that which has followed prospectively most British physicians since 1951. Detailed

smoking histories have been obtained at intervals, and the causes of all deaths have been ascertained. The most recent data were reported in 1977 (21). Figure 8 shows the risk of dying from chronic bronchitis or emphysema in male smokers, expressed as a ratio to the risk of dying of the same conditions in lifelong nonsmokers. Although these data are derived from death certificates and so are subject to some inaccuracy, clearly the risk of death from COPD is far higher in smokers than nonsmokers, and rises with the amount smoked. Smokers of pipes and/or cigars also suffer excess mortality, though to a lesser degree than cigarette smokers. Prospective studies from several other countries involving almost two million people have all reached similar conclusions (20).

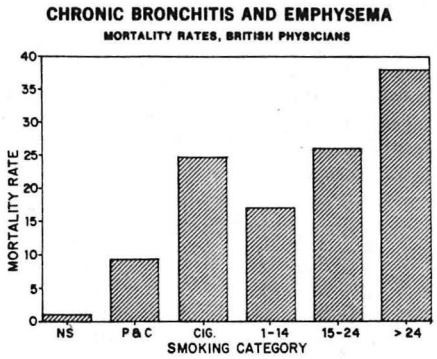

Figure 8. Chronic bronchitis and emphysema mortality rates in male British physicians by smoking category. NS=non-smokers, P+C=pipe and cigar smokers, CIG=all cigarette smokers. Data plotted from reference 21.

The epidemiologic evidence linking cigarette smoking with COPD is overwhelming, but it is only in the last two decades that real progress has been made in understanding the mechanisms whereby smoking causes these diseases. For the purposes of this discussion, emphysema and chronic bronchitis will be discussed separately; one should remember, however, that these diseases almost always coexist to some extent in most patients, and pathogenetic mechanisms may overlap.

Two independent observations in the 1960's form the basis for the current hypothesis for the pathogenesis of emphysema. The first of these observations was that emphysema could be induced in experimental animals by the intratracheal instillation of papain, a proteolytic enzyme (22). The second observation was the strikingly high incidence of early-onset panacinar emphysema in both smokers and nonsmokers whose serum contained abnormally low levels of the endogenous protease inhibitor, alpha-1-antitrypsin (23), now known as alpha-1-protease inhibitor (alpha-1-PI). Taken together, these data suggested that the destruction of alveolar walls which is the hallmark of emphysema could result from either an excess of protease activity in the lung, or from a deficiency of endogenous protease inhibitory activity. The theory of protease-antiprotease imbalance as the cause of

pulmonary emphysema has been widely accepted, although the evidence supporting this model is largely indirect.

The connective tissue framework of the lung consists largely of elastin fibers, and it is this substance which is thought to undergo proteolytic attack during the development of emphysema. The proteolytic enzymes responsible for this degradation are neutral proteases--neutral because they are catalytically active at pH near 7. Normally the lung is protected from the uncontrolled activity of these enzymes by the presence in airway fluid of endogenous protein inhibitors of neutral proteases, including alpha-1-PI, alpha-2-macroglobulin, and bronchial protease inhibitor (BPI). Any condition which can cause an increase in the neutral protease burden in the lung, or which can diminish the activity of the "antiprotease screen" in the lung, can result in the destruction of alveolar walls. Hundreds of studies in the last decade have suggested that cigarette smoking can both increase protease activity and decrease antiprotease activity by a variety of mechanisms.

Neither the source of the neutral proteases responsible for emphysema, nor their exact nature, are known with certainty. However, it is generally assumed that the enzymes are derived from alveolar macrophages (AM) and/or polymorphonuclear leukocytes (PMN) in the lung. Each of these cell types contains an elastase, a collagenase, and a plasminogen activator (24). Human neutrophils also contain cathepsin G and gelatinase. The relative roles of each of these enzymes in the induction of emphysema is unclear, but by far most attention has focused on the elastases of PMN and AM, which are distinct enzymes. Elastase has been emphasized because it is present in large quantities, especially in the PMN; because it has a broad substrate specificity, including elastin, a notoriously insoluble substance; and because, at least in the case of PMN elastase, it is inactivated by alpha-1-PI. It has, in fact, been demonstrated that the endotracheal instillation of human PMN elastase into hamsters results in emphysema (25). Most of the subsequent discussion will therefore focus on elastase, but it should be borne in mind that other neutral proteases may participate in the process.

Table 3. Potential Mechanisms of Smoking-Induced Emphysema

Increased elastolytic burden in the lung
- Recruitment of elastase-bearing inflammatory cells
- Increased elastase content of inflammatory cells
- Enhanced release of elastase by inflammatory cells
  - Chemotactic factor-induced elastase release
  - Cigarette smoke-induced elastase release
  - Cytotoxicity of cigarette smoke for inflammatory cells

Decreased antiprotease activity in the lung
- Direct oxidation of α-1-PI by free radicals in smoke
- Oxidation of α-1-PI by oxygen radicals from activated inflammatory cells

Other
- Direct interference with elastin synthesis

Table 3 shows possible mechanisms whereby cigarette smoking may result in an increased elastase burden in the lung. Bronchoalveolar lavage of smokers consistenly yields larger numbers of AM than are obtained by BAL of nonsmokers (26) . The mechanism whereby these cells are increased in smokers is uncertain, although it may involve in situ proliferation of AM as well as recruitment of blood monocytes to the lung. The stimulus for these events may reside in the particulate fraction of cigarette smoke (26a). Most studies comparing BAL of smokers and nonsmokers have also demonstrated an increase in the number of PMN present in smokers (27). PMN have also recently been demonstrated in increased numbers in alveolar walls in smokers (28). Several possible explanations have been advanced for this PMN recruitment: components of cigarette smoke have been found to be directly chemotactic for PMN (29,30); cigarette smoke condensate has been found to induce the formation of alveolar macrophage chemotactic factor, a powerful PMN chemoattractant, by exposed AM; (27) and smoke has also been found capable of activating the complement system, and so perhaps generating PMN chemotaxins in the lung (31). Once PMN are recruited to the lung the release of elastase may also be enhanced by various mechanisms; both alveolar macrophage chemotactic factor and cigarette smoke itself can cause PMN to release elastase (27,32), and cigarette smoke is directly cytotoxic to PMN (33).

