Studies on the CO burden of each cigarette have determined the body burden of CO per cigarette to be 7.10-8.66 ml (*40*), and the increase in COHb level produced by smoking one cigarette to be .94 to 1.6 percent after 12 hours of abstinence (*40, 53*). The half-life for the washout of CO in healthy college smokers (*40*) was calculated to be from 3 to 5 hours.

Effects on Healthy Individuals

Several studies have been published on the effects of carbon monoxide on healthy individuals. Small doses of CO (COHb levels 2.4-5.4 percent) were found to have no effect on heart rate (*56*). Raven, et al. (*51*), in a study of young men exposed during exercise on a treadmill to 50 ppm CO (COHb levels 2.5 percent in nonsmokers and 4.1 in smokers), found no decrease in maximum aerobic capacity when the subjects were tested at 25° C. In a similar experiment conducted at 35° C by the same researchers (*20*), there was a decrease in maximum aerobic capacity in nonsmokers exposed to 50 ppm CO, but not in smokers despite an increase in the carboxyhemoglobin levels of 1.5 percent in both groups. They postulated a possible physiologic adaptation of smokers to carbon monoxide. Ekblom and Huot (*22*) studied five young men who inhaled CO to reach given COHb levels. They reported that as COHb levels increased, there was a decrease in maximal oxygen uptake and lower heart rates at maximal treadmill exercise.

Sagone, et al. (*54*), in a study of 9 cigarette smokers and 18 nonsmokers ages 20-32, showed significantly higher values for COHb, red cell mass, hemoglobin, and hematocrit in the smokers. Levels of 2,3 DPG were unaltered while oxyhemoglobin affinity P50 and ATP levels were significantly lower in the smokers. The three smokers with highest red cell mass had normal arterial blood gases and one smoker had very high values of red cell mass which returned to normal after he stopped smoking. The authors interpret these data as evidence of tissue hypoxia.

Millar and Gregory (*43*), in a study of both fresh heparinized blood and ACD-stored blood from a blood bank, showed a reduction in the oxygen carrying capacity of up to 10 percent in the blood of cigarette smokers; this reduction persisted for the full 21-day storage life of blood bank blood.

Cole, et al. (*16*), in a study of pregnant women, found COHb levels in the fetus to be 1.8 times as great as those in the

simultaneously measured blood of the mother. Fetal blood was exposed to carbon monoxide in vitro, and fetal hemoglobin was found to have a shift of the oxyhemoglobin disassociation curve to the left as occurs with adult hemoglobin. The higher fetal COHb levels were attributed to the lower fetal Po_2 and a resultant decrease in the ability of oxygen to compete for the fetal hemoglobin. It was felt by the authors that the high COHb levels may be responsible for the lower birth weight of infants born to mothers who smoke.

Effects on Persons with Atherosclerotic Cardiovascular Disease

Aronow and Isbell (*5*) and Anderson, et al. (*1*) have shown a decrease in the mean duration of exercise before the onset of pain in patients with angina pectoris exposed to low levels of carbon monoxide (50 and 100 ppm). Carboxyhemoglobin levels were significantly elevated (2.9 percent after 50 ppm; 4.5 percent after 100 ppm) and the systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate (a measure of cardiac work) were all significantly lower at onset of angina pectoris.

In a continuation of this work, Aronow, et al. (*2, 3*) studied eight patients during two separate cardiac catheterizations, one during which each patient smoked three cigarettes and one during which each patient inhaled carbon monoxide until the maximal coronary sinus COHb level equalled that produced by smoking during the first catheterization. All eight had angiographically demonstrated CHD (> 75 percent obstruction of at least one coronary artery). Smoking increased the systolic and diastolic blood pressure, heart rate, left ventricular end-diastolic pressure (LVEDP), and coronary sinus, arterial, and venous CO levels. No changes were noted in left ventricular contractility (dp/dt), aortic systolic ejection period, or cardiac index, and decreases were found in stroke index and coronary sinus, arterial, and venous Po_2. When carbon monoxide was inhaled, increased LVEDP and coronary sinus, arterial, and venous CO levels were noted; there were no changes in systolic and diastolic blood pressure, heart rate, or systolic ejection period; and decreases in left ventricular dp/dt, stroke index, cardiac index and coronary sinus, arterial, and venous Po_2 were found. These data suggest that carbon monoxide has a negative inotropic effect on myocardial tissue resulting in the decrease in contractility (dp/dt) and stroke index. When the positive effect of nicotine on contractility and heart rate is added by cigarette smoking, the net effect is increased cardiac work for the same cardiac output. In the heart with

coronary artery disease there is a greatly restricted capacity to increase blood flow in response to this increase in cardiac work. The result is early cardiac decompensation manifested by elevation in LVEDP and angina pectoris.

