APPENDIX B

TOXICITY OF NICOTINE

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Introduction

Knowledge of the toxicity of nicotine is important to help understand tobacco-induced human disease as well as to assess the potential risks associated with the therapeutic use of nicotine (e.g., nicotine polacrilex gum) as an aid to assist smoking cessation.

This Appendix provides a brief overview of the toxic actions of nicotine per se, focusing on human studies wherever possible and selecting only those animal data which have direct implications in understanding mechanisms of human disease. The toxicity of cigarette smoke has been extensively reviewed in prior Surgeon General's reports (US DHHS 1982, 1983, 1984, 1985, 1986). In most cases the pathogenesis of tobacco-related diseases, including the role of nicotine, has not been fully elucidated. Therefore the potential contribution of nicotine to development of tobacco-related disease, even if unproved, will be considered.

The chemistry and general pharmacology of nicotine have been reviewed in previous chapters (Chapters II and III) of this report and are not presented in detail in this Appendix. An appreciation of the basic pharmacologic actions of nicotine is, however, a necessary foundation for understanding the issues of toxicity which are discussed in this Appendix.

Acute Intoxication

As discussed in Chapter II, nicotine is a water and lipid soluble drug which, in the free base form, is readily absorbed via respiratory tissues, skin, and the gastrointestinal tract. Nicotine may pass through skin or mucous membranes when in alkaline solutions, in which circumstance nicotine is primarily un-ionized.

In experimental animals, the dose of nicotine which is lethal to 50 percent of animals (LD_{50}) varies widely, depending on the route of administration and the species used. Intravenous (i.v.) LD_{50} doses of nicotine in mice range between 0.3 to 1.8 mg/kg body weight (Borzelleca, Borman, McKennis 1962; Lindner 1963; Wirth and Gosswald 1965; Barlow and McLeod 1969). The intraperitoneal (i.p.) LD_{50} values for nicotine bitartrate in mice and rats have been found to be 13 and 83 mg/kg body weight, respectively, while the values for five inbred hamster strains varied between 125 to 320 mg/kg body weight (Bernfeld and Homburger 1972). The wide variation in sensitivity to the toxic effects of nicotine in rodents appears to be genetically determined (Garg 1969; Marks, Burch, Collins 1983; Miner, Marks, Collins 1984).

In interpreting animal toxicity data it is important to recognize that the rate of administration is an important determinant of toxicity. Rapid i.v. injections result in the highest blood and brain concentrations and produce toxicity at the lowest doses. In contrast,

with oral or i.p. administration higher doses are required to produce toxicity. This is due to presystemic ("first pass") metabolism of nicotine and the gradual time course of absorption as compared with after i.v. dosing. With intermittent dosing, such as practiced by smokers, the total dose of nicotine absorbed per day could exceed the toxic or even lethal dose of a single injection.

In humans, acute exposure to nicotine even in low doses (similar to the amounts consumed by tobacco users) elicits autonomic and somatic reflex effects as described in detail in Chapters II and III. Dizziness, nausea, and/or vomiting are commonly experienced by nonsmokers after low doses of nicotine, such as when people try their first cigarette. However cigarette smokers rapidly become tolerant to these effects (Chapter II).

A number of poisonings and deaths from ingestion of nicotine, primarily involving nicotine-containing pesticides, have been reported in humans (Beeman and Hunter 1937; McNally 1923; Franke and Thomas 1936; Saxena and Scheman 1985). The lethal oral dose of nicotine in adults has been quoted to be 40 to 60 mg (Goldfrank, Melinek, Blum 1980; Larson, Haag, Silvette 1961), but it has not been well documented. Nicotine intoxication produces nausea, vomiting, abdominal pain, diarrhea, headaches, sweating, and pallor. More severe intoxication results in dizziness, weakness, and confusion, progressing to convulsions, hypotension, and coma. Death is usually due to paralysis of respiratory muscles and/or central respiratory failure.

Dermal exposure to nicotine can also lead to intoxication. Such exposures have been reported after spilling or applying nicotine-containing insecticides on the skin or clothes (Lockhart 1933; Faulkner 1933; Benowitz et al. 1987) and as a consequence of occupational contact with tobacco leaves.

Green tobacco sickness, an occupational illness in field workers harvesting tobacco leaves, has been attributed to dermal absorption of nicotine found in the dew on tobacco leaves (Weizenecker and Deal 1970; Gehlbach et al. 1974). The levels of cotinine in the urine of exposed workers exceed those of novice smokers who had smoked three cigarettes in succession (Gehlback et al. 1975). The symptoms of green tobacco illness are described in Table 1 (Gehlbach et al. 1975; Gehlbach, Williams, Freeman 1979). A similar syndrome has been reported in Asian Indian tobacco workers who harvest green tobacco leaves and handle cured tobacco (Ghosh et al. 1979).

