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Introduction

Research indicates that cigarette smoking causes cancer of the lung, larynx, oral cavity, and esophagus, and is significantly associated with pancreas, urinary bladder, and kidney cancer in both men and women (102, 103, 104). This conclusion is based on epidemiologic, pathologic, and experimental evidence collected over the past half-century.

A quarter-century ago lung cancer was found to be related quantitatively to cigarette "tar" cumulatively inhaled. This finding, along with much other evidence, led to the production and widespread use of today's lower "tar" and nicotine cigarettes.²

The evidence summarized in this section demonstrates that lower "tar" and nicotine cigarettes produce lower rates of lung cancer than do their higher "tar," higher nicotine predecessors, but smokers of lower "tar" and nicotine cigarettes still have much higher cancer morbidity and mortality rates than do nonsmokers, as well as a higher incidence of other diseases associated with smoking.

One important research concern is to identify the human carcinogenic chemical or chemicals in the particulate and gas phases of cigarette smoke. Multiple metabolic transformations are available in the human body for the several thousand chemicals in cigarette smoke, a number of which could lead to carcinogenic activity in model animal systems.

Another important research concern is that changes in cigarette composition to reduce "tar," nicotine, and possibly even total smoke exposure may inadvertently increase, or fail to decrease, those chemical constituents still largely unidentified that contribute to cardiovascular and pulmonary diseases, pregnancy complications, and fetal and perinatal deaths.

A third area of concern is that the animal model systems used to predict human disease from cigarette smoking require additional study and correlation with the human situation, if these models are to serve as a basis for modifying cigarette composition. When disease-producing chemicals are identified, their reduction or elimination should be associated in the animal models with a decrease in the disease(s) predicted and without untoward effects.

This section summarizes data on the human cancers associated with lower "tar" and nicotine cigarettes, as compared with the "standard" cigarette of the 1930s or 1940s. In addition, it compares pathologic (autopsy) studies on bronchi of cigarette smokers of a quarter-century ago with bronchi of lower "tar" and nicotine cigarette smokers. Further, the section describes the identification, metabolism, and possible mechanisms of action of certain carcinogenic chemicals in both the particulate and the gas phases of cigarette smoke. Finally, the

² Editor's note: The members of the Working Group preferred the expression filter-tipped, lower "tar," lower nicotine cigarettes. However, the editors have shortened this expression to lower "tar" and nicotine cigarettes because, while all lower "tar" and nicotine cigarettes are filtered, not all filter-tipped cigarettes are lower "tar" and nicotine products.

section presents a series of conclusions and recommendations for research.

Epidemiologic Studies

Background

It has been established that cigarette smoking causes cancer of various organs including the lung, oral cavity, esophagus, and larynx, as well as exhibiting a significant association with cancer of the pancreas, bladder and kidney (102). Epidemiological studies, both retrospective and prospective, have shown a dose-response effect; that is, risk increases with the length of time the individual has smoked and with the number of cigarettes consumed. Such studies have demonstrated that, upon cessation of the smoking habit, risk for developing these cancers declines; the slope of the decline depends on the duration and extent of the former habit. For an individual who has smoked more than 20 cigarettes per day for more than 20 years, no reduction in risk of cancer development is noted for at least 3 years; however, the risk decreases thereafter and, after 10 years of cessation, begins to approach that of one who has never smoked.

From these epidemiological observations, it has been predicted that a smoker's cancer risk would be reduced if the "tar" yield of a cigarette were reduced, provided that the individual does not compensate by more frequent and deeper inhalation of lower "tar" cigarettes.

The trend toward cigarettes with lower "tar" and nicotine started more than 25 years ago with the introduction of a number of filter brands. This trend continued over the years with a greater number of filter brands on the market. Since the early 1970s there has been a rapid increase in production of cigarettes with 15 mg or less "tar" and 1.0 mg or less nicotine. By 1980, brands with these characteristics are expected to account for more than 40 percent of total sales (70). In 1950, the average cigarette had 40 mg "tar" and 2.2 mg nicotine. Today's filter cigarettes average about 14 mg "tar" and 1.0 mg nicotine. The downward trend, particularly in terms of "tar" in filter cigarettes, is continuing. There are increasing numbers of cigarettes yielding 10 mg "tar" or less, and these have only one-fourth the "tar" yields common 30 years ago. Although total consumption has increased from 365 billion cigarettes in 1950 to 620 billion cigarettes in 1979, consumption per capita by persons 18 years of age and over has decreased by 5 percent in recent years—from 4,148 cigarettes in 1973 to 3,924 cigarettes in 1979 (101), reflecting the 30 million smokers who have quit (75). On the other hand, the proportion of smokers who reported that they smoke 25 or more cigarettes per day increased from 23 percent in 1970 to 28 percent in 1978.

Epidemiologic Studies

Three epidemiologic studies—by the American Cancer Society, the American Health Foundation, and the National Cancer Institute—have evaluated the effect of lower “tar” and nicotine cigarettes on lung cancer mortality.

The American Cancer Society conducted a prospective study in which more than a million men and women in 25 States were enrolled in 1959 and traced for 13 years. Subjects completed a questionnaire on smoking habits upon enrollment, and the survivors completed another questionnaire in 1965. An analysis of mortality from lung cancer was made for two 6-year periods: July 1960 to June 1966 and July 1966 to June 1972. The analysis included males and females who, in 1959–60 and in 1965, reported either that they had never smoked regularly or that they smoked cigarettes regularly but never smoked cigars or pipes regularly (36).

On each questionnaire, subjects reported the brand that they usually smoked. From this information and from various reports of “tar” and nicotine published in the years in which the questionnaires were completed, subjects were classified as high “tar” and nicotine (T/N) smokers, medium T/N smokers, and low T/N smokers. In the first period, high T/N brands were defined as cigarettes with 25.8 or more mg of “tar” and 2.0 or more mg of nicotine. Low T/N was defined as brands with less than 17.6 mg “tar” and less than 1.2 mg nicotine. The medium T/N category was between these two groups. By the time the second questionnaire was distributed, there had been an increase in the number of filter brands on the market and a general lowering of T/N levels. Low T/N was defined in the same way as in the first period, but the high T/N category had to be reset at a somewhat lower level.

Smokers in the three groups were compared by a matched groups analysis. In this procedure, the groups were matched by age and other factors, including number of cigarettes smoked per day, age at which smoking began, race, urban or rural residence, occupational exposures, education, income, and prior history of lung cancer or heart disease.

To be counted in the study, at least one person in each of the three T/N groups had to be matched on all the variables mentioned above. The adjusted number of lung cancer deaths was obtained by dividing the number of deaths in each triad by the lowest number in each of the three groups. The adjusted numbers of deaths were then summarized for each of the three T/N groups.

Table 1 shows the number of subjects and the unadjusted and adjusted number of lung cancer deaths in the high, medium, and low T/N groups by sex and time period. In both sexes, deaths were fewest in the low T/N group.