Aronow, et al. have also shown decreased exercise time prior to onset of angina pectoris in persons exercised after riding for 90 minutes on the Los Angeles Freeway (*4*). In a related study, they demonstrated a decrease in exercise time before claudication in a group of patients with intermittent claudication who were exposed to 50 ppm CO (*6*).

Studies on the Pathogenesis of Cardiovascular Disease

In a review of some of their work on carbon monoxide, Astrup and Kjeldsen (*7*) noted that in cholesterol-fed rabbits exposed to 170 ppm carbon monoxide for 7 weeks (COHb 16 percent) and then to 340 ppm for 2 weeks, the cholesterol content of the aorta was 2.5 times higher than that of cholesterol-fed, air breathing controls. Groups of cholesterol-fed rabbits intermittently exposed to carbon monoxide for 12 or 4 hours per day produced three- to fivefold increases in the cholesterol content of their aortas. Cholesterol-fed rabbits made hypoxic at 10 and 16 percent oxygen had 3 to 3.5 times the aortic cholesterol content, while those exposed to 26 and 28 percent oxygen had a considerable decrease in cholesterol accumulation.

Theodore, et al. (*58*) studied the aortas of monkeys, baboons, dogs, rats, and mice fed a normal diet but exposed to very high levels of CO (COHb levels 33 percent) and found no atheromatous changes in their aortas.

Further work by Astrup and Kieldsen (*38*) revealed that in rabbits fed normal diets but exposed to 180 ppm carbon monoxide for 2 weeks, there were local areas in their hearts of partial or total necrosis of myofibrils; in the arteries there was endothelial swelling, formation of subendothelial edema, and degeneration of the myocytes. When the aortas of these rabbits were examined (*37*), the luminal coats showed pronounced changes characterized by severe edematous reaction with extensive swelling and formation of subendothelial blisters and plaques. The authors postulate that carbon monoxide increases endothelial permeability to albumin which results in formation of edema leading to changes indistinguishable from early atherosclerosis.

Evidence that this mechanism may occur in humans is provided by the findings of Parving (*50*) who showed an increased transcapillary escape rate for ^{131}I- labeled albumin in humans exposed to .43 percent CO (COHb 20 percent) for 3 to 5 hours, but not in those made hypoxic to an altitude of 4300 meters (hemoglobin 75 percent saturated).

By exposing rabbits to different concentrations of carbon monoxide (50, 100, and 180 ppm) for varying periods (.5, 2, 4, 8, 24, and 48 hours), Thomsen and Kjeldsen (*59*) were able to show a threshold of 100 ppm of CO for myocardial damage. The demonstration of damage at this level of CO (COHb 8-10 percent) is possibly explained by the ratio of carboxymyoglobin to carboxyhemoglobin which is about 3 to 1 in myocardium at ambient Po_2. Thus, a COHb level of 10 percent would be accompanied by a carboxymyoglobin level of 30 percent in heart muscle. This ratio is even greater under hypoxic conditions with a ratio of 6 to 1 when the arterial Po_2 is below 40 mm Hg (*15*).

Nicotine

In a study of the effects of smoking cigarettes with low and high nicotine content, Hill and Wynder (*30*) noted increasing serum epinephrine levels with increasing nicotine content of the smoke, but serum norepinephrine levels were unchanged. However, increasing serum epinephrine levels with increasing number of low nicotine content cigarettes smoked were also noted.

Acrolein

Egle and Hudgins (*21*) did inhalation studies with acrolein on rats. Inhalation of this aldehyde at concentrations below those encountered in cigarette smoke resulted in a significant increase in blood pressure and heart rate in rats.

CEREBROVASCULAR DISEASE

There has been conflicting evidence on whether there is an increased risk of cerebrovascular disease due to smoking (*61, 62, 63, 64, 65, 66, 67, 68*). A prospective study by Paffenbarger, et al. (*48*) of 3,991 longshoremen followed for 18 years showed no correlation between fatal strokes and smoking. However, both the Dorn study of

U.S. veterans (*33*) and Hammond's study of one million men and women (*25*) showed a small but significant increase in the death rates from cerebrovascular disease among cigarette smokers. The Framingham 18-year followup of men ages 45 to 54 (*42*) and Paffenbarger's study of men who entered Harvard between 1916 and 1940 (*49*) also showed an excess risk of cerebrovascular disease associated with cigarette smoking.