Cigarette smoke may also decrease the level of antiprotease activity in the lung. Cigarette smoke contains highly reactive free radicals, and the active site of alpha-1-PI is sensitive to oxidative inactivation (34). In vitro studies have shown that cigarette smoke can inactivate α-1-PI, rendering it incapable of inhibiting neutrophil elastase (35). AM and PMN from smokers also have enhanced oxidative metabolism (36,37) and release reactive oxygen metabolites, such as superoxide anion, which could directly inactivate antiproteases. Several groups have looked at the activity of alpha-1-PI in the bronchoalveolar lavage fluid of smokers and nonsmokers, with conflicting results (38-40). It remains to be established whether oxidative inactivation of alpha-1-PI in the lung is an important contributory factor in emphysema.

Lest the foregoing theory appear too clearcut, several discordant observations should be noted:

1. AM have been reported to serve protective as well as destructive functions. These include ingestion and partial inactivation of human neutrophil elastase via a specific surface receptor (41) and the synthesis of the antiproteases alpha-2-macrolobulin and alpha-1-PI (42,43).
2. PMN are present in the lungs of smokers in only small numbers. The early histologic lesions in smokers consist of aggregates of AM centered on respiratory bronchioles; PMN are not prominent.
3. PMN contain methionine sulfoxide reductase, an enzyme capable of reactivating oxidatively-inactivated alpha-1-PI (44), and so indirectly inhibiting elastase activity.
4. Neutropenic hamsters develop more emphysema after intratracheal elastase than do normal animals (45).
5. Cigarette smoke has also been shown to interfere with the synthesis and repair of connective tissue components (46).

Pathogenic mechanisms for chronic bronchitis remain poorly defined. In fact considerable evidence suggests that chronic bronchitis may bear little direct relation either to the development of airway obstruction or to mortality. Bates and colleagues followed 200 Canadian veterans with established chronic bronchitis for 12 years (47). They found that only about 10% had major progression of airway obstruction, suggesting that mucus secretion by itself is a poor predictor of functional impairment. Peto and his colleagues have recently reported 20-25 year followup mortality data on 2700 British men studied by respiratory questionnaire and spirometry (48). As expected, they found that the worse the initial lung function, the greater the risk of subsequent death from COPD. The presence of mucus hypersecretion was weakly associated with COPD mortality, but this trend disappeared when adjustment was made for initial degree of lung function. The authors interpreted these findings as showing that mucus hypersecretion and airflow obstruction share the common causative factor of cigarette smoking, but are otherwise unrelated to each other pathogenetically. If correct, this theory implies that airway lesions in addition to, or even instead of, simple mucus hypersecretion lead to clinically important airflow obstruction. It is therefore important to consider the whole range of intrinsic airway abnormalities caused by cigarette smoking when seeking the cause of airflow obstruction. Table 4 lists the histologic airway lesions associated with smoking. The hallmark of chronic bronchitis is hypertrophy and hyperplasia of the submucosal glands of the large bronchi, and this finding also occurs to a lesser degree in smokers, even asymptomatic ones. Goblet cells, which also secrete mucus, occur in larger numbers in smokers than nonsmokers. Other abnormalities which occur with increased frequency in smokers include basal cell hyperplasia, loss of ciliated epithelium, and squamous metaplasia (49). In the small peripheral airways, the most characteristic finding in smokers consists of a respiratory bronchiolitis, with pigmented alveolar macrophages clustering around respiratory bronchioles. Unfortunately these anatomic findings offer little help in elucidating the mechanism of a functional abnormality, i.e., airflow obstruction. More germane may be functional airway lesions associated with smoking; these appear in Table 5.

Table 4. Histologic Airway Lesions Associated with Smoking

Submucosal gland hyperplasia/hypertrophy
Goblet cell hyperplasia
Basal cell hyperplasia
Loss of ciliated epithelium
Squamous metaplasia
Respiratory bronchiolitis

Table 5. Functional Airway Lesions Associated with Smoking

Mucus hypersecretion
Ciliary dysfunction
Enhanced susceptibility to infection
Increased epithelial permeability
Immediate hypersensitivity
Small airways dysfunction

Mucus hypersecretion occurs commonly in smokers, with about half of 2 pack per day smokers reporting cough and sputum production (20). The induction of sputum production by smoke is generally attributed to its "irritant" properties, but the exact mechanism whereby this occurs is unclear. Several endogenous substances present in the airway function as respiratory mucus secretagogues; these include arachidonate metabolites such as prostaglandins and leukotrienes, histamine, and vasoactive intestinal peptide (50). Marom (51) has recently described a substance secreted by stimulated human alveolar macrophages which causes mucus glycoprotein release from cultured airway tissue. Whether any of the agents play a role in smoking-induced mucus secretion is unknown.

Cigarette smoke has been demonstrated in various animal models to depress acutely ciliary beat frequency (52). Studies in humans who smoke show that the clearance from the lungs of radioaerosols is markedly reduced, implying a failure of mucociliary transport (52). The relative contribution of increased and possibly altered mucus and depressed ciliary function to this defective clearance has not been established.

Cigarette smoking induces a number of changes in pulmonary defense mechanisms against infection. In addition to the impairment of mucociliary clearance noted above, smokers demonstrate reductions in several functions of alveolar macrophages (53). Otherwise healthy smokers contract influenza and other nonspecific upper respiratory infections more often than nonsmokers (54,55); their resulting illness also tends to be more severe. Despite this increased susceptibility to infection, however, numerous studies have failed to show permanent loss of lung function as a frequent sequela of acute respiratory infection (13,47).

Normally the epithelium of both the conducting airways and the gas exchange spaces of the lung poses a formidable barrier to the passage of substances in either direction. Recent studies using aerosols of both high and low molecular weight radioactive tracers have shown that cigarette smoking markedly increases the permeability of airway epithelium, probably by transiently disrupting epithelial tight junctions (56-58). Animal studies have revealed airway inflammation which peaks simultaneously with permeability (59). Enhanced epithelial permeability could allow easier access of inhaled antigens to the submucosal and systemic immune apparatus and cause stimulation of irritant receptors, leading to bronchospasm or mediator release (60).