Figure 1 shows the lung cancer mortality ratios based upon the adjusted number of lung cancer deaths. The number of adjusted deaths for high T/N smokers was set at 1.00, and the adjusted number of lung

TABLE 1.—American Cancer Society Matched Groups Study

Sex	Period	High T/N	Medium T/N	Low T/N
<u>Number of subjects at start of period</u>				
Male	1960-1966	68,068	54,999	15,860
Male	1966-1972	29,157	40,090	6,882
Female	1960-1966	44,187	59,750	32,708
Female	1966-1972	22,909	49,198	16,808
<u>Unadjusted number of lung cancer deaths</u>				
Male	1960-1966	567	459	108
Male	1966-1972	437	566	78
Female	1960-1966	65	82	30
Female	1966-1972	89	149	44
<u>Adjusted number of lung cancer deaths</u>				
Male	1960-1966	122.4	117.4	101.0
Male	1966-1972	89.6	84.5	70.6
Female	1960-1966	48.3	41.4	27.4
Female	1966-1972	58.1	42.2	36.2

SOURCE: Hammond et al. (36).

cancer deaths for medium and low T/N smokers was compared with it. The mortality ratio for male low T/N smokers was 0.83 and 0.79 in the two time periods; for females, it was 0.57 and 0.62. The mortality from lung cancer in low T/N cigarette smokers for both sexes over the combined time periods was 26 percent lower than for high T/N smokers. The mortality ratio for smokers of medium T/N cigarettes was lower than for high T/N, but greater than for the low T/N smokers.

Low T/N smokers had mortality ratios considerably higher than men and women who had never smoked. In men, the mortality ratio of nonsmokers for lung cancer was only 9 percent of that of the low T/N smokers; in women, the nonsmoker rate was 43 percent as high in the first 6-year period and 22 percent as high in the second 6-year period.

It is important to note that the T/N level of the brand of cigarettes smoked was not as significant as the number of cigarettes smoked. The adjusted number of deaths in men and women who smoked fewer than 20 high T/N cigarettes per day was compared with those who smoked 20 or more low T/N cigarettes per day. Figure 2 shows the mortality ratios. The less-than-20-cigarettes-per-day high T/N smokers had mortality ratios from 67 percent to 27 percent *lower* than the men and women who smoked 20 or more low T/N cigarettes per day.

A retrospective study of lower "tar" and nicotine cigarettes was conducted by the American Health Foundation (111). Data on lung cancer cases in white males and females were collected, and interviews were conducted in hospitals in six U.S. cities between 1969 and 1976. Control cases were selected from patients in the same hospitals on the basis of an absence of a history of tobacco-related diseases.

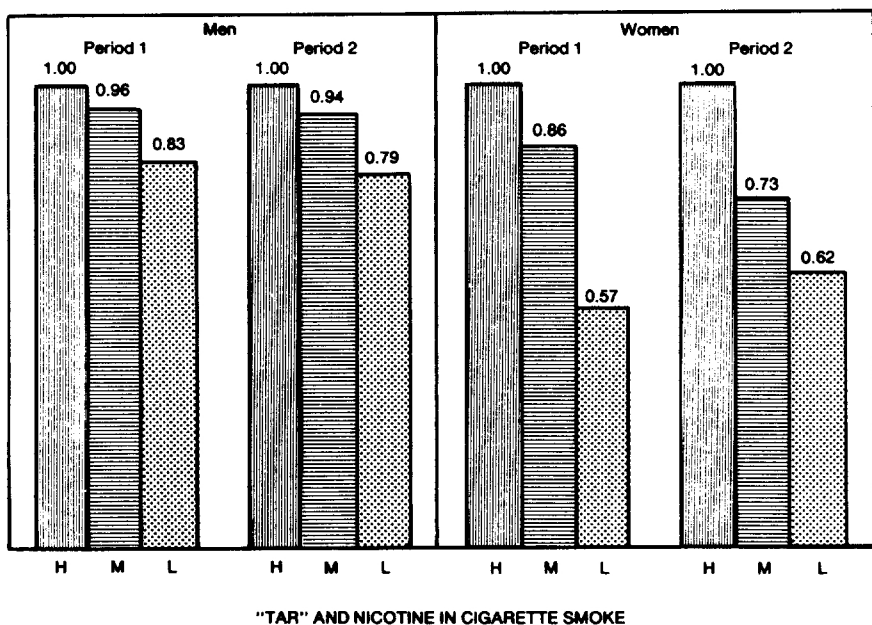


FIGURE 1.—Lung cancer mortality ratios, by amount of "tar" and nicotine in cigarette smoke

NOTE: H=high; M=medium; L=low.

SOURCE: Hammond et al. (56).

Cigarette smokers were classified as long-term filter smokers (those who smoked filter cigarettes currently and for at least 10 years) and nonfilter smokers (current smokers of nonfilter brands).

Relative risks for filter smokers and nonfilter smokers were computed by number of cigarettes smoked per day. Figure 3 shows the relative risk of the male filter smokers as a percent of the risk for nonfilter smokers. The percentages ranged from 61 to 89. Females showed the same pattern, with the relative risk for long-term filter smokers ranging from 38 to 79 percent of the nonfilter group. Only in the heaviest smoking category (a small number of cases) were the relative risks the same.

This risk ratio of filter smokers to nonfilter smokers remained low when the data were adjusted for factors such as duration of smoking, amount of cigarette smoking, age, and alcohol consumption.

The American Health Foundation study also analyzed the risk of larynx cancer for long-term filter smokers versus that for nonsmokers. There were many fewer cases of larynx cancer than of lung cancer, but the same general pattern was observed. In men, the relative risk for long-term filter smokers was between 50 percent and 75 percent of the

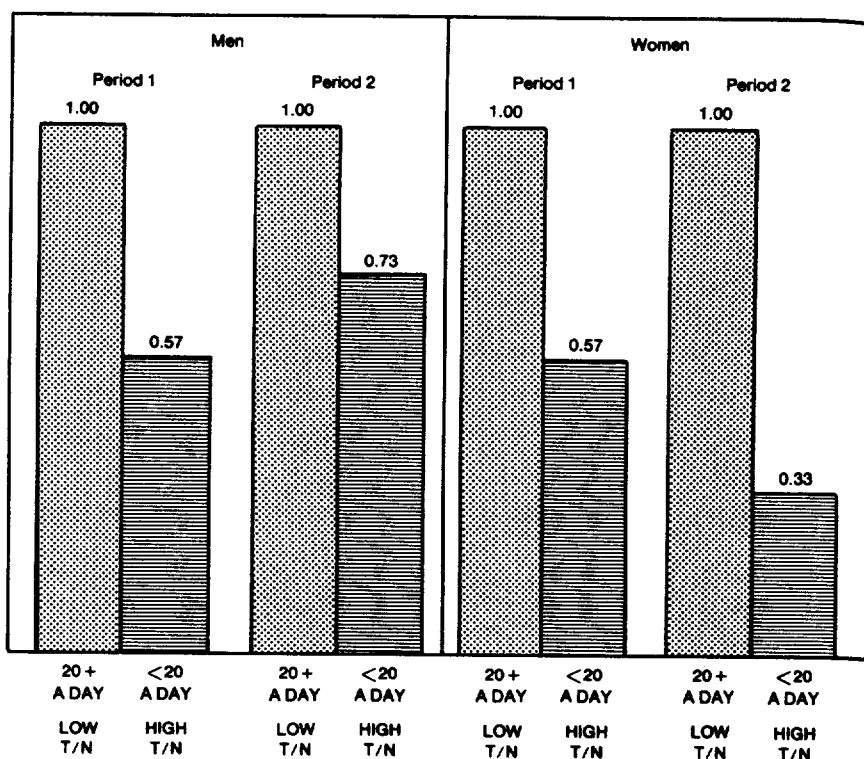


FIGURE 2.—Lung cancer mortality ratios, by number of cigarettes smoked per day and amount of “tar” and nicotine in cigarette smoke

SOURCE: Hammond et al. (36).

risk for nonfilter smokers in various number-of-cigarettes-smoked-per-day categories. Women showed the same pattern.