Tobacco harvesters who use tobacco products, either in the forms of cigarettes or smokeless tobacco, are usually not affected by green tobacco sickness owing to development of tolerance to nicotine (Gehlbach et al. 1974). Tolerance to the toxic effects may even develop during the course of nicotine poisoning, despite the persis-

TABLE l.--Symptoms of systemic nicotine poisoning (Green Tobacco Sickness)

Symptom	Percentage (53 cases)
Nausea, vomiting	98
Pallor	89
Weakness	81
Dizziness. lightheadedness	81
Headache	81
Sweating	56
Abdominal pain	42
Chills	36
Increased salivation	17

SOURCE: Adapted from Gehlhach et al. (1974).

tence of nicotine in the blood at extremely high concentrations (200 to 300 ng/ml) (Benowitz et al. 1987).

Acute intoxication may occur in children following ingestion of tobacco materials. Four children, each of whom ingested two cigarettes, developed salivation, vomiting, diarrhea, tachypnea, tachycardia, and hypertension within 30 min; followed by depressed respiration and cardiac arrhythmia within 40 min; and convulsions within 60 min (Malizia et al. 1983). All recovered and suffered no complication. Another six children who ingested one-half of a cigarette experienced salivation and vomiting only. In a Swedish report (Werner 1969), 355 children who ingested tobacco had only very mild symptoms. Severe poisoning has occurred in children who swallowed tobacco juice (expectorated by tobacco chewers). Although ingestions of tobacco are common, deaths due to ingestion of tobacco are extremely rare, due to early vomiting and first pass metabolism of the nicotine which is absorbed.

Conceivably, intoxication from nicotine polacrilex gum could occur after accidental use by children or nonsmokers, or if an ex-smoker gum-user consumed several pieces at once or in rapid succession. One case report describes a smoker who developed apparent symptoms of nicotine intoxication within 1 min of chewing a piece of 2-mg gum (Mensch and Holden 1984). However, based on the known absorption kinetics and the amount of nicotine in the gum, true nicotine intoxication is unlikely in this case.

Swallowing nicotine polacrilex gum appears not to be of concern for development of toxicity. Although 30 to 85 percent of the nicotine content can be released from the gum into the gastrointestinal tract, the chances of nicotine intoxication are quite low because nicotine is

released slowly (transit time of the gums through the gastro-intestinal tract is 16 to 48 hr) (Brantmark and Fredholm 1974), and because the nicotine which is released undergoes extensive presystemic metabolism. Simultaneous ingestion of 10 unchewed pieces of 4-mg gum resulted in a peak blood concentration of nicotine of less than 10 ng/ml (Brantmark and Fredholm 1974), which is similar to the level attained by a smoker after smoking a single cigarette.

Chronic Nicotine Toxicity

As attested to in the Surgeon General's reports since 1964, smoking causes coronary and peripheral vascular disease (1983), cancer (1982), chronic obstructive lung disease (1984), peptic ulcer disease, and reproductive disturbances, including prematurity (1980). Tobacco smoke is a complex mixture of chemicals, including carbon monoxide, many of which have been implicated in human disease. Nicotine may contribute to tobacco-related disease, but direct causation has not been determined because nicotine is taken up simultaneously with a multitude of other potentially harmful substances that occur in tobacco smoke and smokeless tobacco.

However, particularly now that nicotine per se may be prescribed in the form of gum or other delivery systems, the potential health consequences of chronic nicotine exposure deserve careful consideration.

Cardiovascular Disease

Smoking causes coronary and peripheral vascular disease (US DHHS 1983). Both nicotine and carbon monoxide may contribute to atherosclerotic vascular disease (Figure 1). Nicotine could contribute both to the atherosclerotic process and to acute coronary events by several mechanisms. Nicotine could promote atherosclerotic disease by its actions on lipid metabolism and coagulation, by hemodynamic effects, and/or by causing endothelial injury. Compared to nonsmokers, cigarette smokers have elevated low-density (LDL) and very-low-density lipoproteins (VLDL), as well as reduced high-density lipoprotein (HDL) levels (Criqui et al. 1986; Brischetto et al. 1983), a profile associated with an increased risk of atherosclerosis. Chronic oral nicotine feeding has been shown to increase LDL in monkeys (Cluette-Brown et al. 1986). In one patient the use of nicotine polacrilex gum was reported to increase serum total and LDL cholesterol and triglycerides (Dousset, Gutierres, Dousset 1986). Nicotine may act by releasing free fatty acids, enhancing the conversion of VLDL to LDL, impairing the clearance of LDL and/or by accelerating the metabolism of HDL (Brischetto et al. 1983; Cluette-Brown et al. 1986; Gnasso et al. 1986; Hojnacki et al. 1986).

