

It has been reported (100) that diabetic males who smoke have a 50% greater incidence of clinically detectable arteriosclerosis obliterans in the legs than those who do not smoke. In general, however, there is little information about the relation of smoking to peripheral arteriosclerosis. Most experienced clinicians advise patients with obliterative peripheral arterial disease to stop smoking (45).

Buerger's disease, or thromboangiitis obliterans, has been traditionally associated with smoking, and the literature contains numerous clinical reports describing the arrest of Buerger's disease when smoking is stopped and its reactivation on resumption of smoking. The existence of Buerger's disease as an entity separate from arteriosclerosis obliterans has been recently challenged (101), but well defended (61).

It is apparent that much more work will have to be done to determine what relationship may exist between non-coronary occlusive vascular disease, aneurysmal disease, and smoking.

CHARACTERISTICS OF CIGARETTE SMOKERS

If it could be shown that cigarette smokers and non-smokers had significant constitutional differences apart from any differences that might be caused by smoking itself, then a possibility would exist that some predisposition of smokers to a particular disease might also be of constitutional origin and not caused by smoking. Cigarette smokers have, in fact, been found to differ as a group from non-smokers, but the differences, such as serum cholesterol concentration and resting heart rate, could have resulted from the smoking habit itself, so far as present knowledge indicates.

The concentration of serum cholesterol has been found to be slightly higher in smokers than in non-smokers by a number of investigators (6, 18, 49, 63, 95), but others have found no relationship (1, 54). Dawber (19) found *not only that serum cholesterol was higher in smokers than in non-smokers but also that it remained higher in those who stopped smoking.*

Smokers tend to be leaner than non-smokers, but to gain when they stop smoking (3, 18, 49).

A few personality differences have been reported between cigarette smokers and non-smokers. Friedman's type A men (the coronary type) tended to be heavy smokers (33). Smokers are said to be more easily angered and to eat more when under stress (94). They have been reported to marry oftener, to change jobs more frequently, to be more often hospitalized, and to participate more actively in sports than non-smokers (60).

Thomas (94, 95) has reported that the parents of medical students who smoke have a significantly higher incidence of arteriosclerotic and hypertensive cardiovascular disease than parents of non-smokers. Clearly, this finding is open to more than one interpretation.

Smokers tend to have a higher heart rate than non-smokers (3, 94).

The matter of constitutional predisposition to smoking has been investigated in twins. It has been found (27, 28, 32) that the smoking habits of monozygotic twins are significantly more alike than those of dizygotic twins, even when members of a twin pair are brought up separately.

In spite of some bits of suggestive evidence the existence of basic constitutional differences between smokers and non-smokers is not presently established. The constitutional hypothesis, which links smoking and predisposition to disease, is discussed in detail in Chapter 9, Cancer.

PSYCHO-SOCIAL FACTORS OF SMOKING IN RELATION TO CARDIOVASCULAR DISEASE

Even less conclusive information is available on the role of psycho-social factors of smoking in relation to cardiovascular disease. Studies which have focussed on this are limited in number according to Heinzelmann (44). Even fewer, he found, are those which have specifically examined the relative weight of these variables or their interaction. Reviewing those available, he observes that the evidence is highly fragmentary and uncertain. The findings suggest that the relationship between smoking behavior and coronary heart disease may reflect the influence of stress factors and/or personality mechanisms. However, they permit no definitive statements with respect to the relative role of psycho-social factors and smoking in relation to etiology of the disease.

SUMMARY

Smoking and nicotine administration cause acute cardiovascular effects similar to those induced by stimulation of the autonomic nervous system, but these effects do not account well for the observed association between cigarette smoking and coronary disease. It is established that male cigarette smokers have a higher death rate from coronary disease than non-smoking males. The association of smoking with other cardiovascular disorders is less well established. If cigarette smoking actually caused the higher death rate from coronary disease, it would on this account be responsible for many deaths of middle-aged and elderly males in the United States. Other factors such as high blood pressure, high serum cholesterol, and excessive obesity are also known to be associated with an unusually high death rate from coronary disease. The causative role of these other factors in coronary disease, though not proven, is suspected strongly enough to be a major reason for taking countermeasures against them. It is also more prudent to assume that the established association between cigarette smoking and coronary disease has causative meaning than to suspend judgment until no uncertainty remains.

CONCLUSION

Male cigarette smokers have a higher death date from coronary artery disease than non-smoking males, but it is not clear that the association has causal significance.