Two recent studies provided more data on this topic. Ostfeld, et al. (*46, 47*), in a study of 2,748 people ages 65-74 receiving old age assistance in Cook County, Illinois, were unable to find any relation between cigarette smoking habits at the start of the study and incidence of new strokes or prevalence of transient ischemic attacks. Nomura, et al. (*44*), in a study of the population of Washington County, Maryland, ages 25 and older, were unable to find any relation between cigarette smoking and either mortality or morbidity from stroke. Nomura noted that "in atherosclerotic strokes the Framingham study and Paffenbarger's investigation of former college students included a great percentage of stroke cases under the age of 55. Because these two studies found an association between cigarette smoking and atherosclerotic strokes and the present study did not, it may be that the association is age-dependent."

Hammond (*25*) provides some data which may clarify this relationship. Analysis of his data shows that the difference between cerebrovascular death rates in cigarette smokers and nonsmokers increases as persons get older except in males ages 75-84 (Table 7), indicating that the excess death rates associated with cigarette smoking increase with advancing age. The ratio of the death rates for smokers and nonsmokers (mortality ratio), however, decreases with age, reflecting the fact that cerebrovascular disease death rates attributable to other causes increase with age more rapidly than death rates attributable to smoking. Cigarette smoking may well be a risk factor for stroke at all ages, but other causes of strokes become proportionally so important in older age groups that in studies not based on very large populations the risk due to cigarette smoking is masked by the large total number of strokes due to other causes.

TABLE 7. – Age-standardized deaths rates and mortality ratios for cerebral vascular lesions for men and women by type of smoking (lifetime history) and age at start of study

Type of Smoking	Age Groups			
	45–54	55–64	65–74	75–84
	CVL Death Rates per 100,000 Person-Years			
Men				
Never smoked regularly	28	92	349	1,358
Pipe, cigar	25	100	369	1,371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1,168
Total	35	116	391	1,272
Women				
Never smoked regularly	18	57	228	1,082
Cigarette	38	88	315	1,277
Total	25	64	238	1,091
	CVL Mortality Ratios			
Men				
Never smoked regularly	1.00	1.00	1.00	1.00
Pipe, cigar	0.89	1.09	1.06	1.01
Cigarette and other	1.00	1.40	1.03	0.73
Cigarette only	1.50	1.41	1.37	0.86
Women				
Never smoked regularly	1.00	1.00	1.00	1.00
Cigarette	2.11	1.54	1.38	1.18

NOTE. – CVL = Cerebral vascular lesions.
Source: Hammond, E.C. (*25*).

EFFECTS OF SMOKING ON THE COAGULATION SYSTEM

Several studies have contributed to an understanding of the role of smoking in thrombogenesis. Levine (*41*), in a controlled double blind study, showed that smoking a single cigarette increased the platelet's response to a standard aggregating stimulus (ADP). This phenomenon did not occur when lettuce leaf cigarettes were smoked and was independent of a rise in free fatty acids in the plasma. The author postulates that this may be due to increasing epinephrine levels.

These data may have relevance for two other studies. In the clinical trial of the possible prevention of heart attack by hyperlipidemic drugs in Newcastle, England, (*19*) it was found that cigarette smokers were at increased risk of sudden death. This increased risk was not present in smokers treated with clofibrate. However, the researchers were unable to relate this reduction in risk to any effect of clofibrate on serum lipids. Recently Carvalho, et al. (*14*) evaluated 29 patients with familial hyperbetalipoproteinemia and noted that their platelets had an increased sensitivity to aggregating stimuli (ADP). Treatment with clofibrate returned the ADP sensitivity to normal without significantly altering serum lipids. This demonstrated effect of clofibrate may provide some insight into the Newcastle study. The reduction in the excess risk of sudden death could be due to a clofibrate induced reversal of increased sensitivity to aggregating stimuli produced by smoking.

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

1. Data from one recent incidence study suggest that cigarette smokers are more likely to develop hypertension than are nonsmokers. There is some evidence that suggests that stopping smoking may be accompanied by a rise in blood pressure.

2. Cigarette smoking has been shown to be the major source of elevated carboxyhemoglobin levels, with occupational exposure and air pollution being far less important in most circumstances. Carboxyhemoglobin levels in cigarette smokers are two to three times the levels in nonsmokers and increase with the amounts smoked.