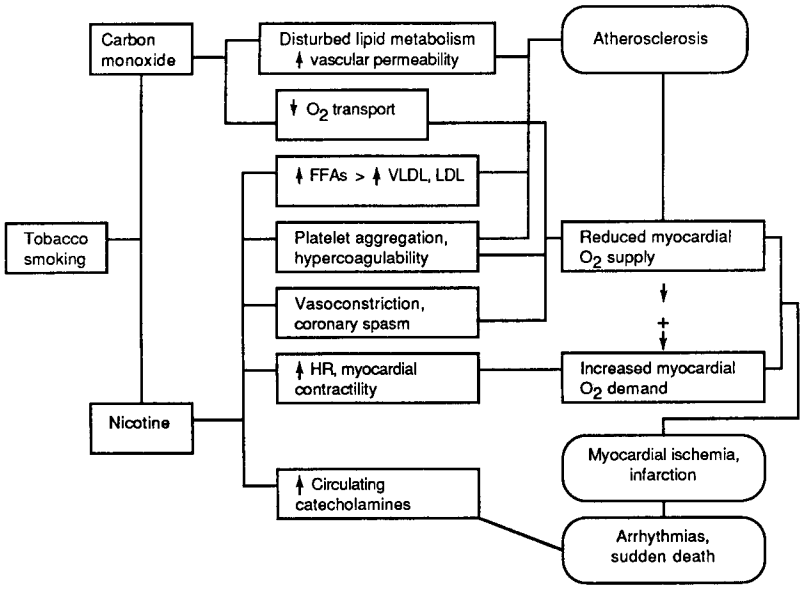

FIGURE 1.—Smoking, nicotine, and coronary heart disease
SOURCE: Benowitz (1986d).

Thrombosis is believed to play an important role in atherogenesis (Mehta and Mehta 1981). Platelets may release a growth hormone which promotes the growth of vascular endothelial cells, contributing to the atherosclerotic plaque (Packham and Mustard 1986). The blood of smokers is known to coagulate more readily than the blood of nonsmokers (Billimoria et al. 1975). According to several studies, platelets of smokers are more reactive, and have a shorter survival than those of nonsmokers (Belch et al. 1984; Siess et al. 1982; Mustard and Murphy 1963). The importance of nicotine as a determinant of platelet hyperaggregability is supported by a study showing that the blood concentrations of nicotine, after smoking different cigarettes, correlated with the platelet aggregation response (Renaud et al. 1984). Nicotine could affect platelets by increasing the release of epinephrine, which is known to enhance platelet reactivity, by inhibiting prostacyclin, an antiaggregatory hormone secreted by endothelial cells, or perhaps directly (Cryer et al. 1976; Sonnenfeld and Wennmalm 1980). Alternatively, by increasing heart rate and cardiac output and thereby increasing blood turbulence or by direct action nicotine may promote endothelial injury.

Structural damage and increased mitotic activity in the aortic endothelial cells of nicotine-treated animals have been reported (Booyse, Osikowicz, Quarfoot 1981; Zimmerman and McGeachie 1985, 1987). Nicotine has also been shown to modulate the structural and functional characteristics of cultured vascular cells (Csonka et al. 1985; Thyberg 1986). In rats, nicotine given i.v. or per p.o. produced dose-dependent increases in circulating anuclear carcasses of endothelial cells (Hladovec 1978). In support of the relevance of animal or in vitro studies to humans, Davis and colleagues (1985) reported an increase in the number of endothelial cells found in venous blood (reflecting endothelial injury) and a decrease in the platelet aggregate ratios (reflecting platelet aggregation) in non-smokers who smoked tobacco but not nontobacco (made from wheat, cocoa, and citrus plants) cigarettes.

The above findings suggest that some substance unique to tobacco, such as nicotine, may contribute to the pathogenesis of atherosclerosis and complications of atherosclerotic vascular disease. Although several potential mechanisms by which nicotine may promote atherogenesis have been considered, nicotine has not been demonstrated to produce or accelerate atherosclerosis in experimental animals. Wald and colleagues (1981) have presented an argument against the role of nicotine in promoting coronary heart disease in that pipe smokers, who consume comparable amounts of nicotine and have similar levels of nicotine but lower levels of carbon monoxide in the blood as cigarette smokers, do not share the same magnitude of increased risk for coronary heart disease. However, the possibility that nicotine inhaled in cigarette smoke, either due to rapid absorption or effects on pulmonary afferent nerves, affects the cardiovascular system differently than nicotine absorbed more slowly through mucous membranes must be considered (Benowitz and Jacob 1987).