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Chapter 12

Other Conditions

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Chapter 12

RELATIONSHIP OF PEPTIC ULCER TO TOBACCO USE

There are five retrospective studies on the relationship of peptic (gastric and duodenal) ulcer to smoking, in which data have been obtained about the smoking habits of peptic ulcer patients and various kinds of control groups (1, 2, 7, 14, 18). Also, in one cross-sectional study, the frequency of peptic ulcer has been determined in a population of individuals with varying smoking habits (11).

Tables 1 and 2 summarize the methods used and the results of these studies. These studies demonstrate an association between cigarette smoking and peptic ulcer which appears to be greater for gastric than for duodenal ulcers. The proportion of non-smokers is higher among the controls than among the ulcer patients in every one of these studies.

No differences were noted with respect to the frequency of heavy smokers in the study of Doll (7) and no consistent relationship with amount smoked was observed by Trowell (18).

In the cross-sectional study of Edwards, et al. (11), a larger proportion of peptic ulcer cases was found among the cigarette smokers, and this proportion increased with amount of cigarette smoking. The heavy cigarette smokers had a frequency of peptic ulcer twice that of those who had never smoked (12 percent as compared to 6 percent).

No association with pipe smoking was noted (1, 11, 14, 18).

In three prospective studies (Table 3) gastric ulcer has been classified separately from duodenal ulcer. The mortality ratios of cigarette smokers from gastric ulcer are high in all three studies (46/0, 5.1 and 4.3). For duodenal ulcers the mortality ratios are more modest (2.2, 2.3 and 1.1). In the remaining four prospective studies only the combined mortality ratios for gastric and duodenal ulcers are available: their results being based on small numbers of deaths, are erratic but their over-all average mortality ratio is about the same as for the three large studies. Consequently, it appears likely that the excess mortality of cigarette smokers from peptic ulcer can be attributed primarily to gastric ulcer. A breakdown by amount smoked (Chapter 8, Table 23) shows no trend. For cigar and pipe smokers the peptic ulcer mortality ratio (total over five studies) is 1.6 but in view of the small number of deaths this elevation is not statistically significant.

Doll, et al., (7) conducted a clinical trial of the effect of stopping smoking on the healing of gastric ulcers. The results were assessed by measuring radiologically the reduction in the size of the ulcer niche. Patients advised to stop smoking had an average 78% reduction in the size of the ulcer, compared to 57% for those who continued to smoke. In view of the probable existence of other factors which may have concomitantly been introduced in the approach to the smokers, and the complex nature of the healing process, it is difficult to interpret this observation.

TABLE 1.—*Summary of methods used in retrospective and cross-sectional studies of peptic ulcer and smoking*

Investigator and Year	Country	Sex	Cases		Controls		Collection of data
			No.	Method of Selection	No.	Method of Selection	
Barnett, (2) 1927	U.S.A.	M	66 Gastric; 178 Duodenal.	Patients admitted between 1913 and 1926. Only cases with complete smoking history selected.	500	Selected at random from the general admissions—males, aged 20–60.	1. Retrospective review of records at Peter Bent Brigham Hospital. 2. Ulcer diagnosis probably well established.
Trowell, (18) 1934	England	M	50 Duodenal	Not stated	400	Selected at random from wards of a general hospital.	1. Interviewed by investigator. 2. Ulcer diagnosis confirmed by X-ray and/or surgery.
Mills, (14) 1950	U.S.A.	M	55	Not stated	275	Sample of population in Columbus, Ohio.	No details given.
Allibone and Flint, (1) 1958	England	M&F	107	Consecutive admissions to hospital of patients with gastric and duodenal hemorrhage or perforation.	107	Matched by age, sex, and time of admission from acute general surgical emergency admissions.	Patients and controls interviewed by same observer.
Doll, Jones, and Pygott (7), 1958	England	M&F	327 Gastric; 338 Duodenal.	Ulcer patients in Doll and Hill Lung Cancer Study plus additional patients in Central Middlesex Hospital.	1,143	Patients with non-ulcer diseases. Each case matched with 2 control patients of same sex, 5-year age group, and same type of place of residence. Male patients matched by social class.	1. Same interviewers and questionnaire in cases and controls. 2. Ulcer diagnosis probably well established.
Edwards, McKeown, and Whitfield (11), 1959	England	M	1,737 men aged 60 and over on 11 General Practitioners' lists were examined and interviewed by these practitioners. Represents about 84% of all such men on these lists. (9% non-response due to death and/or untraced.)				Of 143 considered to have a peptic ulcer, 53 were confirmed by X-ray.