A third epidemiologic study was conducted in Austria (69). This project, part of an international study of smoking by the National Cancer Institute, analyzed data on a sample of 414 lung cancer patients and 828 controls. Cigarettes were categorized into three groups by T/N level: Group I, cigarettes with “tar” yields below 15 mg; Group II, 15 to 24 mg “tar”; and Group III, 25 mg or more “tar.” These groups were assigned values of 1, 2, and 3, respectively, to indicate average exposure.

The average “tar” exposure in cancer patients (2.596) was significantly higher than for controls (2.026). Scores for total “tar” exposure were computed as the product of the number of cigarettes smoked per day, the number of years smoked, and the “tar” level (1, 2, or 3).

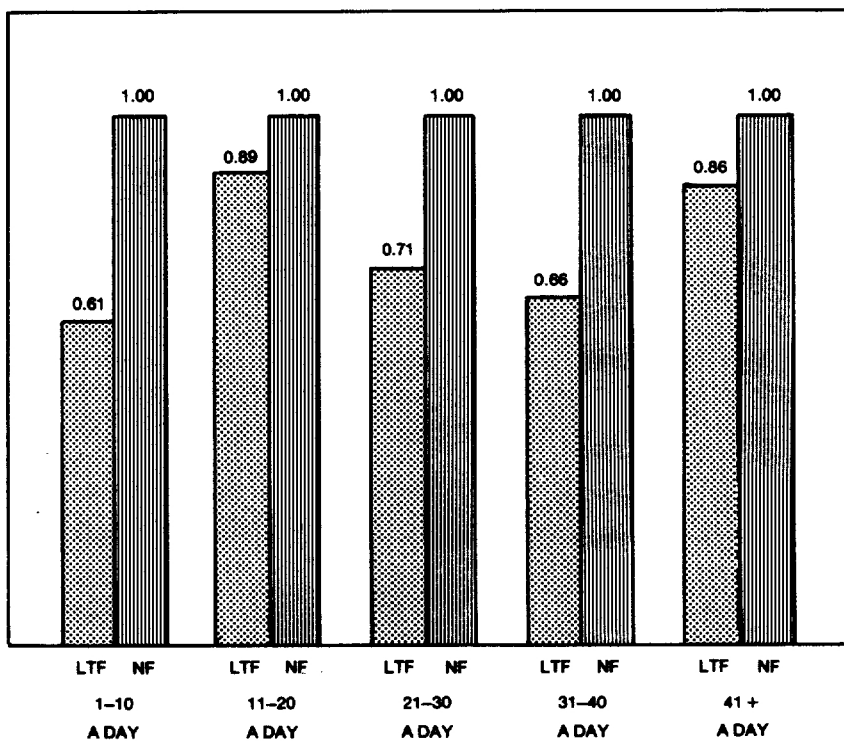


FIGURE 3.—Relative risks of lung cancer in long-term filter smokers (LTF) compared with nonfilter smokers (NF) by number of cigarettes smoked per day, males

SOURCE: Wynder and Stellman (11).

Relative risks were then computed by these scores. These risks increased directly with “tar” exposure scores, from 1.6 for scores lower than 500 to a relative risk of 6.1 for scores higher than 5,000.

Discussion

Cigarette smoke condensate of present cigarettes produces fewer tumors on mouse skin than did that of cigarettes tested some 30 years ago (109). This difference is probably because today’s cigarettes contain more tobacco stems and more reconstituted tobaccos and have cigarette paper with higher porosity, all contributing to smoke condensate that is less tumorigenic to the experimental animal. Changes in chemical composition of the smoke may be a factor. Using just one chemical component as a carcinogenic indicator, researchers have shown that benzo[a]pyrene (BaP) content is significantly lower in today’s cigarettes than in cigarettes of 30 years ago (Figure 4) (49).

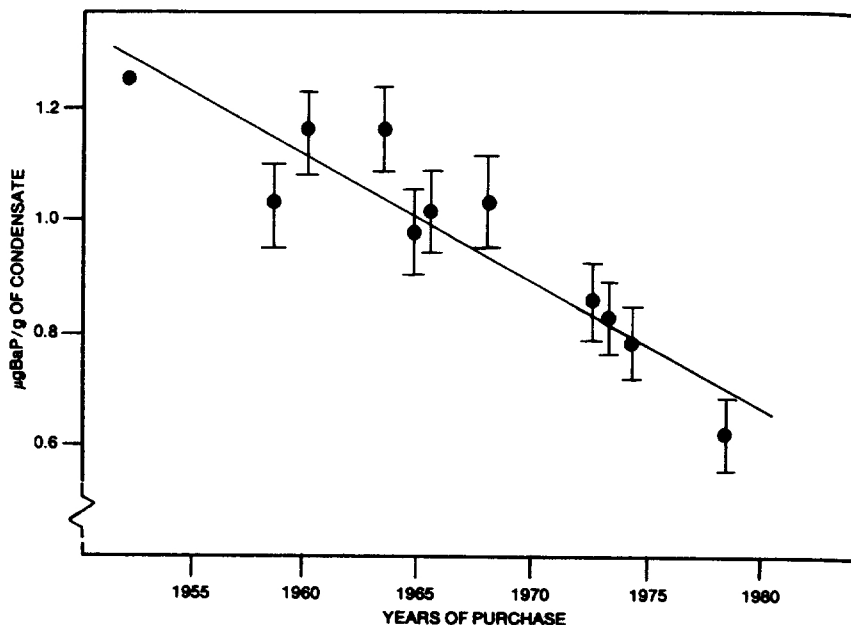


FIGURE 4.—Decrease of benzo[a]pyrene in the smoke of U.S. nonfilter cigarettes (85 mm)

SOURCE: Hoffmann et al. (49).

Many brands of cigarettes classified as lower “tar” and nicotine were introduced in the 1970s and had a remarkable growth in sales. The average “tar” in lower “tar” and nicotine brands in 1978 was about 10 mg. Many brands of cigarettes classified as lower “tar” and nicotine in studies reported in the 1960s and early 1970s would be classified as medium “tar” and nicotine cigarettes in the 1980s. Therefore, it might be assumed that cigarettes with lower “tar” and nicotine yields afford even lower cancer risks. But this is not necessarily true. Studies of smoking patterns suggest that smokers of the lower “tar” and nicotine cigarettes tend to inhale more deeply (44, 98), have higher amounts of carboxyhemoglobin than predicted (106), and have higher than expected carbon monoxide in their exhaled breath (54). On the other hand, the lower “tar” and nicotine cigarettes of 1980 have as little as one-fourth the “tar” and nicotine of the cigarettes of 1950, and even if some compensation takes place, actual net smoker exposure is probably much lower.