Based on its pharmacologic actions, it is likely that nicotine plays a role in causing or aggravating acute coronary events. Myocardial infarction can be due to one or more of three precipitating factors - excessive oxygen and substrate demand, thrombosis, and coronary spasm. Nicotine increases heart rate and blood pressure and, therefore, myocardial oxygen consumption. Carbon monoxide inhaled in cigarette smoke reduces the oxygen carrying and releasing capacity of the blood. When a healthy person smokes a cigarette, coronary blood flow increases to meet the increased demand (Nicod et al. 1984). In the presence of coronary artery stenosis, coronary blood flow cannot increase and ischemia may develop, resulting in angina pectoris, myocardial dysfunction, or myocardial infarction (Jain et al. 1977). Nicotine may also directly reduce the increase in coronary blood flow which occurs in response to increased metabolic demand, or even cause an inappropriate decrease in coronary blood

flow, so that flow no longer matches increased myocardial oxygen consumption (Kaijser and Berglund 1985; Klein et al. 1984; Nicod et al. 1984; Martin et al. 1984). The decrease in coronary blood flow with smoking appears to result from alpha-adrenergically mediated coronary vasoconstriction, due to sympathetic activation and/or increased circulating catecholamines, either of which is likely to be an effect of nicotine (Winniford et al. 1986). Chronic nicotine exposure has been reported to increase the size of experimentally induced myocardial infarcts in dogs (Sridharan et al. 1985).

Nicotine consumed in the form of nicotine gum has been studied in patients with coronary artery disease. Nicotine gum (4-mg) increased myocardial contractility in healthy people, but in patients with coronary artery disease nicotine gum decreased contractility in the ischemic regions of the myocardium, consistent with aggravation of ischemia (Bayer, Bohn, Strauer 1985). In the most severe cases of coronary artery disease, overall contractility decreased after nicotine polacrilex gum. This study supports the idea that nicotine contributes to smoking-induced myocardial ischemia in susceptible people.

In addition to creating an imbalance between myocardial oxygen supply and demand, nicotine may promote thrombosis, as discussed previously. Nicotine may also induce coronary spasm by sympathetic activation or inhibition of prostacyclin. Coronary spasm has been observed during cigarette smoking (Maouad et al. 1984).

Sudden cardiac death in smokers might result from ischemia, as discussed above, combined with the arrhythmogenic effects of increased amounts of circulating catecholamines released by nicotine. However, smoking has not been demonstrated to increase the prevalence or magnitude of ventricular ectopy in patients with ischemic heart disease (Davis et al. 1985; Meyers et al. 1988). Cigarette smoking, most likely mediated by nicotine, facilitates AV nodal conduction, which could result in an increased ventricular response during atrial fibrillation (Bekheit and Fletcher 1976; Peters et al. 1988). Thus, even if the frequency of arrhythmias is not increased by smoking, the actions of nicotine may render those arrhythmias which do occur more life-threatening.

With respect to the arrhythmogenicity of nicotine, two case reports are of note. The first concerns a man who developed atrial fibrillation with a rapid ventricular response rate (150) while chewing 30 pieces of 2-mg nicotine polacrilex gum per day (Stewart and Catterall 1985). The other case was that of a man with known paroxysmal atrial fibrillation who developed a recurrence 5 min after chewing the day's first piece of nicotine gum (Rigotti and Eagle 1986).

Cigarette smoking has been associated with an increased risk of cardiomyopathy, that is a generalized reduction in contractility of

heart muscle (Hartz et al. 1984). Cigarette smoke exposure induces cardiomyopathy in rabbits (Gvozdjáková et al. 1984). A role of nicotine is suggested by a study in which dogs received injections of nicotine for 22 months and developed impaired contraction of the heart muscle with evidence of some interstitial fibrosis on anatomical examination (Ahmed et al. 1976).

Exercise tolerance in patients with intermittent claudication improves after stopping cigarette smoking (Jonason and Bergstrom 1987; Quick and Cotton 1982). Nicotine could aggravate peripheral vascular disease by constricting small collateral arteries and/or by inducing local thrombosis. The effect of nicotine replacement therapy on symptoms of peripheral vascular disease, as on exercise tolerance, in comparison to cigarette smoking, requires further investigation.

On balance, short-term nicotine administration, such as nicotine replacement therapy as an adjunct to smoking cessation therapy, presents little cardiovascular risk to healthy individuals. Patients with coronary or peripheral vascular disease are likely to suffer some increase in risk when taking nicotine, but considerably less risk than with cigarette smoking, which exposes them also to both carbon monoxide and higher levels of nicotine.

Hypertension

Although cigarette smoking and nicotine per se increase blood pressure, cigarette smoking alone is not a risk factor for chronic hypertension (Green, Jucha, Luz 1986). Conceivably, factors such as lower body weight or altered dietary intake, which may be associated with cigarette smoking, might lower blood pressure to compensate for any blood pressure elevation due to nicotine.