The role of immediate type hypersensitivity in the development of fixed airflow obstruction has been debated for years. Recent observations by Burrows and colleagues, in epidemiologic studies in Tucson, lend some support to such a component (61,62). These workers found that smokers had higher serum IgE levels than did nonsmokers, though the smokers were less atopic as measured by skin test reactivity. Furthermore, in symptomatic smokers, increasing IgE levels correlated with worsening lung function. The authors suggested that smoking led to elevated IgE levels, either directly or indirectly, and this IgE may be causally related to airflow obstruction. Why smokers should have increased IgE is unclear. Smoke could contain tobacco antigens which sensitize the smoker, leading to a true allergic reaction. The existence of tobacco allergy is controversial; and it has still not been convincingly demonstrated that such allergy occurs, much less contributes to permanent lung dysfunction. IgE could also be increased in smokers because of the increased epithelial permeability noted earlier, allowing sensitization by inhaled antigens. On balance, the existing evidence that immediate hypersensitivity plays a role in inducing airflow obstruction in non-asthmatic patients seems tenuous.

Because most of the airflow obstruction in established COPD occurs in small airways of the lung (i.e., those < 2 mm diameter), a great deal of effort has been expended in detecting early dysfunction of the small airways in young asymptomatic smokers (63). The assumption underlying this effort has been that those persons who have small airway dysfunction early in life are those most likely to develop overt COPD later. A number of abnormalities of small airway function have been found in young smokers using relatively sophisticated tests. However, no data have appeared relating these abnormalities to ultimate prognosis. In view of the relative difficulty of these tests, their intrinsic variability and broad normal ranges, and lack of correlation with outcome, performance of these studies at present has little value outside the research setting.

Lung Cancer

Lung cancer represents a major public health concern in the United States. The mortality rate for this tumor in men has increased fourteen-fold over the last 5 decades, although recent evidence indicates that the mortality rate in men is decelerating. Women have been spared this epidemic until more recently, but now the lung cancer death rate in women is accelerating at a pace such that it will overtake breast cancer as the leading cause of cancer death in women in the United States, probably this year. Overall, lung cancer causes more than 5% of all the deaths for all ages in this country (64).

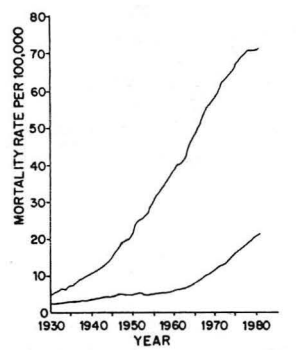

Figure 9. Age-adjusted lung cancer mortality rates for men (upper curve) and women (lower curve), 1930-1981. From reference 64.

This phenomenal increase in lung cancer mortality results from the combination of a striking increase in incidence and very modest improvement in 5 year survival. Since therapy is so disappointing, establishment and removal of

causality assume great importance. All but a few skeptics and the tobacco industry accept the fact that most cases of lung cancer in this country are caused by smoking - one informed estimate attributes 85% of cases directly to smoking (65).

The body of data causally linking smoking to lung cancer comprises several major lines of evidence:

1. Lung cancer mortality of smokers greatly exceeds that of nonsmokers.
2. Pathologic studies of the airways of smokers show premalignant changes not present in nonsmokers.
3. Animal studies have shown cigarette smoke and some of its constituents capable of causing various types of cancer.

Large prospective studies from several countries have shown that the relative risk of dying from lung cancer (i.e. mortality rate in smokers/mortality rate in nonsmokers) averages about 10 in men and 3 in women (65). The study of British physicians mentioned earlier also analyzed lung cancer mortality by smoking habits. Figure 10 shows data obtained in this study (21).

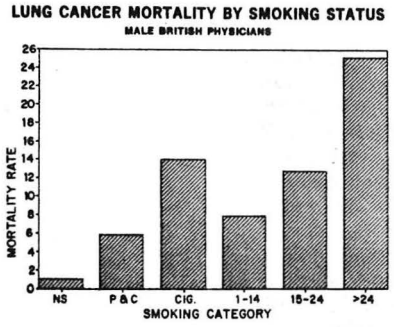

Figure 10. Lung cancer mortality rates in male British physicians by smoking status. Categories as in Figure 8. Data plotted from reference 21.

Lung cancer mortality in all cigarette smokers exceeds that in nonsmokers by 14-fold, with a clear dose-response relationship between amount smoked and mortality rate. Other studies show that lung cancer mortality varies directly with depth of inhalation of cigarettes and inversely with age of initiation of smoking. Pipe and cigar smokers are about 5 times more likely to die of lung cancer than are nonsmokers, though other investigators have found mortality ratios as low as two. The relative safety of pipe and cigar smoking is probably attributable to the alkalinity of their smoke, which causes irritation, and is difficult to inhale.

The airways of smokers demonstrate epithelial histologic changes not present

in nonsmokers. Ever since the classic autopsy studies of Auerbach (49), it has been recognized that smokers' respiratory epithelium shows basal cell hyperplasia, loss of cilia, and cellular atypia. Presumably these signs of epithelial injury are followed by squamous metaplasia, dysplasia, carcinoma in situ, and finally invasive carcinoma. All of the aforementioned premalignant histologic findings are rare in the lungs of nonsmokers, as is bronchogenic carcinoma itself.

Attempts to induce bronchogenic carcinoma in animals have been largely unsuccessful for several reasons: the prolonged smoke exposure required for the development of lung cancer; the long latent period of the disease; the intrinsic reluctance of animals to inhale cigarette smoke, necessitating unphysiologic approaches to exposure; and ventilatory patterns in animals different from those of humans. Nevertheless several models are available for testing the carcinogenicity of cigarette smoke and its components (65). These include application of smoke condensate to mouse skin and inhalation of smoke by hamsters. By use of such methods, many carcinogens have been identified in cigarette smoke, especially in the particulate phase. Some of these substances are listed in Table 6. Because of the complexity of smoke constituents and their interactions, it has proved difficult to incriminate a specific agent of paramount importance. Polynuclear aromatic hydrocarbons such as benzo(a)pyrene are particularly potent tumor initiators, and are thought to be particularly significant in tobacco smoke carcinogenesis.

Table 6. Carcinogens in Tobacco Smoke

Gas Phase
- Formaldehyde
- Hydrazine
- Vinyl Chloride
- Urethane
- 2-Nitropropane
- Quinoline
- Volatile N-Nitrosamines

Particulate Phase
- Benzo(a)pyrene
- 5-Methylchrysene
- Dibenz(a,h)anthracene
- Benzo(b)fluoranthene
- Benzo(j)fluoranthene
- Dibenzo(a,h)pyrene
- Dibenzo(a,i)pyrene
- Dibenz(a,j)acridine
- Indeno(1,2,3-cd)pyrene
- Benzo(c)phenanthrene
- Benz(a)anthracene
- 2-Methylfluoranthene

Passive Smoking

The most controversial issue of the smoking debate concerns the health effects of passive smoking, i.e., the inhalation of tobacco smoke by those who do not themselves smoke. The data demonstrating harmful effects in nonsmokers have provided the impetus for stricter smoking laws in several states (66,67), and the tobacco industry itself views this issue as the greatest threat to its survival (68).