3. Elevated carboxyhemoglobin levels have been shown to decrease maximal oxygen uptake in healthy people as well as to decrease the exercise tolerance of persons with angina pectoris and intermittent claudication. The carboxyhemoglobin levels at which these effects take place are well within the range produced by cigarette smoking.

4. Carbon monoxide at levels of exposure commonly reached by cigarette smokers has been shown to decrease cardiac contractility in persons with coronary heart disease.

5. Carbon monoxide has been shown to produce changes like those of early atherosclerosis in the aortas of rabbits.

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CHAPTER 2
Cancer

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INTRODUCTION

The major relationships between smoking and various cancers have been documented in previous reports on the health consequences of smoking (*18, 19, 20, 21, 22, 23, 24, 25*). Based on evaluations of detailed epidemiologic, clinical, autopsy, and experimental data accumulated over the last 30 years, cigarette smoking has been clearly identified as a causative factor for lung cancer. The risk of developing lung cancer increases directly with increasing cigarette smoke exposure as measured by number of cigarettes smoked per day, total lifetime number of cigarettes smoked, number of years of smoking, age at initiation of smoking, and depth of inhalation. Lung cancer death rates for women are lower than for men but have increased dramatically over the last 15 years coincident with the increasing number of women smokers. This increase has occurred in spite of the fact that women smokers use fewer cigarettes per day, more frequently choose cigarettes with filter tips and low tar and nicotine delivery, and tend to inhale less than men. A person who stops smoking has a decreased risk of developing lung cancer compared to the continuing smoker, but the risk remains greater than the nonsmoker's for as long as 10 to 15 years after the person stops smoking.

Cigarette smoking is a significant etiologic factor in the development of cancer of the larynx, oral cavity, pharynx, esophagus, and urinary bladder and is associated with cancer of the pancreas.

Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures to produce a greater risk of developing lung cancer than from occupational exposure alone. Uranium mining and the asbestos industries are occupations which have only slightly increased lung cancer rates for nonsmokers but dramatically elevated rates for cigarette smokers.

Pipe and cigar smokers experience mortality rates from cancer of the oral cavity, larynx, pharynx, and esophagus approximately equal to those of cigarette smokers. Their risk of developing cancer of the lung is lower than the risk of cigarette smokers, but it is significantly above that of nonsmokers. This is probably due to the

fact that pipe, cigar, and cigarette smokers experience similar smoke exposure of the upper respiratory tract, while cigarette smokers (due to their greater tendency to inhale) have a greater exposure of their lungs to smoke than pipe or cigar smokers.

The bronchial epithelium of smokers often shows premalignant changes such as squamous metaplasia, atypical squamous metaplasia, and carcinoma *in situ*. The pathogenesis of these changes is related to the various carcinogenic and co-carcinogenic substances in cigarette smoke; the exact mechanism of these carcinogens remains under investigation.

LUNG CANCER

Epidemiologic Studies

Harris (*3*) has reviewed the reports of lung cancer in nonsmokers and compared them to a representative hospital series and has shown marked differences in the pathological types between the two groups (Table 1). When only nonsmokers are examined, the excess of squamous and oat cell carcinoma in men compared to women is not observed. Adenocarcinoma is by far the most common type of lung cancer in nonsmokers while squamous cell is by far the most common when smokers are included. The strength of the relationship between smoking and the development of lung cancer differs markedly with the type of lung tumor. Squamous and oat cell carcinoma are very closely related to smoking behavior while, according to this study, bronchiolar carcinoma shows no excess risk attributable to smoking. Harris also presented the percentages of different histologic types of cancer found in several industrial exposures (Table 2); these percent distribution patterns resembled those found in smokers far more closely than those found in nonsmokers.

Wynder, et al. (*26*), in a retrospective study of 350 lung cancer patients and hospitalized controls, noted that the relative risk of developing lung cancer was far less in those smokers who had smoked filter cigarettes for more than 10 years than in smokers of plain cigarettes (26.8 and 46.2, respectively). Even with smokers of filter cigarettes, the risk increased with increasing number of cigarettes smoked and was significantly greater than the risk of nonsmokers.

Smoking and Air Pollution

Because of the magnitude of the association between smoking and the development of epidermoid lung cancer, it is difficult to

TABLE 1. – ***Distribution by type of lung cancers in a composite series of nonsmokers and a representative hospital series***

Type of cancer	Distribution (Percent)			
	Nonsmokers		All Patients	
	Men	Women	Men	Women
Squamous cell carcinoma	14	12	47	22
Oat cell carcinoma	4	4	17	11
Bronchiolar carcinoma	–	5	8	23
Adenocarcinoma	57	54	10	20
Large cell anaplastic carcinoma	8	8	17	19
Carcinoid	14	16	0.6	4
Other specific types	–	< 1	1	2
Undifferentiated[1]	4	2	–	–
Total number of cases	51	274	1,903	315

[1] Includes oat cell carcinoma and large cell anaplastic carcinoma.