However, progression of chronic hypertension to accelerated or malignant hypertension is much more likely in cigarette smokers (Isles et al. 1979; Petitti and Klatsky 1983). Nicotine could contribute to this progression by aggravating vasoconstriction, either via sympathetic activation or inhibition of prostaglandin synthesis. Animal studies indicate that nicotine may reduce renal blood flow which, in a patient with marginal renal blood flow due to hypertensive vascular disease, could cause renal ischemia and aggravate hypertension (Downey, Crystal, Bashour 1981). Thus, there is concern about nicotine replacement therapies in patients with severe hypertension.

Tobacco, most likely due to effect of nicotine, may interact with particular hypertensive diseases. For example, a patient with pheochromocytoma (a catecholamine-secreting tumor) developed paroxysmal hypertension and angina pectoris following the use of oral snuff (McPhaul et al. 1984). Within 10 min, blood pressure increased from 110/70 mmHg to 300/103 mmHg and heart rate from

70 to 110. Rechallenge with snuff after surgical removal of the pheochromocytoma revealed only a mild blood pressure increase. Another patient with previously controlled essential hypertension presented with a blood pressure of 210/115 mmHg prior to surgery (Wells et al. 1986). A mass of snuff was found in the patient's cheek. The snuff was removed and blood pressure returned to 150/85 mmHg within 15 min.

Wound Healing

Adequate blood flow to the skin is important for wound healing. Cigarette smoking and nicotine polacrilex gum reduce skin blood flow (Fredholm and Sawe 1981; Allison and Roth 1969; Carlsson and Wennmalm 1983). In rats, exposure to cigarette smoke decreases survival of surgical flaps (Kaufman et al. 1984; Lawrence et al. 1984; Craig and Rees 1985). Cigarette smoking has been associated with a twelvefold increased risk of experiencing skin slough after facelift surgery (Rees, Liverett, Guy 1984). It is conceivable that nicotine substitution therapy might also delay wound healing, but no human data are as yet available.

Reproductive Hazards

Teratogenicity

Nicotine rapidly crosses the placenta and enters the fetus (Suzuki et al. 1974). Nishimura and Nakai (1958), Landauer (1960), and Khan and coworkers (1981) have described teratogenic effects of high doses of nicotine, which interfered with skeletogenesis in mice and chick embryos. Chronic nicotine treatments of pregnant rats throughout gestation produced subtle neurological changes which manifested themselves as behavioral or electrophysiological alterations in the offspring (Peters and Ngan 1982; Hudson, Meisami, Timiras 1973; Martin and Becker 1971). Wang, Chen, and Schraufnagel (1984) found that pre- and postnatal exposure to nicotine induced structural changes in the lungs of fetal mice. Maternal exposure to nicotine also inhibited glucose metabolism in fetal lung tissue (Maritz 1986). Thus, several studies suggest that nicotine, at least in high doses, may have toxic effects on the fetus.

Whether cigarette smoking is associated with increased rates of congenital malformations in humans is controversial. Several studies show no association or a lower incidence of malformations in offspring of smoking mothers (Comstock and Lundin 1967; Goujard, Rumeau, Schwartz 1975; Meyer and Tonascia 1977; Evans, Newcombe, Campbell 1979; Shiono, Klebanoff, Berendes 1986; Hemminki, Mutanen, Salonieni 1983), but others report positive associations (Himmelberger, Brown, Cohen 1978; Fedrick 1978; Kelsey et al. 1978). One study has reported an association between paternal

smoking and the incidence of congenital malformations (Mau and Netter 1974).

Pregnancy

Cigarette smoking during pregnancy increases the risk of low birth weight, prematurity, spontaneous abortion, and perinatal mortality in humans, which has been referred to as the fetal tobacco syndrome (Nieburg et al. 1985) (also reviewed in detail in the 1980 Surgeon General's Report). Nicotine influences implantation and embryo development in some laboratory animal studies (Hudson and Timiras 1972; Card and Mitchell 1979; Hammer and Mitchell 1979). At least one adverse outcome, reduced birth weight, is correlated with the level of cotinine, the major metabolite of nicotine, in the mother's serum (Haddow et al. 1987).

Nicotine in high concentrations markedly decreases the in vitro development of rabbit preimplantation embryos and inhibits DNA synthesis (Balling and Beier 1985). Injection of nicotine, 7.5 mg twice each day from proestrus through pregnancy in rats, resulted in a delay in the entry of the ovum into the uterus, implantation, and subsequent development of the ovum (Yoshinaga et al. 1979). It was suggested that nicotine acted by delaying progesterone secretion, which is necessary to prepare the uterus for implantation, and by other disturbances of hormone release. Another study in rats reported that low doses of nicotine injected subcutaneously (0.1 mg/kg/day) from day 14 to the end of pregnancy had no effect on litter size or fetal development, but higher doses (1 mg/kg/day), comparable to those consumed by heavy smokers, reduced litter size and increased the number of still births (Hamosh, Simon, Hamosh 1979). Further research is needed to determine if there are direct adverse effects of nicotine on the embryo or fetus at levels of nicotine comparable to those observed in cigarette smokers.