In order to demonstrate a causal connection between passive smoking and disease, several questions must be answered:

1. Are toxic substances present in the smoke that nonsmokers inhale, and in what concentrations?
2. Are these toxic substances present in home or work environments in sufficient concentrations to pose health hazards to nonsmokers?
3. Do nonsmokers in such environments inhale and retain these substances in harmful quantities?
4. What are the data relating the presence of lung disease with passive smoking?

The smoke drawn through the butt end of a cigarette and inhaled by a smoker is mainstream smoke; that smoke which is emitted by the burning end of the cigarette into the surrounding environment is sidestream smoke. Because the combustion conditions at the tip of a cigarette change during inhalation, and because most of the time a cigarette is lit it is not being inhaled, sidestream smoke differs qualitatively and quantitatively from mainstream smoke (3). Table 7 shows the ratio of the contents of several substances found in sidestream and mainstream smoke. Sidestream smoke contains more of many constituents than does mainstream smoke; among these are such toxic substances as carbon monoxide, acetonitrile, nitrosamines, and benzo(a)pyrene. The concentration of these substances in ambient air in natural environments varies widely depending on many factors: the number and type of cigarettes smoked; the size and ventilation of the room; and the mixing of air within the room (69). Many investigators have measured levels of various tobacco smoke constitutents in natural environments such as bars, restaurants, cars, and offices. Figure 11 summarizes some of these results (70) for carbon monoxide and total particulates, representatives of the vapor and particulate phase respectively. The vertical axis shows the concentration of these substances in ambient air, with each circle a mean value measured in a different study. The horizontal lines represent ambient air quality standards for communities. Clearly constituents of tobacco smoke vary widely in different indoor environments. Although indoor concentrations are usually fairly low, sometimes they exceed standards for air quality.

Table 7. Ratio of Sidestream to Mainstream Smoke Contents

	Substance	SS/MS Ratio
Gas Phase	Carbon Dioxide	8.1
	Carbon Monoxide	2.5
	Methane	3.1
	Acetylene	0.8
	Ammonia	73.0
	Hydrogen Cyanide	0.3
	Methylfuran	3.4
	Acetonitrile	3.9
	Pyridine	10.0
	Dimethylnitrosamine	52.0
Particulate Phase	Tar	1.3
	Water	2.4
	Toluene	5.6
	Phenol	2.6
	Methylnaphthalene	28.0
	Pyrene	3.6
	Benzo(a)pyrene	3.4
	Aniline	30.0
	Nicotine	2.7
	2-Naphthylamine	39.0

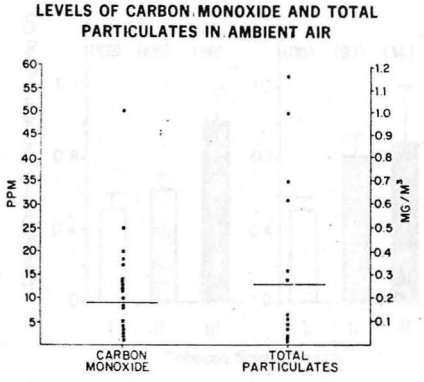

Figure 11. Levels of carbon monoxide and total particulates in ambient air. Each point is the mean of data from one study. Horizontal lines denote air quality standards for respective substances. Data plotted from reference 70.

If measurement of smoke constituents in air has yielded disparate results, assessment of the amount of these substances inhaled and retained by passive smokers has proved even more difficult. Quantification of the passive exposure to smoke is vital to the study of long-term health effects of passive smoking; at present the history is the most widely used measure of exposure, but it is clear that this is a poor quantitive tool (71). Carbon monoxide, thiocyanate, and nicotine levels in various body fluids have been assayed to estimate exposure, but all have limitations (72). Probably the best available measure of exposure is the level of cotinine in the urine. Cotinine is the principal metabolite of nicotine; unlike nicotine, it has a long half-life in the body, so it reflects cumulative exposure over several hours (73). Several studies have now demonstrated that the urinary cotinine levels of passive smokers exceed those of true nonsmokers (73-75). Figure 12 from Matsukura (75) illustrates the correlation of urinary cotinine excretion with degree of passive smoking. On the vertical axis is urinary cotinine concentration; on the horizontal axis is the subjective "smokiness" of the environment in which the nonsmokers live and work. Note that as the smokiness increases, so does the urinary cotinine; the effect is more pronounced for the home than work. Figure 13 from the same paper (75) shows the correlation of cotinine excretion with the level of active smoking. Urinary cotinine is again on the vertical axis, and amount actively smoked on the horizontal axis. Comparing this graph with the preceding one, it is clear that the nonsmokers who live and work in even the smokiest environments have cotinine levels less than those who actively smoke less than three cigarettes per day. This finding has been consistent in several studies: even the heaviest passive smoker has urinary cotinine levels only a few percent of those of active smokers. Three cigarettes per day is probably the maximum "cigarette equivalent" inhaled by passive smokers (76).

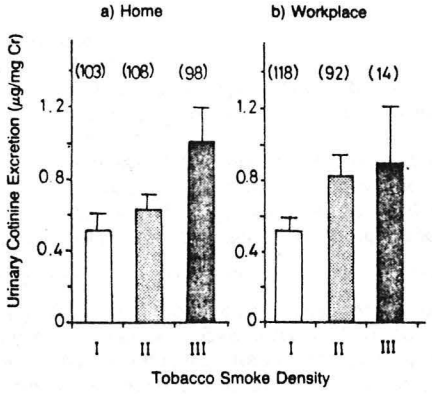

Figure 12. Urinary cotinine excretion by degree of passive smoking in the home (a) and workplace (b). I, II, and III represent groups exposed to progressively smokier environments. From reference 75.

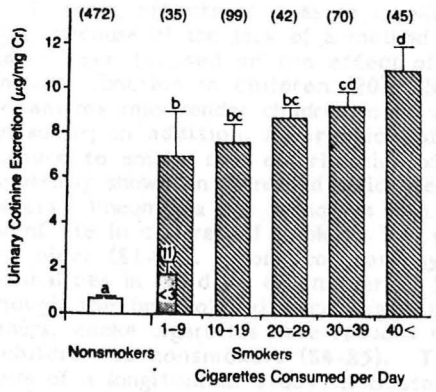

Figure 13. Urinary cotinine excretion by degree of active smoking. Note the much larger range of the vertical scale than in the previous figure. From reference 75.