TABLE 2.—Summary of results of retrospective and cross-sectional studies of peptic ulcer and smoking

Investigator	Percent Non-smokers		Percent Heavy Smokers or Average Amounts Used	
	Cases	Controls	Cases	Controls
Barnett (2)	Total 18 Gastric 15 Duodenal 20	25		
Trowell (18)	Duodenal 8	17	Cigarettes: 12.0 per day Pipe: 1.6 oz. per week	11.1 per day. 2.15 oz. per week.
Mills (14)	18	35		
Allibone and Flint (1)	38	54		
Doll et al. (7)	<i>Gastric</i> M 1.3 F 51.1 <i>Duodenal</i> M 2.1 F 53.7	4.7 66.8 5.8 62.0	<i>Gastric</i> M 10.6 F 1.1 <i>Duodenal</i> M 10.2 F 1.9	11.3 1.1 12.7 1.9
Edwards et al. (11)	Percent of Peptic Ulcer by Smoking Category			
	Never smoked.....			6.0
	Formerly smoked.....			6.7
	Cigarettes:			
	1-9 per day.....			9.4
	10-19 per day.....			9.8
	20 plus per day.....			12.0
	Pipe.....			6.5
	Pipe and cigarettes.....			8.5

TABLE 3.—Expected and observed deaths and mortality ratios for ulcer of stomach and duodenum* among current cigarette smokers, from seven prospective studies

Investigator	Type of Ulcer	Number of Deaths		Mortality Ratio
		Observed	Expected	
Hammond and Horn (13)**	Gastric.....	46	0	2.2
	Duodenal.....	54	25	
	Both types.....	100	425	
Dorn (8)**	Gastric.....	31	6.1	5.1
	Duodenal.....	36	15.4	2.3
	Both types.....	67	21.5	3.1
Hammond (12)	Gastric.....	42	9.7	4.3
	Duodenal.....	32	28.9	1.1
	Both types.....	74	38.6	1.9
Doll and Hill (6)	Both types.....	14	0	
Dunn et al., Occupational (9)	Both types.....	12	23.1	0.5
Dunn et al., Legion (10)	Both types.....	12	1.8	6.8
Best et al. (5)	Both types.....	54	7.9	6.9

*Includes ISC numbers 540, 541.

**The Hammond and Horn data are from their original published report; the other results listed include more recent data as tabulated for the Committee (see Chapter 8).

Numerous investigators have studied the clinical and physiological effects of smoking on gastric motility and acid secretion in humans with and without peptic ulcer. Great variation of gastric motility and secretion was observed in response to cigarette smoking.

Some workers found inhibition of gastric motility (15, 17). Batterman (3) showed three types of response in normal subjects and ulcer patients after smoking one cigarette. In one-third no effect was observed, another third complete inhibition of motor activity for a time, and in the rest a period of hypermotility was followed by normal or subnormal activity. Smoking appears to produce variable effects also on gastric secretion. In a few studies, gastric secretion increased, while in others no change was observed or there was depression of secretory activity (4, 15, 16, 17). Additional studies of the effect of smoking on gastric secretory activity and motility are needed to explain the biological meaning of the statistical association between cigarette smoking and peptic ulcer.

CONCLUSION

Epidemiological studies indicate an association between cigarette smoking and peptic ulcer which is greater for gastric than for duodenal ulcer.

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TOBACCO AMBLYOPIA

For more than a century clinicians have attributed certain cases of amblyopia—dimness of vision unexplained by an organic lesion—to the use of tobacco.

The distinguishing characteristic of tobacco amblyopia is a specific type of centrocecal scotoma. Since this disease was defined as a distinct clinical entity for the first time in 1930 (4), the medical literature prior to this date is of relatively little value in the critical evaluation of the problem (3). No epidemiological studies with adequate controls are available to establish for this disease a relative risk among smokers and nonsmokers.

Clinical impressions associate tobacco amblyopia with pipe and cigar smoking and very rarely with cigarette smoking.

It has been suggested that this disease, which is now rare in the United States, occurs mainly in individuals with a nutritional deficiency which presumably renders the retina or optic nerve unduly sensitive to tobacco (1, 5).