There is evidence that machines that measure “tar” and nicotine content are not suitable for measurements of smoke from lower “tar” and nicotine cigarettes with perforated filter tips (62) and that the

“tar” and nicotine in the inhaled smoke may be more than indicated by the test procedures.

Epidemiological studies thus far have only studied cohorts who began their smoking careers with the old nonfilter, high “tar” and nicotine cigarette. Only in the years to come can we determine the risk of those individuals who began smoking with lower “tar” and nicotine cigarettes, and it is important to study this risk.

As the “tar” yields of cigarettes decrease further, it is probable that flavor additives will be increasingly used. Their potential biologic activities need to be investigated and monitored on an ongoing basis.

Epidemiological data in addition to chemical and biological findings show the reduced risk among lower “tar” and nicotine cigarette smokers, which was predicted because of chemical and biological data previously known. No such clear demonstration of effect exists, however, for cardiovascular disease, chronic obstructive pulmonary disease, or pregnancy. The character and mechanisms of smoke components causing these diseases probably differ significantly from those acting in carcinogenesis.

Pathologic Studies

Histological changes in the tracheobronchial tree in noncancer patients can be observed at autopsy in direct proportion to the number of cigarettes smoked per day during life. Lung cancer patients have the most advanced histological changes in their remaining epithelium (4, 6). Ex-smokers who quit for at least 5 years show greatly reduced histologic changes. This finding, together with the observation of cells with disintegrating nuclei in the epithelial lining, suggests that a healing process has taken place in these cases (5).

To evaluate the effect of smoking lower “tar” and nicotine cigarettes on histologic changes in bronchial epithelium, male patients who died of causes other than lung cancer in 1970–77 were compared with those who died in 1955–60 (3). None of the men who died in the later period could have, in the last 5 to 10 years of their lives, smoked cigarettes that were as high in “tar” and nicotine content as the cigarettes smoked by men who died in the earlier period. Sections from the tracheobronchial tree of 211 men who died in the earlier period and of 234 men who died in the later period were put in random order for microscopic study. A total of 20,424 sections were read, an average of 46 sections per patient. Histologic changes studied included basal cell hyperplasia, loss of cilia, and occurrence of cells with atypical nuclei. Smokers had these changes far more frequently than did nonsmokers, and within each group the percent with these changes increased with the reported number of cigarettes smoked per day. Nonsmokers in both time periods had about the same proportion of these changes. But in each smoking category (adjusted for age), the men who died in 1970–77

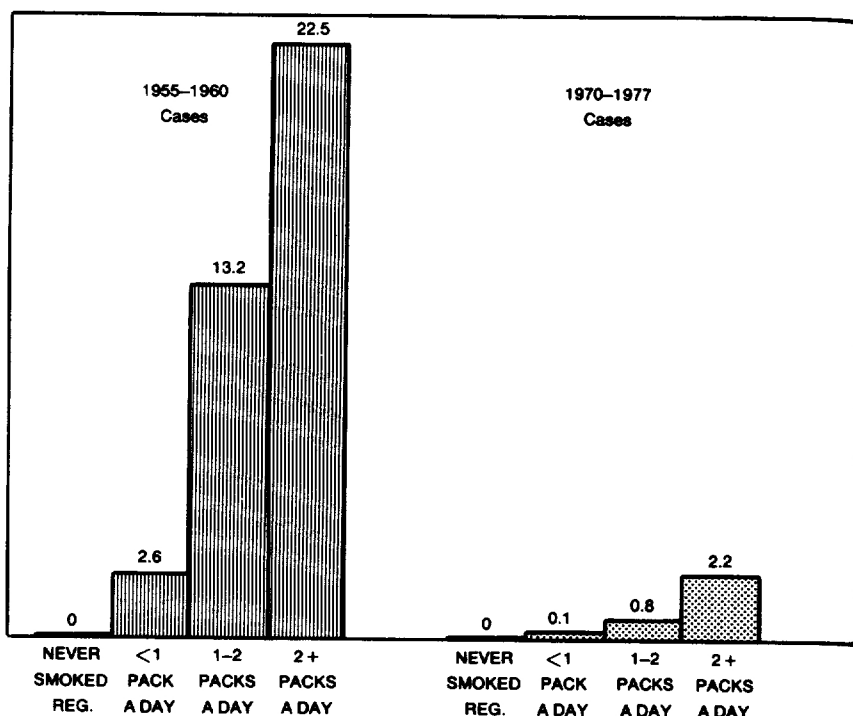


FIGURE 5.—Percent of sections with advanced lesions by smoking habit in two periods

SOURCE: Auerbach et al. (5).

had far fewer histological changes than those who died in 1955-60. Figure 5 shows the percentages with the most advanced histologic change recorded (carcinoma-in-situ) in the 1955-60 and 1970-77 groups. These changes were not found in nonsmokers in either group, and they were found far more frequently in smokers in the 1955-60 cases than in the 1970-77 cases. In two-pack-a-day smokers, 22.5 percent of the 1955-60 group had this advanced change, compared with only 2.2 percent of the two-pack-a-day smokers in the 1970-77 group.

Discussion

Epidemiologic and experimental pathologic studies yield some evidence that filter, lower "tar" and nicotine cigarettes produce fewer neoplasms than the nonfilter cigarettes of 25 to 30 years ago. While it is not always possible to directly extrapolate data on animal experimental carcinogenesis studies to man, the data summarized in this section show the predicted lower mouse skin tumorigenesis of filtered, lower "tar" and nicotine cigarette "tar" on an equal weight basis. Post-

mortem studies of the human lung further support the finding that the filter, lower "tar" and nicotine cigarettes are less oncogenic than the nonfilter cigarettes of 25 to 50 years ago.

Experimental Chemical Carcinogenesis

While epidemiologic, pathologic, and experimental studies all point to polycyclic hydrocarbons within the "tar" moiety of inhaled cigarette smoke as potential carcinogens for man, additional work is needed to determine whether nicotine plays a major role as a cocarcinogen. Further, nicotine and nor nicotine give rise to two carcinogenic nitrosamines that are found only in tobacco products. Tables 2, 3, 4, and 5 list known carcinogenic agents in both the particulate and the gas phases of cigarette smoke.

Russell (90) recently suggested that a lower "tar," medium nicotine cigarette would be more attractive to smokers and tend to promote their use while minimizing health risk. This action cannot be supported without further research on nicotine's effects in carcinogenesis. Studies should address not only nicotine carcinogenesis, but also the chemical's effects on the cardiovascular, gastrointestinal, endocrine, and central nervous systems. Nicotine has been found to have potent physiologic effects on these systems.