What matters most, however, is not how much the passive smoker inhales, but the health effects of what is inhaled. Table 8 lists the respiratory effects which have been attributed to passive smoking.

Table 8. Respiratory Disorders Due to Passive Smoking

Acute
- Annoyance
- Irritation of eyes, nose, throat
- Worsening of asthmatic symptoms

Chronic
- Increased frequency of respiratory illness and abnormal lung function in children of smokers
- Abnormal lung function in adult passive smokers
- Increased incidence of lung cancer in spouses of smokers

By far the most commonly reported effect of cigarette smoke on nonsmokers is simple annoyance. Eye irritation occurs in about 70% of exposed nonsmokers, followed by headache, nasal irritation, and cough (77). Pulmonary functions have been measured during and after smoke exposure in healthy volunteers; only slight, inconsequential effects were found (78).

Asthmatics report wheezing twice as frequently as do non-asthmatics when exposed to cigarette smoke. Results of pulmonary function testing in these

subjects have been reported to worsen with exposure (79), but a better controlled study of 14 asthmatics showed no such effect (80). The latter finding seems difficult to reconcile with most physicians' clinical experience, and certainly does not preclude the possibility of worsened pulmonary function in some asthmatics exposed to sidestream smoke.

Chronic effects of passive smoking have proved far more difficult to study, largely because of the lack of a method to quantify exposure accurately. Many studies have focused on the effect of parental smoking on respiratory illness and pulmonary function in children (20). Smaller airways and less mature defense mechanisms may render children more vulnerable to the effects of passive smoking than adults; in addition, retardation of normal lung growth may require lower exposure to smoke than deterioration of established function. Several studies have consistently shown an increased incidence of respiratory symptoms in children of smokers. Pneumonia and bronchitis also occur with increased frequency in the first year of life in children of smokers; this effect weakens or disappears as children grow older (81-83). More controversy surrounds the issue of pulmonary function abnormalities in children of smokers. Studies have yielded conflicting results, although the bulk of evidence suggests that children whose parents, especially mothers, smoke cigarettes have reduced rate of growth of lung function compared to children of nonsmokers (84-85). Tager and colleagues recently reported the results of a longitudinal study in Boston in which they prospectively measured pulmonary function in 1,100 children over 7 years (86). These investigators found that maternal smoking significantly lowered the rate of increase in FEV_1 in children and adolescents. Using their regression model of lung growth, the authors estimated that a 16 year old male passsive smoker would attain only 93% of his predicted FEV_1. Such a decrement may not seem significant; but this child is doubly jeopardized: he starts adult life with less lung function than he should, and he is more likely to become an active smoker himself (3), by virtue of his smoking parent(s). No study has yet followed the children of smokers into adulthood to see if they are at increased risk of obstructive lung disease.

The effects of passive smoking on the lung function of adults are even less clearcut. White and Froeb (87) studied 2100 middle-aged persons enrolled in a physical fitness course. They found that nonsmokers exposed to cigarette smoke for more than 20 years in their work environment had lower FEF_{25-75} than did nonexposed workers. The passive smokers had a decrement in lung function about equal to that seen in light smokers and noninhalers, i.e. the FEF_{25-75} was about 10% less than in active and passive nonsmokers. The FEV_1 was not decreased in passive smokers. Comstock (88), in a study of 1700 adults, found a suggestive trend toward an increased occurrence of abnormal FEV_1 in passive smokers, but this did not reach statistical significance. Kauffmann (89) measured pulmonary function in about 7800 French adults. She found that the FEF_{25-75} was lower in female passive smokers over the age of 40, presumably reflecting 15-20 years of exposure to their husbands' cigarette smoke. The decrement in lung function followed a dose-response relationship with husbands' smoking in those women not employed outside the home, i.e., those in whom the only exposure to smoke arose from the husband. To summarize the data in adults, passive smoking does appear to cause a small reduction in lung function after prolonged exposure. The observed mean decrease in lung function is of dubious significance. However, by analogy with active smokers, this small mean change may represent no effect in most passive smokers and an important effect in a few. This possibility should be

investigated before it is concluded that passive smoking causes no important pulmonary functional changes in adults.

Certainly the best-publicized effect attributed to passive smoking is the induction of lung cancer. In 1981 Hirayama (90,91) reported the results of a prospective study of over 91,000 non-smoking Japanese women. He found that the mortality from lung cancer among these women varied with the smoking habits of their husbands. Women married to men who smoked more than one pack per day were almost twice as likely to die from lung cancer as were women married to nonsmokers. The more the husband smoked, the greater the risk of lung cancer for the wife. Simultaneously, a case-control study from Greece (92,93) was published which reported similar findings: nonsmoking women with lung cancer were more likely to be married to smokers than were nonsmoking women hospitalized for other reasons (the controls). Each of these studies had methodologic flaws: Hirayama's statistical methods were questioned, and some of the cases in the Greek study lacked histologic confirmation. Later in 1981 Garfinkel (94) reported data from two large prospective studies in the United States. He found a trend toward increasing lung cancer mortality in the wives of smokers compared to nonsmokers; this did not achieve statistical significance, and the risk did not increase with increasing smoke exposure. This study, too, was flawed, in that the analysis was confined to about half of the nonsmoking women because the smoking habits of the husbands of the rest were unknown. Finally, Correa (95) and colleagues performed a case-control study in Louisiana on newly diagnosed cases. They found that the odds ratio for women whose husbands smoked less than two packs per day of cigarettes was 1.18 compared to women married to nonsmokers; if the husbands smoked more than two packs per day, the odds ratio rose to 3.52. Overall, women married to smokers were twice as likely to develop lung cancer as women married to nonsmokers. Figure 14 summarizes these studies. The relative risk for lung cancer for nonsmokers is shown by spouses' smoking habits: nonsmokers, light smokers, or heavy smokers. In each study the nonsmoking group mortality is standardized to 1.0. The weight of evidence suggests that nonsmoking women married to smokers are more likely to die of lung cancer, and their risk varies directly with how heavily their husbands smoke.