Objective attempts at experimentation have been extremely rare and most of the literature is related to uncontrolled clinical impressions (2).

CONCLUSION

Tobacco amblyopia had been related to pipe and cigar smoking by clinical impressions. The association has not been substantiated by epidemiological or experimental studies.

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SMOKING AND CIRRHOSIS OF THE LIVER

Epidemiological studies have noted an association between cigarette smoking and mortality from cirrhosis of the liver. The mean mortality ratio for cirrhosis of the liver calculated from all prospective studies was 2.2 (Table 19, Chapter 8). The individual ratios in six of these studies ranged from 1.3 in the Canadian veterans study (1) to 4.0 in the California occupational study (3). The earliest prospective study, by Doll and Hill (2) reported no deaths from cirrhosis of the liver among non-smokers.

The small amount of information on the biological effects of nicotine and tobacco smoke on the liver of experimental animals is contradictory (5).

In several studies (4, 6, 7) it has been reported that heavy smokers also tend to drink alcoholic liquors excessively. It is well established that heavy consumption of alcohol and nutritional deficiencies are associated with increased mortality from cirrhosis of the liver. The increased death rate from cirrhosis among smokers may reflect the consumption of alcohol and associated nutritional deficiencies rather than the effect of cigarette smoking.

CONCLUSION

Increased mortality of smokers from cirrhosis of the liver has been shown in the prospective studies. The data are not sufficient to support a direct or causal association.

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MATERNAL SMOKING AND INFANT BIRTH WEIGHT

Five retrospective and two prospective studies have shown an association between maternal smoking during pregnancy and birth weight of the infant (2, 4, 5, 6, 8, 9, 10). Women smoking during pregnancy have babies of lower birth weight than non-smokers of the same social class. They have also a significantly greater number of premature deliveries (defined as birth weight of 2,500 grams or less) than the non-smoking controls.

While several studies reported a slightly greater neonatal death rate of the children of smokers (2, 5), others did not demonstrate any significant difference in the fetal and neonatal death rates of the two groups (6, 7).

Studies on alterations of placental morphology and function as a response to smoking are insufficient for judgment. The difference in infant weight may be due to vasoconstriction of the placental blood vessels (1) or to toxic substances such as CO in the circulation of the smoker and fetus (3).

It is not known whether the lower birth weight of the infants of smokers has any clinical significance. In one of the groups studied (5) there was less need for surgical induction of labor among mothers who smoked.

CONCLUSIONS

1. Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight.
2. Information is lacking on the mechanism by which this decrease in birth weight is produced.
3. It is not known whether this decrease in birth weight has any influence on the biological fitness of the newborn.

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SMOKING AND ACCIDENTS

Smoking has been associated with a variety of accidents. Among these, fires have the most obvious and important consequences.

In a special study of home accident fatalities in 1952 through 1953, the Public Health Service and the National Safety Council reported that 231 (18%) of 1,274 deaths from fires of known origin were due to cigarettes, cigars or pipes (1).

The Metropolitan Life Insurance Company reported that of 352 deaths in 1956 and 1957 among their policyholders from fires and burns with known causes in and about the home, 57 (16%) were due to smoking (2).

Of physiological responses related to driving, smoking degrades detectably only the differential brightness threshold and this effect increases with amount of smoking (4). The epidemiological data available on the effects of smoking on traffic accidents are inconclusive.

It has been shown that a level of carboxyhemoglobin of 5 percent—a level which is not uncommon among heavy cigarette smokers (3, 6)—depresses visual perception to as great an extent as anoxia at 8,000 to 10,000 feet altitude (4, 5).

CONCLUSION

Smoking is associated with accidental deaths from fires in the home. No conclusive information is available on the effects of smoking on traffic accidents.

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Chapter 13

Characterization of the
Tobacco Habit and
Beneficial Effects of Tobacco

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Chapter 13

CHARACTERIZATION OF THE TOBACCO HABIT

NICOTINE

Of the known chemical substances present in tobacco and tobacco smoke, only nicotine has been given serious pharmacological consideration in relationship to the tobacco habit. Lewin (17) stated. "The decisive factor in the effects of tobacco, desired or undesired, is nicotine . . . and it matters little whether it passes directly into the organism or is smoked." Support for this statement is based mostly on rationalizations from smoking behavior, analogy to other habits involving pharmacological agents and, to a much lesser extent, on established scientific fact. The latter may be summarized briefly as follows:

1. Only plants with active pharmacological principles have been employed habitually by large populations over long periods; e.g., tobacco (nicotine); coffee, tea, and cocoa (caffeine); betel nut morsel (arecoline); marihuana (cannabinols); khat (pseudoephedrine); opium (morphine); coca leaves (cocaine); and others (see Lewin, 17).