The following discussion briefly considers the probable routes of metabolism and binding to critical cellular components of the chemicals in the particulate and gas phases of cigarette smoke thought most likely to be carcinogenic for man.

Most procarcinogens are metabolized through a mixed function oxidase system, which is composed of the hemoprotein cytochrome P-450, NADPH-dependent cytochrome P-450 reductase, and phospholipid. Various forms of P-450 have been characterized immunologically (99), and some have been separated electrophoretically (78). The amino acid composition and partial sequences of some forms of P-450 have been elucidated recently (15). A treatise on the physicochemical characteristics and physiological function of P-450 has also appeared (78). The different forms of P-450 may have differential effects in the production of metabolites (33, 81, 91). Metabolic activation of most carcinogens by the P-450 mediated oxygenases is considered to afford structures that are strong electrophiles and thus prone to attach to cellular nucleophiles, including proteins, nucleic acids, and other macromolecules (21, 72, 73).

Polycyclic aromatic hydrocarbons present in tobacco smoke are typified by benzo[a]pyrene (BaP). BaP is found in the soil and atmospheric particulates of cities, with relatively high concentrations around highways, airports, factories, and similar installations (51). Since it occurs in pyrolysis products, such materials as soot, tar, and charcoal-broiled or thoroughly roasted foods all have measurable

levels. BaP also has been identified in forest soils, in volcano effluents (50), in marine sediments, and even in the deeper layers of soil from the permafrost regions of the earth (52).

BaP was among the first polycyclic aromatic hydrocarbons isolated from coal tar and has been used for various experimental purposes for 50 years.

On the basis of metabolic studies with phenanthrene, Boyland (16) hypothesized that hydrocarbons were metabolized through arene oxide or epoxide intermediates. Such intermediates could account for the identification of phenols, dihydrodiols, premercapturic acids, and mercapturic acids as metabolites of phenanthrene or naphthalene, all depending on whether the epoxide reacted with water or glutathione or rearranged nonenzymatically.

The information gathered from various experiments *in vitro* with metabolites of BaP, DNA adducts, and presumed intermediates led to the conclusion that both the dihydrodiol and epoxide moieties were required for carcinogenic activation of BaP and other polycyclic hydrocarbons. In the case of BaP, the potent carcinogenicity of the 7,8-dihydrodiol indicated that it was probably an intermediate toward the final activated carcinogen (57).

A number of studies have substantiated the concept that a "bay" region is involved in transformation of most polycyclic hydrocarbons to the activated intermediate (74, 96, 108).

The diol epoxide of BaP thus appears to be the metabolically derived strong electrophile that is capable of reacting with critical constituents in the cell. The reaction of this activated intermediate with nucleic acids has been followed both *in vivo* and *in vitro* (59, 61, 76).

P₁-450 is also a component of the enzyme system called aryl hydrocarbon hydroxylase (AHH) (2). The major phenolic detoxification product, 3-hydroxybenzo[a]pyrene, results from nonenzymatic rearrangement of the initial 2,3-epoxide formed by the P₁-450 (112). The phenols are amenable to conjugation by glucuronyl transferase or sulfotransferase, leading to solubilization and more rapid excretion. The available evidence suggests that in different strains of mice high AHH inducibility leads to increased susceptibility to hydrocarbon-induced tumors. The genetics of AHH inducibility in mice have been thoroughly discussed (77, 78, 79). Attempts have been made to extend some aspects of the AHH work to humans, despite the variability in results noted in human populations (2).

Although there is currently more emphasis on the reactions of the electrophilic species from carcinogens with nucleic acids, the binding of carcinogens to proteins had been noted many years earlier (71). More recent efforts have shown that ligandin, a hepatic protein that binds anionic metabolites of glucocorticoids (67), also binds some carcinogens such as polycyclic aromatic hydrocarbons and aminoazo dyes but not aromatic amides (68).

Aromatic amines are found in tobacco smoke. These compounds are formed during the burning of tobacco, including toluidines, 2-naphthylamine, and unknown aminofluorenes. These compounds are also activated through the P-450 system similar to that for the aromatic hydrocarbons. Ring-hydroxylated products of aromatic amines apparently are detoxification products. For most of the carcinogenic aromatic amines or amides investigated, N-hydroxylation apparently was the activation route.

Further reaction of the N-hydroxy compounds was found necessary to afford forms capable of reacting with nucleic acids or proteins. Acetate, glucuronide, sulfate, or even phosphate esters of the N-hydroxy amide had the required characteristics; the products from *in vitro* reactions with nucleic acid were the same as those isolated from reactions *in vivo*. In some but not all cases, the carcinogenicity of the parent amide or amine roughly correlated with the enzyme levels in a target organ.

One of the most readily obtained of the activated esters, N-acetoxy-N-2-fluorenylacetylamide (N-AcO-FAA) has been employed in many model experiments to study effects on the structure and function of nucleic acids. N-AcO-FAA forms a major adduct with DNA where approximately 84 percent of the fluorene residue was linked to the C-8 of guanine by arylamidation, affording N-(deoxyguanosin-8-yl)-2-fluorenylacetylamide, which retained the N-acetyl group (28).

An additional means for activation and adduct formation of aromatic amine derivatives has been investigated by C.M. King et al. (58). An enzyme termed N-O-acyltransferase forms derivatives that are quite reactive and readily form adducts with RNA.

More recent work points toward attachment by the activated aromatic amines and amides to still other positions on the bases of nucleic acids (10, 55, 56).

Numerous model studies with N-AcO-FAA modified nucleic acids have shown a change in function of the altered nucleic acid. However, none has shown the exact role in the process of carcinogenesis; this remains an area for further investigation (94).

Although the aminoazo dyes and aromatic amines or amides are activated in a similar fashion and both bind to proteins, the proteins involved differed somewhat (8, 9, 68, 97).

Relatively less emphasis has been placed recently on carcinogen-protein interactions than on carcinogen-nucleic acid interactions. In view of the essential function of the proteins, it seems their interactions with carcinogens require more investigation.

N-Nitroso compounds found in tobacco smoke include those derived from nicotine, nitrosornicotine and related compounds, N-nitrosodiethanolamine, and nitrosodimethylamine. Metabolic activation of dialkylnitrosamines is necessary for expression of their toxic and hepatocarcinogenic effects. Oxidative metabolism of dimethylnitrosa-

mine, for example, is accomplished by the liver microsomal P-450 system yielding an unstable (α -hydroxymethyl)methylnitrosamine, which forms formaldehyde and an unstable methylnitrosamine. In turn, this molecular species collapses with release of nitrogen and formation of the methyl carbonium ion, CH_3^+ , which alkylates proteins, nucleic acids, and probably other cellular constituents. The intermediacy of the (α -hydroxymethyl)methylnitrosamine is substantiated by the potent mutagenicity and outstanding carcinogenicity of the more stable (α -acetoxymethyl)methylnitrosamine (11). More recent studies suggest that other oxidation pathways may also be involved (66).