Source: Harris, C.C. (*3*).

TABLE 2. – *Distribution by type of lung cancer in populations with specific occupational exposures*

Type of cancer	Distribution (%) in populations with exposure to–				
	Arsenic	Nickel	Chromium	Hematite	Asbestos
Squamous cell carcinoma	40	57	48	33	44
Oat cell carcinoma	13	43	16	60	6
Adenocarcinoma	7	–	24	–	25
Oat cell or anaplastic carcinoma	40	–	–	–	24
Anaplastic	–	–	12	7	1

Source: Harris, C.C. (*3*).

evaluate the effects of other possible causes of lung cancer such as air pollution. Higgins (*4*) recently analyzed respiratory cancer mortality in Great Britain and the United States. In the United States, although the age-specific death rates for males continued to increase, the rate of increase was not as great as in the past. Female lung cancer mortality rates, by contrast, have increased steadily since about 1955. If these increases continue, the American Cancer Society estimates that lung cancer among women will move from fourth to third place in 1975 as the site responsible for the greatest number of deaths due to cancer among women (*1*). In England and Wales, Higgins noted that between 1940 and 1969 lung cancer rates for men declined in the age group under 55 and increased only in men over 65. After adjusting for cigarette smoking, an independent effect of air pollution was sought. It was found that the lung cancer death rates for men ages 25-64 in greater London decreased more than the rates in the rest of the country; he attributed this decrease to the greater decline in smoke pollution in London than elsewhere.

Exfoliative Cytology

Microscopic examination of respiratory epithelial cells shed into the sputum has become a useful aid in the diagnosis of lung cancer and has been employed in many lung cancer screening programs for selected high risk groups. Saccomanno, et al. (*11*) have conducted periodic cytologic examinations of the sputum of uranium miners and a group of nonmining controls. Many of these individuals developed abnormal squamous cell metaplasia that progressed in several cases to become invasive carcinoma. Both cigarette smoking and radiation exposure from uranium mining were associated with an increased prevalence of these cytologic changes. Of the two factors, cigarette smoking was noted to be the more important (in both miners and nonminers) for the development of atypia and carcinoma *in situ*. Neither cigarette smoking nor uranium mining could be correlated with the length of time it took for these changes to progress from one pathologic stage to the next.

Schreiber, et al. (*15*) studied exfoliative cytology of the lungs of hamsters treated with intratracheal injection of the carcinogen benzo(a)pyrene. They noted progression from mild atypia to squamous metaplasia, to moderate and marked atypia, to changes indicative of cancer. These cytologic changes in animals exposed to carcinogens are comparable to those found in humans who smoke cigarettes.

EXPERIMENTAL CARCINOGENICITY

Carcinogens in Cigarette Smoke

A great deal of effort has been expended to identify those substances in cigarette smoke that cause malignant changes. The hope is that, if these carcinogenic substances can be identified and removed from cigarette smoke, the risk of developing lung cancer as a result of smoking can be reduced. Carcinogenic substances which act as tumor initiators, accelerators, and promoters in experimental animal systems have been identified in cigarette smoke.

Hoffman and Wynder (*6*) conducted an extensive analysis of the tumorigenicity of tobacco smoke. Using the gas phase of cigarette smoke, they identified certain known carcinogens but were unable to induce carcinoma in the respiratory tract of experimental animals. They interpreted these results as indicating that the levels of carcinogens present in the gas phase alone are below the concentrations necessary for tumor activity.

In the same study, Hoffmann and Wynder examined the particulate phase of tobacco and identified several carcinogens. The majority of tumor initiators in the particulate phase were polynuclear aromatic hydrocarbons and alkylated polynuclear aromatic hydrocarbons. They found that a significant inhibition of pyrosynthesis of these substances leads to a significant reduction of the tumorigenicity of tobacco smoke. They also identified several tumor accelerators – substances which accelerate the carcinogenicity and tumor initiating activity of the polycyclic aromatic hydrocarbons. The tumor accelerators found were *trans*-4, 4'-dichlorostilbene, *N*-alkyl indoles, and *N*-alkyl carbazoles. They also reported that the tumor promoters in cigarette smoke occur in the acidic portion of the particulate matter but did not further characterize them.