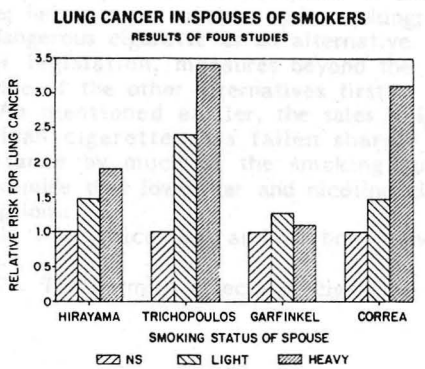

Figure 14. Lung cancer in spouses of smokers. Results of four studies are shown as relative risk for lung cancer by smoking habits of spouse: nonsmoker, light, heavy (criteria for these categories vary among the studies).

To summarize the data on the passive smoking issue, it appears that exposure to others' cigarette smoke does have some definite adverse effects: these include annoyance and eye irritation in the majority of nonsmokers; more frequent respiratory infections in children, especially young children, of smokers; and probable reduction in normal lung growth in older children. Evidence for other adverse respiratory effects of passive smoking is incomplete and contradictory, but suggestive: these include acute worsening of lung function in persons with pre-existing lung disease, abnormalities of small airway function in adults, and lung cancer in spouses of persons who smoke. Ironically, passive smoking may cause the most devastating effects, not in strangers casually exposed to smoke in public places, but in spouses and children in the home of the smoker.

The magnitude of the health consequences of passive smoking in this country remains to be determined. Such a determination depends critically on the availability of some objective means to quantify smoke exposure, possibly urinary cotinine levels. Several pieces of data thus far suggest that the extent of the adverse effects of passive smoking will be relatively minor, at least in comparison to those of active smoking:

1. Levels of various smoke constituents measured in natural environments and in body fluids of nonsmokers suggest a low level of exposure, probably the equivalent of smoking less than one or two cigarettes per day.
2. The relative risk associated with passive smoking in most of the studies cited so far is generally low, rarely exceeding 2.
3. Probably a reasonable maximum estimate for the risks of passive smoking can be obtained by looking at the risks for noninhaling smokers of cigarettes, pipes, and cigars, since these persons are obligatory passive smokers of their own smoke. In general, the risks associated with these practices are far lower than those associated with active smoking with inhalation, though substantially greater than risk for nonsmokers.

All of the foregoing notwithstanding, the magnitude of the passive smoking problem must be clearly defined. Any increase in disease, however slight, will be much less acceptable by virtue of the fact that the risk is incurred involuntarily by the passive smoker. It will be for society to decide how much disease due to passive smoke exposure it will accept.

"Safe" Cigarettes

General strategies to control the smoking problem in this country assume three forms: prevent the initiation of smoking by nonsmokers, especially young people; help current smokers quit smoking; and, if smoking cessation fails, provide a less dangerous cigarette as an alternative. The first goal will require education and/or legislation, measures beyond the scope of this talk. I will discuss the less desirable of the other alternatives first.

As mentioned earlier, the sales weighted average tar and nicotine content of American cigarettes has fallen sharply over the last two decades, indicating acceptance by much of the smoking public of the concept of "safer" cigarettes. The premise that lower tar and nicotine cigarettes are safer is based on several assumptions:

1. Tar, nicotine, and carbon monoxide are the major toxins in cigarette smoke.
2. The harmful effects of cigarette smoking are dose related.

3. Cigarettes which yield less tar, nicotine, and carbon monoxide cause less disease.

Although the first two assumptions are largely correct, the third is suspect. Before examining it in detail, however, it is necessary to understand how cigarettes are made "safe".

Tar, nicotine, and carbon monoxide yield of U.S. cigarettes is measured regularly by the Federal Trade Commission (96) using a smoking machine which draws one 2-second puff of 35 ml volume every minute until a specified length of butt remains. Cigarette manufacturers use several strategies to obtain lower tar and nicotine yields, but it is important to recognize that the yields are measured only under these rigidly defined conditions.

The general public's conception of low tar and nicotine cigarettes is that these substances are somehow removed from the cigarettes. To a limited extent this may be true: over the decade from 1968 to 1978, average tar yield fell about 32% (97). The average tobacco content per cigarettes decreased 24%, accounting for three quarters of the decrease in tar yield. At least over long time periods, one strategy in tar reduction has simply been tobacco reduction.

In general, however, low tar and nicotine cigarettes do not "contain" less of these substances than higher yield brands. Benowitz and colleagues (98) measured the total nicotine of various U.S. cigarettes and compared those values with the nicotine yield as reported by FTC. They found no correlation between nicotine content and FTC nicotine yield, i.e., low tar cigarettes contain as much nicotine as high yield brands.

How, then, are reduced yields achieved? Filters trap large amounts of tar and nicotine, and so comprise a major element of yield reduction. However, because of poor ventilation, filters increase carbon monoxide yield. This problem has been circumvented by the use of porous wrapper paper, perforations in the filter, or longitudinal channels in the filter. All these modifications result in the entrainment of room air when the cigarette is puffed, with consequent dilution of the smoke and reduction in concentration of toxins. The use of paper and tobacco which burn faster leads to fewer puffs by the smoking machine and so lower yield. Other manipulations include use of reconstituted sheet tobacco, genetic alteration in tobacco plants, and use of tobacco substitutes. Low yield cigarettes also tend to have more additives to enhance flavor.

Many studies have now shown consistently that smokers who switch to low tar cigarettes "compensate," that is, they change their smoking behavior to increase the yield of the cigarette (20). The exact stimuli for compensation are unclear, but the most widely held theory suggests that smokers try to maintain constant nicotine blood levels (99). Tar and overall "strength" of cigarettes may also influence the intensity with which they are smoked (100). Mechanisms of compensation include increases in puff volume and possibly puffs per cigarette and blocking of ventilation holes in the filter with fingers or lips. The effect of the compensation phenomenon is that smokers of low tar cigarettes may receive amounts of tar, nicotine, and carbon monoxide far in excess of those predicted on the basis of nominal yields as determined by FTC, though still somewhat less than the yield they would receive from a higher tar cigarette. Several, though not all, studies have shown a poor correlation between nominal FTC yields of nicotine and carbon monoxide on the one hand, and measures of actual exposure, such as levels of carboxyhemoglobin and blood nicotine, on the other (97,101-102).

Very little direct information exists regarding the relation between cigarette

tar yield and the incidence of lung disease. Some generalizations are possible, based on a few studies:

1. The incidence of respiratory symptoms such as cough and sputum production does decrease with decreasing tar yield (103).