Tobacco and its resultant smoke contain two carcinogenic N-nitrosamines that are formed from nicotine and nor nicotine (Table 2) (46, 47). N-Nitrosornicotine (NNN) gives rise to α -hydroxy N-nitrosamines, which are unstable and decompose finally to oxocarbenium ions, the suspected ultimate carcinogenic forms of NNN. Most of the oxocarbenium ions react with water, yielding a keto alcohol and a hydroxyaldehyde (19). The other carcinogenic and tobacco specific N-nitrosamine is 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which is also α -hydroxylated. The methyl hydroxylation product gives rise *via* an oxidiazohydroxide to the same carbonium ion as the 2'-hydroxylation of NNN (42).

Alkylnitrosoureas afford alkylating moieties without the need for metabolic activation; spontaneous decomposition occurs at alkaline pH values. However, the organs affected by alkylnitrosoureas may vary, depending on the route of administration and the animal model.

Nitrosomethylurea, most widely used in model experiments, can cause tumors in brain, breast, stomach, liver, heart, skin, kidney, intestinal tract, bladder, trachea, and peripheral nervous system (107); administration to pregnant animals often leads to tumors of the nervous system in the offspring many months later (60).

The alkylating moiety (carbonium ion) formed from a nitroso compound may attach to a variety of positions in the nucleic acids bases, on the phosphate backbone, or on the ribose portion of the RNA.

Environmentally, nitrosamines and related structures represent a problem, since they may be formed endogenously from secondary or tertiary amines, amides, or ureas and nitrite, available from reduction of nitrate by bacteria of the salivary plaque. Nitrate has a widespread distribution in dietary vegetables and grains. Although each individual has therefore the capacity to form nitroso compounds, endogenous nitrosation can sometimes be inhibited by ascorbic acid, propyl gallate, or other compounds that compete with the amine or amide for nitrous acid. This is not a panacea, for ascorbic acid may enhance nitrosation of certain amines (18). Furthermore, innocuous nitroso compounds, such as nitrosoproline, or even some aliphatic nitro alcohols, can provide a nitroso group to form carcinogenic nitrosamines or amides by transni-

triosation (26, 95). Although certain bacteria are instrumental in formation of nitrosamines within the organism (40), bacteria also degrade nitrosamines (89), leading to a balance between endogenous formation and decomposition of nitroso compounds. During the chewing of tobacco, N-nitrosornicotine is formed in the oral cavity (41). Although it has not been demonstrated, it may be assumed that under certain conditions the carcinogens NNN and NNK can also be formed from nicotine in other organs or sites in man.

Another carcinogen, vinyl chloride, has also been identified in tobacco smoke. Metabolically, vinyl chloride is activated through the P-450 system by formation of a halogenated epoxide (7, 43, 113). Such an epoxide may yield halogenated aldehydes or alcohols through rearrangement (45, 113) or through derivatives of glutathione through S-transferase (45).

In summary, most of the identified carcinogens found in tobacco smoke are activated through the P-450 system to electrophilic compounds, which react with proteins, nucleic acids, perhaps lipids, and other cellular constituents. Since there are many constituents of tobacco smoke, only the activation pathways of BaP, typical aromatic amines, nitrosamines, and vinyl chloride have been presented here. The activation pathways of the other carcinogens found in tobacco smoke may be similar.

Although the pathogenesis of several types of cancer, chronic obstructive pulmonary diseases, and cardiovascular diseases is linked to different tobacco smoke constituents, the epidemiologic associations with cigarette smoking are dose related for each of these diseases (34, 36, 37, 38, 102). Thus, the first goal in production of a "less hazardous cigarette" was to reduce total smoke delivery. Because the causal relation between smoking and lung cancer was the first established, primary emphasis was placed on reducing the carcinogenic "tar" of cigarette smoke (110).

Tumor Initiation and Cocarcinogens

Inhalation studies with Syrian golden hamsters and bioassays on mouse skin, rabbit ears, and the connective tissue of mice and rats have clearly indicated that the major carcinogenicity of cigarette smoke resides in its particulate phase (23, 43, 109). Although the presence of volatile carcinogens in the gas phase has been well established (Table 2), the models available at present do not allow detection of a carcinogenic effect of the gas phase because of the low sensitivity of the systems (23).

Extensive fractionation studies combined with bioassays have supported the concept that the concentration in cigarette "tar" of certain polynuclear aromatic hydrocarbons (PAH), which are known human carcinogens (35, 69, 86), is too low to account for their activity

TABLE 2.—Known carcinogenic agents in the gas phase of cigarette smoke*

Agent	Concentration in one cigarette			Ref.
	Range reported		Cigarette ^a	
Dimethylnitrosamine	1	- 200 ng	18 ng	1,2,4
Ethylmethylnitrosamine	0.1	- 10 ng	1.8 ng	1,2,4
Diethylnitrosamine	0	- 10 ng	1.5 ng	1,2,4
Nitrosopyrrolidine	2	- 42 ng	11 ng	1,2,4
Other nitrosamines ^b	0	- 20 ng	?	1,2,4
Hydrazine	24	- 43 ng	32 ng	5,6
Vinyl chloride	1	- 16 ng	12 ng	3,7
Acrylonitrile	3.2	- 15 µg	10 µg	8,9
2-Nitropropane	0.73	- 1.21 µg	0.92 µg	10,11
Urethane	20	- 38 ng	35 ng	12,13

*This table is not complete, since the gas phase may also contain such carcinogens as arsine, nickel carbonyl, possible volatile chlorinated olefins, nitro-olefins, and others currently unknown.

^aLeading U.S. cigarette (85 mm) without filter tip.

^bThe four N-nitrosamines identified on occasion only in the smoke of special cigarettes were di-n-butyl nitrosamine, di-n-propyl nitrosamine, methyl-n-butyl nitrosamine, and N-nitrosopiperidine.

as complete carcinogens. These PAH, however, are active as tumor initiators and thus contribute to the induction of tumors by tobacco "tar," which contains an abundance of cocarcinogens (20, 48). Tables 3 and 4 list the tumor initiators and cocarcinogens in cigarette smoke known at this time. Large-scale model studies on mouse skin and inhalation studies with Syrian golden hamsters have shown that a significant reduction of "tar" and a selective reduction of tumor initiators and cocarcinogens will lead to a significant reduction of the carcinogenic potential of cigarette smoke (13, 23, 24, 29, 30, 31, 32, 48).

Recently, a study has indicated that nicotine (and possibly other tobacco alkaloids) may be active as a cocarcinogen (14), while another study did not show acrolein to have cocarcinogenic properties (27). Further detailed investigations are required.

Organ-Specific Carcinogens

This approach toward the less hazardous cigarette has been criticized by several groups as one-sided because it has been concerned only with "tar," nicotine, and tumor initiators such as PAH and with cocarcinogens, rather than with organ-specific carcinogens (85, 88, 102).

Table 5 lists the known organ-specific carcinogens. In the case of polonium-210, a recent indepth study raises doubts on the significance of ²¹⁰Po as a factor contributing to lung cancer in smokers. Nevertheless, it may be prudent to reduce the ²¹⁰Po content of tobacco products (39).

