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 Säwe 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 twofold 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 (1956), 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 Landin 1967; Goujard, Rumeau, Schwartz 1975; Meyer and Tonascia 1977; Evans, Newcombe, Campbell 1979; Shiono, Klebanoff, Berendes 1986; Hemminki, Mutanen, Salonen 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. Leluk 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, Loisiliier 1964; Boyland 1968), which subsequent investigations did not confirm (Schmahl 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-pyrldylbutan-1-ol; NNK, 4-(methylamino)-1-3-pyrldyl-1-butanone; NNN, N-nitrosonornicotine; NAB, N'-nitrosoanabasine; NAT, N'-nitrosoanatabine.

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

<table>
<thead>
<tr>
<th>Tobacco product</th>
<th>NNN (ppb)</th>
<th>NNK (ppb)</th>
<th>NAT + NAB (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokeless tobacco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing tobacco</td>
<td>5500-6200</td>
<td>100-3000</td>
<td>500-7000</td>
</tr>
<tr>
<td>Snuff</td>
<td>800-89,000</td>
<td>200-8,300</td>
<td>200-4000</td>
</tr>
<tr>
<td>Mainstream smoke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette, NF</td>
<td>120-350</td>
<td>80-770</td>
<td>140-990</td>
</tr>
<tr>
<td>Cigarette, French Black, NF</td>
<td>500</td>
<td>220</td>
<td>350</td>
</tr>
<tr>
<td>Cigarette, F</td>
<td>50-310</td>
<td>30-150</td>
<td>60-370</td>
</tr>
<tr>
<td>Little cigar, F</td>
<td>5500</td>
<td>4200</td>
<td>1700</td>
</tr>
<tr>
<td>Cigar, F</td>
<td>3200</td>
<td>1900</td>
<td>1900</td>
</tr>
<tr>
<td>Sidestream smoke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette, NF</td>
<td>1700</td>
<td>410</td>
<td>270</td>
</tr>
<tr>
<td>Cigarette, F</td>
<td>150</td>
<td>190</td>
<td>150</td>
</tr>
</tbody>
</table>

NOTE: NNN, N'-nitrosonornicotine; NNK, 4-methylnitrosamino-1-3-pyrldyl-1-butanone; NAT, N'-nitrosoanatabine; NF, without filter tip; F, with filter tip. Chewmg tobacco and snuff also contain < 200 ppb NNAL, 4-(methylamino)-1-3-pyrldylbutan-1-ol.

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. 1986).
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 lyssolecithin, 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, non-smoking 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.
References


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