2. Denicotinized tobacco has not found general public acceptance as a substitute (16, pp. 531-532).

3. Chewing tobacco and using snuff, although providing oral gratification, also furnish nicotine for absorption to produce systemic effects (34).

4. Many but not all smokers can detect a reduction in nicotine content of cigarettes (9).

5. The administration of nicotine mimics the subjective effects of smoking (13). In uncontrolled experiments Johnston administered nicotine hypodermically, intravenously, or orally to smokers and non-smokers. Non-smokers found the effects "queer," whereas many smokers, including Johnston himself, claimed the subjective effects to be identical to those obtained by inhaling cigarette smoke and found that the urge to smoke was greatly reduced during nicotine administration.

In spite of the anecdotal nature of most of this information, the facts are that nicotine is present in tobacco in significant amounts, is absorbed readily from all routes of administration, and exerts detectable pharmacological effects on many organs and structures including the nervous system. The classical pharmacological characterization of nicotine—cellular stimulation followed by depression which is noted in isolated tissue and organ systems—has been invoked to explain the widely differing subjective responses of smokers, many of whom describe the effects as stimulating ("smoking relieves the depression of the spirits"), while others obtain a soothing and tranquilizing effect (16, p. 533).

Wilder (33) summarized the literature by noting ". . . observations that cigarette smoking obviously serves a dual purpose: it will mostly pick us up

when we are tired or depressed and will relax and sedate us when we are tense and excited." In order to ascribe such biphasic effects solely to the direct action of nicotine it would be necessary to discount psychological responses and alterations in mood from all other types of stimuli associated with smoking or the use of tobacco, an obvious impossibility. Although Knapp and Domino (15) have shown nicotine in small amounts to exert potent arousal effects in the electroencephalogram in animals, this evidence is difficult to interpret as it relates to smoking in man. A consensus among modern authors (27) appears to be that smoking, and presumably nicotine, exert a predominantly tranquilizing and relaxing effect. The act of smoking is of such complexity that the difficulties associated with objective analysis of whether smoking induces pleasure by creating euphoria or by relieving dysphoria renders objective analysis virtually impossible. The anecdotal literature suggests that sedation plays a more important subjective role in pipe and cigar smoking than with cigarette smoking. Since most pipe and cigar smokers do not inhale, this suggests that bronchial and pulmonary irritation from cigarette smoke after inhaling may contribute an important sensory input to the central nervous system which could modify the sedative effects of nicotine, so that some individuals would describe the experience as stimulating rather than sedative. Heavy cigarette smokers who inhale often describe the act as a pleasant sensory experience which constitutes for them one of the prime drives to continue to smoke. Freedman (10) used the term "pulmonary erotism." Mulhall (19) and Robicsek (22) have commented on this concept. An interesting psychoanalytical approach by Jonas (14), which postulates central nervous system counterirritation to constant pulmonary irritation from smoking, is based upon this concept. If pulmonary irritation is a pleasure factor it probably is not related to nicotine alone but to other irritants in smoke and could represent a non-specific increase in afferent sensory discharge from the whole respiratory tract. A gap in knowledge exists in this area. Furthermore, until carefully controlled experiments with nicotine are conducted in man, the literature will be burdened further with anecdote and hypothesis rather than fact.

DISTINCTION BETWEEN DRUG ADDICTION AND DRUG HABITUATION

Smokers and users of tobacco in other forms usually develop some degree of dependence upon the practice, some to the point where significant emotional disturbances occur if they are deprived of its use. The evidence indicates this dependence to be psychogenic in origin. In medical and scientific terminology the practice should be labeled *habituation* to distinguish it clearly from *addiction*, since the biological effects of tobacco, like coffee and other caffeine-containing beverages, betel morsel chewing and the like, are not comparable to those produced by morphine, alcohol, barbiturates, and many other potent addicting drugs. In fact, to make this distinction, the World Health Organization Expert Committee on Drugs Liable to Produce Addiction (35) created the following definitions which are accepted throughout the world as the basis for control of potentially dangerous drugs.