Among the aromatic amines, certain individual compounds are known human bladder carcinogens (e.g., 2-naphthylamine, 4-biphenyla-

TABLE 3.—Tumor-initiating agents in the particulate phase of tobacco smoke*

Compound	Relative activity as complete carcinogen ^a	Ng/cigarette
Benzo[<i>a</i>]pyrene	+++	10-50
5-Methylchrysene	+++	0.6
Dibenz[<i>a,h</i>]anthracene	++	40
Benzo[<i>b</i>]fluoranthene	++	30
Benzo[<i>k</i>]fluoranthene	++	60
Dibenzo[<i>a,h</i>]pyrene	++	pr ^b
Dibenzo[<i>a,i</i>]pyrene	++	pr ^b
Dibenz[<i>a,j</i>]acridine	++	3-10
Indeno[1,2,3- <i>c,d</i>]pyrene	+	4
Benzo[<i>c</i>]phenanthrene	+	pr ^b
Benzo[<i>a</i>]anthracene	+	40-70
Chrysene	+ ?	40-60
Benzo[<i>e</i>]pyrene	+ ?	5-40
2-, 3-Methylchrysene	+ ?	7
1-, 6-Methylchrysene	-	10
2-Methylfluoranthene	+	34
3-Methylfluoranthene	?	40
Dibenz[<i>a,c</i>]anthracene	(+)	pr ^b
Dibenz[<i>a,h</i>]acridine	(+)	0.1
Dibenzo[<i>c,g</i>]carbazole	(+)	0.7

*Incomplete list; all listed compounds are active as tumor initiators on mouse skin.

^aRelative carcinogenic activity on mouse skin as measured in our laboratory on Swiss albino (Ha/ICR/Mil) mice; ?, carcinogenicity unknown; (+), not tested in own laboratory.

^bPr stands for present, but no quantitative data given.

SOURCE: Hoffmann et al. (48).

mine, and benzidine) (83). Doll (22) has discussed the aromatic amines as likely contributors to the increased risk of cigarette smokers for bladder cancer. These carcinogenic compounds are primarily pyrosynthesized from the tobacco proteins (84, 92). Except for the development of a process to reduce the protein content of tobacco (100), no efforts toward the reduction of aromatic amines in cigarette smoke have been reported.

A major group of organ-specific carcinogens in cigarette smoke are the N-nitrosamines. The volatile nitrosamines, for which protein and nitrate are precursors, can be selectively reduced by filtration (17). The tobacco-specific N-nitrosamines in tobacco and in smoke are formed during tobacco curing as well as during smoking. So far, N'-nitrosornicotine (NNN), 4-(N-methyl-N-nitrosamine)-1-(3-pyridyl)-1-butanone (NNK), and N'-nitrosoanatabine (NAT) have been identified. These compounds are formed from the major tobacco alkaloids: nicotine (NNN and NNK), nornicotine (NNN), and anatabine (NAT). The total concentration of these three nitrosamines varies between 0.7 and 10.0 µg/cigarette (47). NNN is a moderately active carcinogen in mice, rats, and Syrian golden hamsters, whereas NNK is a strong carcinogen in the respiratory tract of all three species; NAT has so far not been

TABLE 4.—Cocarcinogenic agents in the particulate matter of tobacco smoke*

Compound ^a	Cocarcinogenic activity ^b	Ng/cigarette
I. Neutral fraction		
Pyrene (-)	+	50-200
Methylpyrenes (?)	?	50-300
Fluoranthene (-)	+	100-260
Methylfluoranthenes (+;?)	?	180
Benzo[<i>g,h,i</i>]perylene (-)	+	60
Benzo[<i>e</i>]pyrene (+)	+	30
Other PAH's (+)	?	?
Naphthalenes (-)	+	360-6,300
1-Methylindoles (-)	+	880
9-Methylcarbazoles (-)	+	140
4,4'-Dichlorostilbene (-)	+	1,500 (115) ^c
Other neutral compounds (?)	?	?
II. Acidic fraction		
Catechol (-)	+	40,000-350,000
3-Methylcatechol (-)	+	11,000-20,000
4-Methylcatechol (-)	+	15,000-21,000
4-Ethylcatechol (-)	+	10,000-24,000
4-n-Propylcatechol (?)	?	= 5,000
Other catechols and phenols (?)	?	?
Other acidic agents (?)	?	?

*Incomplete list.

^aIn parentheses, complete carcinogenic activity on mouse skin; (?), unknown.

^b+, active; ?, unknown.

^cValue from 1968 U.S. cigarettes; today's values would be lower, because DDT and DDD decreased in the U.S. tobaccos.

SOURCE: Hoffmann et al. (48).

bioassayed. Although conclusive epidemiologic data are not available, "NNN should be regarded for practical purposes as if it were carcinogenic to humans" (53). Research programs on the reduction of these tobacco-specific carcinogens in cigarette smoke and their possible *in vivo* formation in the smoker from nicotine, nor nicotine, anatabine, and other tobacco alkaloids need to be undertaken.

A neglected area may be the reduction of other organ-specific carcinogens in cigarette smoke, such as nitro-arenes and pesticides that may give rise to carcinogens such as maleic hydrazide diethanolamine (MH-30).

Carbon Monoxide in Cigarette Smoke

Until a few years ago the reduction of carbon monoxide in cigarette smoke had not been seriously studied. In fact, in 1976 a report from the United Kingdom demonstrated that unperforated filter cigarettes can deliver higher carbon monoxide values (13-18 mg/cig) than nonfilter

TABLE 5.—Organ-specific carcinogens in the particulate matter of cigarette smoke

Carcinogen	Concentration/cigarette	Carcinogenicity*
I. Esophagus	0.1–4.0 µg	+
N'-Nitrosornicotine	130–5,500 ng	+
4-(N-Methyl-N-nitrosamino)-1-(3-Pyridyl)-1-butanone	0.1–0.4 µg	+
N'-Nitrosoanatabine	0.2–4.6 µg	+
Nitrosopiperidine	0–9 ng	+
Unknown unsymmetrical nitrosamines	?	+
II. Lung		
Polonium-210	0.03–1.3 pCi	+
Nickel compounds	0–600 ng	+
Cadmium compounds	9–70 ng	?
Unknowns	?	?
III. Pancreas		
Nitrosamines	?	+
Unknowns	?	?
IV. Kidney and bladder		
β-Naphthylamine	22 ng	+
χ-Aminofluorene	+	+
χ-Aminostilbene	+	+
o-Toluidine	+	+
Unknown aromatic amines	?	?
o-Nitrotoluene	21 ng	?
Unknown nitro compounds	?	?
Di-n-butyl nitrosamine	0–3 ng	+
Other nitrosamines	?	+

*+ Activity confirmed; ? Activity unconfirmed.
SOURCE: Hoffmann et al. (48).

cigarettes (9–16 mg/cig) (105). This finding has been confirmed in both Germany and the United States (49). An increasing number of the cigarette brands sold in the United States have perforated filter tips, at present amounting to approximately 50 percent. The filter perforation leads to air dilution of the smoke and to changes in the burning profile of the cigarette, and thus, to a significant reduction of the carbon monoxide content of the smoke (Table 6). Filter tip perforation similarly reduces the nitrogen oxides in cigarette smoke (82).