A likely mechanism for the reproductive problems in pregnant cigarette smokers is placental insufficiency, which is supported by evidence of placental hypoperfusion in cigarette smoking mothers (Naeye 1978; Philipp, Pateisky, Endler 1984). The factors most likely to affect the placenta are carbon monoxide and nicotine, both agents having the potential of impairing oxygen supply to the fetus.

Inhalation of carbon monoxide results in elevation of both maternal and fetal carboxyhemoglobin (Asmussen and Kjeldsen 1975; Longo 1977). Nicotine infusion in pregnant sheep increases uterine vascular resistance and reduces uterine blood flow, effects which appear to be mediated by catecholamine release (Ayromlooi, Desiderio, Tobias 1981; Resnick, Brink, Wilkes 1979). Both cigarette smoking and nicotine gum increase fetal heart rate during the second trimester in humans, consistent with sympathetic activation (Lehtovirta et al. 1983). During the third trimester in humans,

cigarette smoking or nicotine gum chewing decreases fetal heart rate and reduces fetal breathing movements, both of which may be signs of fetal hypoxia (Lehtovirta et al. 1983; Gennser, Marsal, Brantmark 1975; Manning and Feyerabend 1976). Elevated levels of catecholamines in amniotic fluid in human smokers during the third trimester indicate sympathetic activation in the fetus, consistent with fetal hypoxia and/or direct effects of nicotine (Divers et al. 1981). The above findings suggest that nicotine contributes to the adverse effects of cigarette smoking on reproduction probably by acting on the utero-placental circulation. Besides producing functional changes, carbon monoxide and nicotine might also be responsible for the injury to the intimal ultrastructure of the umbilical artery seen in smoking mothers (Asmussen and Kjeldson 1975). Fetal hypoxemia has also been considered as a contributory cause of behavioral abnormalities, such as hyperactivity, short attention span, lower scores on spelling and reading tests, which occurred at a higher frequency in children whose mothers had smoked throughout pregnancy than in those born to nonsmoking mothers (Naeye and Peters 1984).

Pulmonary Toxicity

Cigarette smoking is the major cause of chronic obstructive lung disease (US DHHS 1984). Nicotine may directly or indirectly influence the development of emphysema in smokers. It rapidly accumulates in the pulmonary epithelial cells and some of its metabolites are retained in the lung for prolonged periods (Waddell and Marlowe 1976; Szuts et al. 1978).

Chronic bronchial wall inflammation with accumulation of alveolar macrophages and polymorphonuclear neutrophils into the lung occur in response to habitual cigarette smoke exposure (Janoff 1983, 1985). Macrophages and neutrophils release elastase, an enzyme that destroys alveolar structure. Stone and colleagues (1983) found that alpha-1-antitrypsin, an inhibitor of elastase, may also be partially inactivated by cigarette smoke, probably related to effects of oxidant gases. Nicotine, which possesses chemotactic properties for neutrophils (Totti et al. 1984; Jay, Kojima, Gillespie 1986) and can stimulate the production of elastase as shown for the pancreas in vivo (Morosco et al. 1981), may play a role in increasing elastase levels in the lungs. In addition, nicotine may adversely affect the repair of connective tissue since it has been reported to cause structural alterations and inhibition of collagen synthesis in fibroblast cultures (Chamson et al. 1980; Chamson, Frey, Hivert 1982; Hurst and Gilbert 1979).

Several other studies suggest that nicotine may contribute to the development of emphysema in smokers. Lai and Diamond (1987) showed that repeated inhalation of smoke from high, but not from

low, nicotine cigarettes significantly augmented experimentally induced emphysema in rats. Lelcuk and coworkers (1986) reported that nicotine instilled directly into the airways induced edema. In the rat, a variety of ingredients of both the particulate and vapor phase of cigarette smoke are capable of increasing vascular permeability and producing edema in the tracheobronchial mucosa (Lundberg et al. 1983). This effect, which was traced to the stimulation of substance P-containing pulmonary vagal afferent neurons, was duplicated by nicotine (Lundberg, Saria, Martling 1982). In the guinea pig, inhaled cigarette smoke damaged the mucosal barrier and increased permeability to horseradish peroxidase by disrupting the intercellular tight junctions of the bronchial epithelium (Boucher et al. 1980). In smokers, Mason and coworkers (1983) documented an increase in pulmonary epithelial permeability in all lung regions using a radioaerosol procedure. In contrast, neither aerosolized nor injected nicotine, given over a period of 2 to 3 weeks, causes secretory cell hyperplasia (Rogers, Williams, Jeffery 1986) and there is little evidence that nicotine contributes to the development of chronic bronchitis. Further research is needed to define the magnitude of the contribution of nicotine to the pathogenesis of smoking-induced chronic lung disease.