Hoffmann, et al. (*5*) reported identifying the nitrosamine, *N*'-nitrosonornicotine, in concentrations of 1.9 to 6.6 micrograms per gram in unburned tobacco and levels of 88.6 μg/g in one sample of finely cut chewing tobacco. This is one of the highest concentrations of an environmental nitrosamine (a family of compounds containing several organic carcinogens) yet identified; concentrations in food and drink rarely exceed 0.1 μg/g. This substance is readily extractable from tobacco by water and so would be present in high concentrations in the saliva of persons who chew

tobacco. As yet, *N*'-nitrosonornicotine has not been established as carcinogenic, and even the known carcinogenic nitrosamines are not felt to act topically.

Asbestos

The combination of cigarette smoking and asbestos exposure has been shown to result in a particularly high risk of developing lung cancer. Selikoff, et al. (*16*) have shown that asbestos workers who smoke have 90 times greater risk of developing lung cancer than nonsmoking, nonexposed people. Shabad, et al. (*17*) recently studied the possible causes of the synergistic effect of cigarette smoke and asbestos. They studied the carcinogenic activity of different types of asbestos in the U.S.S.R. and noted that all samples of chrysotile asbestos had traces of benzo(a)pyrene (a polycyclic aromatic hydrocarbon carcinogen found in cigarette smoke). In addition, they noted that chrysotile asbestos had a high adsorption activity for benzo(a)pyrene. This was not found in the other types of asbestos tested (anthophyllite and magnesiaarfvedsonite). In these animal studies, 20 percent of the rats exposed to chrysotile asbestos developed precancerous lesions; inhalation of chrysotile plus benzo(a)pyrene or of chrysotile plus cigarette smoke increased the frequency of the lesions to 57 and 38 percent, respectively. The synergism between asbestos and smoking may be the result of the adsorption of carcinogens onto asbestos, therefore prolonging their retention in the lung.

Infection and Carcinogenicity

There has been some discussion concerning the association between lung cancer and chronic bronchitis. Both diseases can be caused by cigarette smoking; however, chronic bronchitis may also influence the development of lung cancer by some independent mechanism. Schreiber, et al. (*14*) administered *N*-nitrosoheptamethyleneimine to germfree rats, specific-pathogen-free rats, and rats with chronic murine pneumonia. The incidence of lung neoplasms was 17 percent in germfree males, 37 percent in specific pathogen-free males, and 83 percent in infected males. An incidence of 90 to 100 percent occurred among females in all three experimental groups. They concluded that chronic respiratory infection may enhance the neoplastic response of the lungs to a systemic carcinogen.

OTHER CANCERS

Oral and Laryngeal Cancer

Schottenfeld, et al. (*13*) have studied the role of smoking on the development of multiple primary cancers of the upper digestive system, larynx, and lung. They followed 733 patients surviving a first primary epidermoid cancer of the oral cavity, pharynx, or larynx for 5 years. The average annual incidence for a second primary was higher in men (18.2/1000) than in women (15.4/1000). Both men and women who developed a second primary tumor had heavier tobacco exposure prior to their first cancer than those who did not develop a second malignancy. The authors were unable to show a significant relationship between smoking habits after removal of the first primary and development of a second primary. They postulate that this failure to show an association is due to the long induction period between presence of a carcinogen and occurrence of the cancer, and they expect that a relationship, if present, may become apparent after 7 or 8 years of followup.

Genitourinary Cancer

Schmauz and Cole (*12*) studied 43 persons with cancer of the renal pelvis or ureter and noted that smoking was only a risk factor at very high levels of consumption (over 2½ packs per day), despite its being related to cancer of the bladder at all levels of smoking. They postulate that, due to the rapid transit of urine through the renal pelvis and ureter, very high levels of exposure are required to have any effect whereas the bladder stores urine for some time and even small amounts of carcinogens in the urine may be sufficient to influence the bladder epithelium.

Nasopharyngeal Cancer

Lin, et al. (*10*), in a retrospective study of nasopharyngeal cancer in Taiwan using neighborhood controls, found smoking to be significantly associated with the development of nasopharyngeal carcinoma. A person smoking over 20 cigarettes per day had twice the risk of a nonsmoker of developing nasopharyngeal cancer.

ARYL HYDROCARBON HYDROXYLASE (AHH)

Due to the great variation in the amount of smoking exposure before the development of lung cancer, attempts have been made to