Smokers' Compensation

Studies by Russell and his group (90, 98) and recently by Hill and Marquardt (44) have demonstrated that many smokers who switch to lower "tar" and nicotine cigarettes will compensate for the loss in smoke nicotine (and possibly other agents) by intensifying their smoke intake, puffing more frequently, and drawing larger volumes per puff. In the case of cigarettes with perforated filter tips, the occlusion of the filter vents by the fingertips may be an additional compensation

TABLE 6.—Carbon monoxide in smoke of cigarettes

	Carbon monoxide (mg/cigarette)		
	Nonfilter	Regular filter	Perforated filter
U.S. (90% of av 1977/1978 sales) ^a	11.6-17.0 (N = 8)	14.4-20.0 (N = 23)	2.8-12.8 (N = 9)
U.K. (1975) ^b	9-16 (N = 9)	13-18 (N = 10)	—
Germany (1975)	16-21 (N = 7)	15.5-22.5 (N = 17)	—
Germany (1978)	14.5-19.9 (N = 16)	8.6-13.5 (N = 15)	2.2-13.8 (N = 9)

^aAverage values for nonfilter cigarettes, 14.9 mg; for regular filter cigarettes, 17.1 mg; for perforated filter cigarettes, 8.9 mg.

^bAverage values for nonfilter cigarettes, 12.5 mg; for filter cigarettes, 16.1 mg.

N = number of brands tested.

SOURCE: Hoffmann et al. (43).

technique that smokers may develop either intentionally or subconsciously (62). These factors of "smoker compensation" must be considered in the evaluation of lower "tar" and nicotine cigarettes. Filtered, lower "tar" and nicotine cigarettes that are less vulnerable to increasing the smoke and nicotine deliveries are needed. Such products are envisioned by scientists in the tobacco health field. Attempting to minimize smoker compensation by selectively reducing "tar" and other smoke compounds while maintaining nicotine yield may carry serious disadvantages. First, maintaining nicotine delivery may reinforce physiologic habituation, and interfere with smoking cessation attempts (93). Second, nicotine gives rise to the tobacco-specific carcinogenic N-nitrosamines, NNN and NNK, and nicotine itself may be carcinogenic (see Experimental Chemical Carcinogenesis within this section). Finally, nicotine is suspected to be a major smoke constituent correlated with the increased risk of cardiovascular disease among cigarette smokers.

Transplacental Carcinogenesis

The possible transplacental effect of cigarette smoking on carcinogenesis should be investigated. Recently, it has been shown that cigarette "tar" is an active transplacental carcinogen in Syrian golden hamsters (80). Furthermore, a number of smoke constituents are active as transplacental carcinogens in the experimental animal (25). These include volatile N-nitrosamines, benzo[a]pyrene, o-toluidine, ethyl carbamate, and vinyl chloride (87). Other major tobacco carcinogens including the benzofluoranthenes, NNN, and NNK need to be bioas-

sayed for their transplacental activity and to be considered with respect to lower "tar" cigarettes.

Flavor Additives

The development of lower "tar" and nicotine cigarettes has tended to yield products that lacked the taste components to which the smoker had become accustomed. In order to keep such products acceptable to the consumer, the manufacturers reconstitute aroma or flavor. There are several ways in which this can be achieved. Flavor extracts of tobacco can be added to the lower-yield blends. Other plant extracts can be used to supplement the flavor spectrum, synthetic flavors can be added, or a combination of techniques can be applied (64, 65). Powdered cocoa, one flavoring additive that is probably used in U.S. cigarettes, has been found to increase mouse skin tumorigenicity of the "tar" from a standard experimental cigarette at each of two dose levels (31).

The burning of cigarettes with flavor additives produced increased and perhaps novel types of semivolatiles agents, including traces of mutagenic compounds. The mutagenic agents were found in the basic fraction of the semivolatiles portion obtained from heating the tobacco mixtures. Chemically, the agents thus far identified were substituted pyrazines and other aza-arenes with and without amino groups (64).

The exact delineation of the chemical structure of additives, their pyrolytic products, the possible carcinogenic properties, and the quantities found in smoke of lower "tar" cigarettes is urgently needed in order to assure the consumer that the filter, lower "tar" and nicotine cigarette does not carry additional or new health risks.

Conclusions and Recommendations

1. Both retrospective and prospective epidemiologic studies in man have shown a dose-response relationship between cigarette smoking and the occurrence of cancer of the lung, larynx, esophagus, oral cavity, and bladder with a less clear quantitative relationship to cancers of the pancreas and kidney. Smoke dose was measured by various parameters, including numbers of cigarettes (daily or lifetime), duration of habit, depth of inhalation, and number of puffs per cigarette.

The highest priority in the field of public health is that individuals who have not started smoking should not begin and that those who currently smoke should quit.

2. Those individuals who start smoking with a filter-tipped, lower "tar" and nicotine cigarette, or who switch after a period of time from high "tar" and nicotine cigarettes to the lower "tar" and nicotine cigarettes, will have a lower incidence of lung cancer, but an incidence far in excess of the nonsmoker.

Specifically, high priority should be given to continued and long-term retrospective and prospective epidemiologic studies on *all* tobacco-related diseases, with specific reference to brand of cigarettes smoked, number of cigarettes, manner of smoking, inhalation, etc., along with generation of data on "tar," nicotine, carbon monoxide, and other chemical content, as determined by the most up-to-date scientific methods. This same epidemiologic survey should include studies of individuals in high-risk occupations, of groups such as teenagers, minorities, and people of varying socioeconomic status, of men compared with women, and of different ages at which smoking began. Concern expressed by the group was, because cigarette composition in the United States is changing rapidly, without continued, well-planned, long-term studies, it will be difficult to know what effect the changing composition is having on the health of the American people.

3. An administrative mechanism to focus major interest on tobacco and the diseases caused by smoking tobacco should be established. Such a mechanism should include involvement of basic scientists, epidemiologists, physicians, statisticians, social scientists, and related experts concerned with smoking. There should be a stable source of funding for both new and established investigators to work together on tobacco and health problems over a period of time, since the answers to the questions raised over the past quarter-century will not come quickly, considering the magnitude and duration of the problem in the United States.

Moreover, institutions and programs should be encouraged to train scientists for smoking research and to maintain a core group of physicians, scientists, and educators to consider various aspects of smoking research issues.

4. Additional work in carcinogenesis should be performed:
 - a. It should be determined whether nitrosamines are formed from cigarette smoke in the human body and, if so, whether they are formed in significant concentrations. A key concern is whether nicotine itself forms nitrosamines in biologically significant quantities following reaction with nitrous oxides. The role of nicotine in human carcinogenesis should be identified.
 - b. Tobacco additives and flavoring agents should be studied by appropriate methods for carcinogenicity and other toxicities, before their commercial use is permitted, and study data should be made available to the appropriate agencies.
 - c. A continuing study of lower "tar" and nicotine cigarettes for carcinogenicity might detect changes resulting from new or different manufacturing practices or from new additives or flavoring agents that might act synergistically.
 - d. The gas phase of cigarette smoke should be examined more fully for carcinogenicity.