2. Thus far, no evidence supports the hypothesis that low tar cigarettes result in a lower incidence of emphysema or airflow obstruction. However, no large, long-term longitudinal studies have addressed this issue.

3. The airways of smokers of low tar cigarettes show fewer epithelial changes at autopsy than do the airways of smokers of higher tar cigarettes (104).

4. Several studies demonstrate a reduced mortality rate from lung cancer for smokers of filter vs. nonfilter cigarettes (105) and low vs. high tar cigarettes (106). However, smokers of even low tar cigarettes experience lung cancer mortality rates much higher than the rates of nonsmokers or ex-smokers (105-106).

In summary, "safer" cigarettes yield less tar, nicotine, and carbon monoxide under the highly artificial conditions of smoking machine testing than they do in actual practice when smoked by people. Little available evidence suggests that their use results in reduced incidence of airflow obstruction or emphysema; they may be more effective in decreasing, but certainly not abolishing, the excess incidence of lung cancer. Physicians advising their smoking patients to switch to low tar cigarettes should be aware of the limitations of this approach, and cognizant of the fact that this alternative is far inferior to total smoking cessation.

Smoking Cessation

Thirty million Americans have quit smoking since the 1960's, but smoking cessation remains an unattainable goal for millions more. I will briefly review the health benefits which the smoker can reasonably hope to achieve with cessation; the role of the physician in helping the patient who wishes to stop smoking; and methods of smoking cessation, with particular emphasis on the use of nicotine chewing gum.

The effects of smoking cessation on the development of COPD have been extensively studied (20). Most smokers lose their symptoms of cough, sputum production, and wheeze after stopping, though residual symptoms are more likely in heavier smokers (106). Several studies have demonstrated improvement in various tests of small airways function (106,107), but the significance of this observation for subsequent development of COPD is unknown. With regard to the FEV_1, the response to cessation differs. The FEV_1 does not improve; lung function which has been lost cannot be regained. However, the rate of decline of FEV_1 returns toward normal (108). Hughes (109) has recently shown that this occurs even in patients with serious pulmonary function impairment, i.e., FEV_1 of approximately 1.4 liters. Well-matched groups of continuing smokers and former smokers with established COPD were followed a minimum of three years. The rate of decline of the FEV_1 in the continuing smokers was about 57 ml per year; in the group of former smokers, the rate of decline averaged 15 ml per year. Even in the sickest of patients with COPD, those on home oxygen therapy, there may be a benefit in smoking cessation. Flenley and coworkers have shown that in polycythemic patients receiving home oxygen, only those who quit smoking reduce their red cell mass (110). These last two studies provide grounds for encouraging smoking cessation even in patients with far-advanced disease.

The most graphic demonstration of the benefits of smoking cessation appears in mortality rates for continuing and former smokers. Figure 15 shows data from the study of British physicians (21), a group particularly suited for such a study because of the high prevalence of smoking cessation. Depicted are COPD mortality rates for nonsmokers, current smokers, and former smokers by years since cessation. Note that mortality rates rise for the first nine years after cessation above those for continuing smokers; this effect is thought to be due to high rates of cessation among those with symptoms from established disease. Eventually the mortality rate falls well below that for current smokers, though it never attains the level of nonsmokers. Figure 16 shows data from the same study for lung cancer mortality. Note the same pattern of an initial rise in mortality in the first few years, followed by a fall to levels approaching those of nonsmokers. Other prospective studies have demonstrated similar results from cessation of smoking (20).

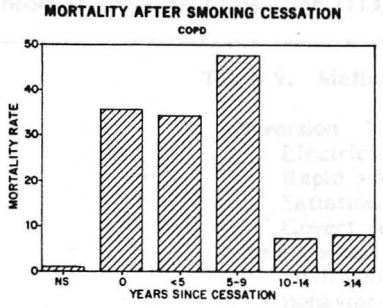

Figure 15. Mortality after smoking cessation due to COPD. Years since cessation on horizontal axis. NS=nonsmokers, O=current smokers. Data plotted from reference 21.

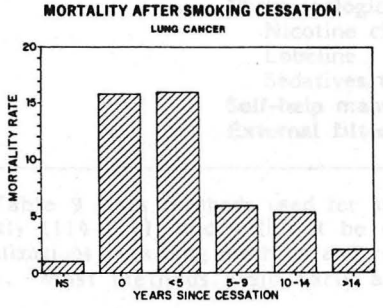

Figure 16. Mortality after smoking cessation due to lung cancer. Years since cessation on horizontal axis. NS=nonsmokers, O=current smokers. Data plotted from reference 21.

Most physicians, of course, know the hazards of smoking, as evidenced by the dramatic decline in smoking among physicians in the last two decades (3). Yet physicians in general remain pessimistic about the impact they have on their smoking patients: a survey of Massachusetts primary care physicians found that only 3% thought they were "very successful" in getting their smoking patients to quit (111). This attitude is not entirely justified. A study from Great Britain found that 5% of all smokers seeing general practitioners quit smoking for a year only on the basis of their physician's advice, a pamphlet, and a warning that followup would occur (112).

Seventy percent of smokers say they would quit if advised to do so by their physician (3), but most physicians find this improbable at best. Nevertheless physicians can encourage smoking cessation in several ways:

1. Advise patients to stop and follow up on this advice at a later visit;
2. Provide appropriate literature and referral to smoking cessation programs;
3. Provide information about the efficacy of various methods of smoking cessation;
4. Relate smoking cessation to a particular patient's health status.

The last function applies uniquely to the physician and bears special importance, since the presence of symptoms or overt disease markedly improves the likelihood of permanent cessation (113).

Table 9. Methods of Smoking Cessation

Aversion
Electric shock
Rapid smoking
Satiation
Covert sensitization
Self-Control
Environmental planning
Behavioral programming
Cognitive controls
Behavior Modification
Acupuncture
Hypnosis
Biofeedback
Relaxation training
Pharmacologic
Nicotine chewing gum
Lobeline
Sedatives/tranquilizers
Self-help manuals
External filters

Table 9 lists methods used for smoking cessation. These have been reviewed recently (114-116), and will not be discussed individually in detail. Several generalizations regarding methods and results are possible:

1. Most methods yield early abstinence rates of 60-80%, which fall to

15-25% at one year.

2. Successful quitting occurs more often in men than women (117), older smokers than younger (117), lighter smokers than heavier (115), and those with smoking-related disease than without (113,117).