Nicotine can also worsen pulmonary function in smokers who already have lung disease. Acute exposure to nicotine induces constriction of both central and peripheral airways (Yamatake, Sasagawa, Yanaura 1978). The increase in airway resistance by nicotine involves vagal reflexes and stimulation of parasympathetic ganglia in the bronchial wall (Nakamura et al. 1986). The magnitude of bronchoconstriction observed in experimental animals and humans following acute inhalation of cigarette smoke is correlated with the level of nicotine in the smoke (Shepherd, Collins, Silverman 1979; Rees, Chowienczyk, Clark 1982; Lee et al. 1983; Nakamura et al. 1985; Hartiala et al. 1985; Beck et al. 1986), suggesting that nicotine may be an important factor in the increased airway resistance of smokers.

Genotoxicity and Carcinogenicity

Smoking of cigarettes is causally related to cancer of the respiratory tract, the upper digestive tract, pancreas, renal pelvis, and bladder; cigarette smokers also face an increased risk for cancer of the cervix (US DHHS 1982; IARC 1986). Many carcinogenic agents have been identified in cigarette smoke, however, not a single component nor chemical group(s) of components is solely responsible for the carcinogenic activity of cigarette smoke in the various organs. Laboratory bioassays suggest that polynuclear aromatic hydrocarbons and N-nitrosamines play significant roles in the induction of cancer in smokers (US DHHS 1982; IARC 1986). Nicotine, the

principal alkaloid in tobacco smoke, has also been examined for its genotoxic and carcinogenic activity. In the Ames' *Salmonella typhimurium* mutagenesis and mammalian cell cytogenetic assays, nicotine did not possess any genotoxic activity, although it induced reparable DNA damage in the *Escherichia coli* pol A+/A- system (Bishun et al. 1972; Florin et al. 1980; Riebe, Westphal, Fortnagel 1982; Riebe and Westphal 1983).

In earlier studies, nicotine and its primary metabolites were reported to possess weak tumorigenic activity (Truhaut, De Clercq, Loisillier 1964; Boyland 1968), which subsequent investigations did not confirm (Schmähl and Osswald 1968; Martin et al. 1979; Toth 1982; LaVoie et al. 1985). Nicotine lacked cocarcinogenic activity in the urethane-induced mouse pulmonary adenoma model (Freelander and French 1956), but was found to be a cocarcinogen in the benzo(a)pyrene-tetradecanoyl phorbol acetate mouse skin tumorigenesis model (Bock 1980). The mechanism of cocarcinogenic activity is not clearly understood. Two primary metabolites of nicotine, cotinine and nicotine-N'-oxide, failed to promote N-(4-(5-nitro-2-furyl)-2 thiazyl) formamide (FANFT)-induced urinary bladder tumors in rats (LaVoie et al. 1985). On balance, it appears that nicotine does not possess direct carcinogenic activity.

During processing and pyrolysis of tobacco, nicotine can be N'-nitrosated to form N'-nitrosonornicotine and other related compounds (Figure 2) (Hoffmann and Brunnemann 1983; Hoffmann and Hecht 1985). These tobacco-specific N'nitrosoamines are found in substantial concentrations in American snuff, as well as in mainstream tobacco smoke (Table 2), and in the saliva of snuff dippers (Hoffmann and Adams 1981; Palladino et al. 1986). Tobacco specific N-nitrosoamines are highly carcinogenic in animals and are suspected to contribute to cancer related to cigarette smoking and smokeless tobacco use (Hoffmann, LaVoie, Hecht 1985; Hoffmann and Hecht 1985). There is also concern that nicotine may be N-nitrosated within the human body. Endogenous formation of N-nitrosoproline (a noncarcinogenic marker of endogenous N-nitrosation) has been documented in cigarette smokers (Hoffmann and Brunnemann 1983; Tsuda et al. 1986). Whether nicotine-derived nitrosoamines are formed endogenously in amounts sufficient to contribute to cancer in humans exposed to nicotine per se (such as with nicotine replacement therapy) remains to be determined.

Gastrointestinal Disease

In peptic ulcer disease, cigarette smoking is a risk factor for its development, and an even stronger risk factor for delayed healing, failure to respond to therapy, and relapse (Kikendall, Evaul, Johnson 1984). In animals, nicotine potentiates peptic ulcer formation induced by histamine or pentagastrin (Konturek et al. 1971; Lee

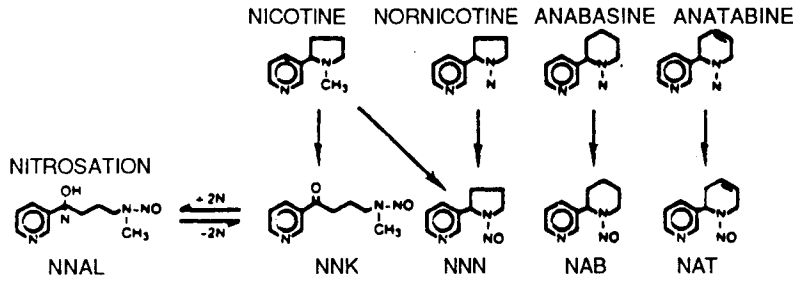

FIGURE 2.—Formation of tobacco-specific nitrosamines

NOTE: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine; NAB, N'-nitrosoanabasine NAT, N'-nitrosoanatabine.

SOURCE: US DHHS (1986).

TABLE 2.—Tobacco-specific nitrosamines in commercial U.S. tobacco products

Tobacco product	NNN	NNK	NAT + NAB
Smokeless tobacco			
Chewing tobacco[1] (ppb)	3500–8200	100–3000	500–7000
Snuff[1] (ppb)	800–89,000	200–8300	200–4000
Mainstream smoke			
Cigarette, NF (ng/cig)	120–950	80–770	140–990
Cigarette, French Black, NF	500	220	350
Cigarette, F (ng/cig)	50–310	30–150	60–370
Little cigar, F (ng/cigar)	5500	4200	1700
Cigar (ng/cigar)	3200	1900	1900
Sidestream smoke			
Cigarette, NF (ng/cig)	1700	410	270
Cigarette, F (ng/cig)	150	190	150

NOTE: NNN, N'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N'-nitrosoanatabine; NAB, N'-nitrosoanabasine; NF, without filter tip; F, with filter tip.

[1] Chewing tobacco and snuff also contain $\leq$ 200 ppb NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)butan-1-ol.

SOURCE: Hoffmann, LaVoie, Hecht (1985).

and Gruber 1952). Several mechanisms by which nicotine acts in this regard have been proposed. (1) Chronic treatment in rats increases basal acid secretion, an effect which appears to be mediated by parasympathetic mechanisms (Thompson and George 1972). Chronic cigarette smoking may induce hypersecretion of acid in response to secretory stimuli. (2) Infusion of nicotine in animals and cigarette smoking by people reduces pancreatic bicarbonate secretion, which normally neutralizes acid entering the duodenum (Solomon et al.

1974; Murthy et al. 1977). This could result in increased acid delivery to the duodenum, thereby increasing the risk of ulceration. (3) Smoking may impair the mucosal barrier to acid-mediated injury. Smoking, apparently acting through nicotine, decreases mucosal blood flow and inhibits mucosal prostaglandin synthesis, both of which may impair the effectiveness of the gastric mucosal barrier, which protects the stomach lining against acid (Chujoh and Nakazawa 1981; Kawano et al. 1982; Quimby et al. 1986). (4) Cigarette smoking reduces both lower esophageal and pyloric sphincter pressures (Chattopadhyay, Greaney, Irvin 1977; Valenzuela, Defilippi, Csendes 1976), resulting in gastroesophageal reflux and duodenogastric reflux, respectively. The former may result in reflux symptoms (heartburn) (Stanciu and Bennett 1972), while the latter may cause reflux of bile acids and lysolecithin, which are known to break down the gastric mucous barrier. A direct role of nicotine is suggested by studies in opposums showing that intravenous nicotine reduces lower esophageal sphincter pressure (Rattan and Goyal 1975).

The relative importance of local exposure to nicotine (as from swallowing nicotine from nicotine polacrilex gum) versus exposure to nicotine via the bloodstream in producing the above effects is unclear. In view of the extremely high concentrations of nicotine in saliva as compared to blood, local toxicity must be considered until proven otherwise to be an additional risk of nicotine polacrilex chewing gum for patients with ulcer disease or symptoms of esophageal reflux.

Summary and Conclusions

1. At high exposure levels, nicotine is a potent and potentially lethal poison. Human poisonings occur primarily as a result of accidental ingestion or skin contact with nicotine-containing insecticides or, in children, after ingestion of tobacco or tobacco juices.
2. Mild nicotine intoxication occurs in first-time smokers, nonsmoking workers who harvest tobacco leaves, and people who chew excessive amounts of nicotine gum. Tolerance to these effects develops rapidly.
3. Nicotine exposure in long-term tobacco users is substantial, affecting many organ systems (Chapters II and III). Pharmacologic actions of nicotine may contribute to the pathogenesis of smoking-related diseases, although direct causation has not yet been determined. Of particular concern are cardiovascular disease, complications of hypertension, reproductive disorders, cancer, and gastrointestinal disorders, including peptic ulcer disease and gastroesophageal reflux.

4. The risks of short-term nicotine replacement therapy as an aid to smoking cessation in healthy people are acceptable and substantially outweighed by the risks of cigarette smoking.

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