3. Success rates of commercial programs are poorly documented and rarely reported (116). Those which rely on one modality alone succeed less frequently than those based on several complementary approaches.

4. Of the 30 million former smokers in the U.S., 95% quit with either no intervention at all, or at most, the advice of a physician (3).

One specific method has received considerable attention recently - nicotine chewing gum. Again the physician's role here is unique, since the method involves a drug dispensed only by prescription.

The rationale for the use of nicotine chewing gum in smoking cessation rests on the hypothesis that smokers regulate their nicotine intake to reduce withdrawal symptoms. If nicotine is supplied by a non-tobacco source, then tobacco consumption will decrease. Although there is compelling evidence that nicotine addiction maintains the smoking habit of many smokers, this is by no means universally true. Nicotine chewing gum (Nicorette; Merrell-Dow) contains 2 mg of nicotine in a buffered ion exchange resin formulated for optimal buccal absorption. Chewing one piece of gum as directed results in a plasma nicotine level somewhat lower than that obtained with smoking a cigarette (118), and without the peaks ("nicotine hits"). The gum is designed to be used in conjunction with other cessation modalities, such as behavior modification. Patients are told to chew a piece slowly whenever they feel the urge to smoke. It is recommended that the drug not be used longer than 3-6 months, but some former smokers have used it much longer. Its use is contraindicated in pregnancy and relatively contraindicated in patients with cardiovascular disease. Common side effects include hiccups, nausea, and mouth or jaw soreness.

Table 10. Placebo-Controlled Trials of Nicotine Chewing Gum

Reference	Placebo	Gum	Duration	Source of Subjects
119	5%	23%	6 months	Smoking Clinic
120	14%	31%	1 year	Smoking Clinic
121	8.7%	12.7%	1 year	Smoking Clinic
122	45%	63%	6 months	Smoking Clinic
123	20%	30%	1 year	Smoking Clinic
124	16%	29%	1 year	Smoking Clinic
125	11.4%	9.8%	1 year	Patients with smoking-related diseases
126	9.9%	8.1	6 months	General Practice

Table 10 summarizes results of several placebo-controlled trials of nicotine chewing gum in smoking cessation. Shown are the abstinence rates at followup in placebo and nicotine groups, duration of followup, and source of subjects. Two observations emerge from these data:

1. Widely variable success rates occur in placebo and active groups, with better results in smoking clinics than practice populations.
2. In most studies the active gum has succeeded more often than placebo, though sometimes by a narrow margin.

The exact role of nicotine chewing gum in smoking cessation remains to be determined. At present, the drug should be used in smokers who are motivated to quit, who have failed previously in such attempts, and who demonstrate dependence on nicotine (i.e., heavy smokers of high nicotine cigarettes who inhale and smoke early in the morning). The mere provision of the gum does not suffice; it must be associated with counselling and preferably other smoking cessation activities, such as behavior modification. The hazards of long-term dependence on the gum are undefined but probably less than those of continued smoking.

Conclusions

Over twenty years after the appearance of the first Surgeon General's report, cigarette smoking continues to cause hundreds of thousands of deaths every year. Although progress has occurred in defining mechanisms of lung injury, many questions remain. It now seems clear that smoking poses some hazard to nonsmokers. Use of "safer" cigarettes has been widely accepted by the public with little documentation of benefit. Cessation of smoking remains elusive for many, and the use of nicotine chewing gum is at best a small gain. The situation is perhaps best summarized by Warner and Murt (127), who have estimated the number of smoking-related deaths between 1964 and 1978, and compared this estimate with the number of such deaths that would have occurred in the absence of the antismoking campaign of the last two decades. Figure 17 shows their results. About 200,000 lives have been saved because people quit smoking or never started. During the same time period, however, about 3.7 million smoking-related deaths occurred. Clearly, the smoking problem persists.

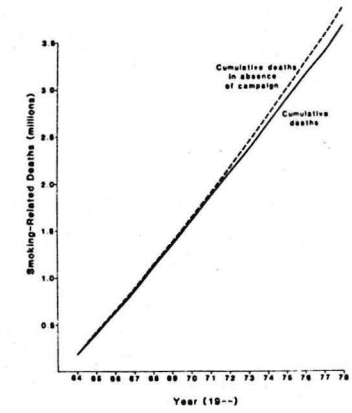

Figure 17. Cumulative smoking-related deaths 1964-1978. Solid line is actual number of deaths; dashed line, those estimated to have occurred in absence of anti-smoking campaign. From reference 127.

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APPENDIX I

DISEASES/CONDITIONS ASSOCIATED WITH SMOKING

Cardiovascular Diseases

- Aggravation of exercise induced angina
- Arteriosclerotic aneurysm of the aorta
- Arteriosclerotic perhipheral vascular disease
- Myocardial infarction
- Stroke (?)
- Sudden death
- Thromboangiitis obliterans

Cancer

- Larynx
- Oral Cavity
- Esophagus
- Urinary bladder
- Kidney
- Pancreas

Perinatal Effects of Maternal Smoking

- Reduced birth weight
- Increased mortality
- Sudden infant death syndrome

Miscellaneous

- Peptic ulcer disease
- Alteration of drug metabolism
- Polycythemia
- Peripheral blood leukocytosis

APPENDIX II

SOURCES OF INFORMATION ON SMOKING

Office on Smoking and Health
Park Building 1-10
Rockville, MD 20857
(General information, reports of Surgeon General)

Federal Trade Commission, Dallas Office
767-7050
(FTC reports of tar, nicotine, and CO contents of U.S. cigarettes)

Quit for Good Kit
Office of Cancer Communications
National Cancer Institute
Building 31, Room 10A18
Bethesda, MD 20205
(Booklets for physicians and patients)

American Lung Association - Dallas Area
521-2183
(Manuals, videotape, clinics)

American Cancer Society - Texas Division
631-3850
(Manuals, clinics)

American Heart Association - Dallas Chapter
748-7212
(Manuals, clinics)

Doctors Ought to Care (DOC)
c/o Thomas Houston, M.D.
Floyd Medical Center
304 Turner-McCall Boulevard
Rome, GA 30161
(Physician antismoking advocacy group)

Action on Smoking and Health (ASH)
2013 H Street NW
Washington, DC 20006
(Lay antismoking advocacy group)

Texas Clean Indoor Air Association
11005 Garland Road, Suite 200
Dallas, TX 75218
324-3880
(Local antismoking advocacy group)

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