

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, Loissillier 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



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 opossums 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

- AHMED, S.S., MOSCHOS, C.B., LYONS, M.M., OLDEWERTEL, H.A., COUMBIS, R.J., REGAN, T.J. Cardiovascular effects of long-term cigarette smoking and nicotine administration. *American Journal of Cardiology* 37:33-40, January 1976.
- ALLISON, R.D., ROTH, G.M. Central and peripheral vascular effects during cigarette smoking. *Archives of Environmental Health* 19:189-198, August 1969.
- ASMUSSEN, I., KJELDSEN, K. Intimal ultrastructure of human umbilical arteries. Observations on arteries from newborn children of smoking and nonsmoking mothers. *Circulation Research* 36(5):579-589, May 1975.
- AYROMLOOI, J., DESIDERIO, D., TOBIAS, M. Effect of nicotine sulfate on the hemodynamics and acid base balance of chronically instrumented pregnant sheep. *Developmental Pharmacology and Therapeutics* 3:205-213, 1981.
- BALLING, R., BEIER, H.M. Direct effects of nicotine on rabbit preimplantation embryos. *Toxicology* 34(4):309-313, March 1985.
- BARLOW, R.B., McLEOD, L.J. Some studies on cytosine and its methylated derivatives. *British Journal of Pharmacology* 35(1):161-174, 1969.
- BAYER, F., BOHN, I.L., STRAUER, B.E. Das kontraktionsverhalten des linken ventrikels unter nikotinoxposition. [The comportment of the contraction behavior of the left ventricle under nicotine exposition.] *Therapiewoche* 35:1968-1974, 1985.
- BECK, E.R., TAYLOR, R.F., LEE, L.Y., FRAZIER, D.T. Bronchoconstriction and apnea induced by cigarette smoke: Nicotine dose dependence. *Lung* 164:293-301, 1986.
- BEEMAN, J.A., HUNTER, W.C. Fatal nicotine poisoning. A report of twenty-four cases. *Archives of Pathology* 24:481-485, 1937.
- BEKHEIT, S., FLETCHER, E. The effects of smoking on myocardial conduction in the human heart. *American Heart Journal* 91(6):712-720, June 1976.
- BELCH, J.J.F., McARDLE, B.M., BURNS, P., LOWE, G.D.O., FORBES, C.D. The effects of acute smoking on platelet behaviour, fibrinolysis and haemorrheology in habitual smokers. *Thrombosis Haemostasis* 51(1):6-8, February 28, 1984.
- BENOWITZ, N.L., JACOB, P. III Metabolism, pharmacokinetics and pharmacodynamics of nicotine in man. In: Martin, W.R., Van Loon, G.R., Iwamoto, E.T., Davis, L. (eds.) *Tobacco Smoking and Nicotine: A Neurobiological Approach*. New York: Plenum Press, 1987, pp. 357-373.
- BENOWITZ, N.L., LAKE, T., KELLER, K.H., LEE, B.L. Prolonged absorption with development of tolerance to toxic effects after cutaneous exposure to nicotine. *Clinical Pharmacology and Therapeutics* 42(1):119-220, 1987.
- BERNFELD, P., HOMBURGER, F. High nicotine tolerance of Syrian golden hamsters. (Abstract.) *Toxicology and Applied Pharmacology* 22(2):324-325, June 1972.
- BILLIMORIA, J.D., POZNER, H., METSELAAR, B., BEST, F.W., JAMES, D.C.O. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. *Atherosclerosis* 21(1):61-76, January-February 1975.
- BISHUN, N.P., LLOYD, N., RAVEN, R.W., WILLIAMS, D.C. The in vitro and in vivo cytogenetic effects of nicotine. *Acta Biologica Academiae Scientiarum Hungaricae* 23(2):175-180, 1972.
- BOCK, F.G. Carcinogenic properties of nicotine. In: Gori, G., Bock, F.G. (eds.) *Banbury Report 3. A Safe Cigarette?* New York: Cold Spring Harbor Laboratory, 1980, pp. 129-139.
- BOUYSE, F.M., OSIKOWICZ, G., QUARFOOT, A.J. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. *American Journal of Pathology* 102(2):229-238, February 1981.
- BORZELLECA, J.F., BORMAN, E.R., McKENNIS, H. Studies on the respiratory and cardiovascular effects of (-)-cotinine. *Journal of Pharmacology and Experimental Therapeutics* 137(3):313-318, September 1962.

- BOUCHER, R.C., JOHNSON, J., INOUE, S., HULBERT, W., HOGG, J.C. The effect of cigarette smoke on the permeability of guinea-pig airways. *Laboratory Investigation* 43(1):94-100, July 1980.
- BOYLAND E. The possible carcinogenic action of alkaloids of tobacco and betel nut. *Planta Medica* 11(Supplement):13-22, 1968.
- BRANTMARK, B., FREDHOLM, B. *Absorption of Nicotine from Swallowed Intact Buffered Nicorette Chewing Gum*, A. B. Leo Research Report No. 897. Helsingborg, Sweden, 1974.
- BRISCHETTO, C.S., CONNOR, W.E., CONNOR, S.L., MATARAZZO, J.D. Plasma lipid and lipoprotein profiles of cigarette smokers from randomly selected families: Enhancement of hyperlipidemia and depression of high-density lipoprotein. *American Journal of Cardiology* 52(7):675-680, October 1, 1983.
- CARLSSON, I., WENNMALM, A. Effect of cigarette smoking on reactive hyperaemia in the human finger. *Clinical Physiology* 3:453-469, 1983.
- CARD, J.P., MITCHELL, J.A. The effects of nicotine on implantation in the rat. *Biology of Reproduction* 20:532-539, April 1979.
- CHAMSON, A., FREY, J., HIVERT, M. Effects of tobacco smoke extracts on collagen biosynthesis by fibroblast cell cultures. *Journal of Toxicology and Environmental Health* 9(5/6):921-932, May-June 1982.
- CHAMSON, A., GARRONE, R., AUGER, C., FREY, J. Effects of tobacco smoke extract on the ultrastructure of fibroblasts in culture. *Journal of Submicroscopic Cytology* 12(3):401-406, July 1980.
- CHATTOPADHYAY, D.K., GREANEY, M.G., IRVIN, T.T. Effect of cigarette smoking on the lower oesophageal sphincter. Assessment of normal and symptomatic patients using the rapid pull-through technique of oesophageal manometry. *Gut* 18(10):833-835, October 1977.
- CHUJOH, C., NAKAZAWA, S. Inenmaku shogai ni kansura jikkenteki kenkyu toku ni sakusan kaiyo nochiyu ni oyobosu kitsuen no eikyo ni tsuite. [Experimental study for the gastric mucosal damage.] *Japanese Journal of Gastroenterology* 78(12):2285-2294, 1981.
- CLUETTE-BROWN, J., MULLIGAN, J., DOYLE, K., HAGAN, S., OSMOLSKI, T., HOJNACKI, J. Oral nicotine induces an atherogenic lipoprotein profile. *Proceedings of the Society for Experimental Biology and Medicine* 182(3):409-413, July 1986.
- COMSTOCK, G.W., LUNDIN, F.E. Jr. Parental smoking and perinatal mortality. *American Journal of Obstetrics and Gynecology* 98(5):708-718, July 1, 1967.
- CRAIG, S., REES, T.D. The effects of smoking on experimental skin flaps in hamsters. *Plastic and Reconstructive Surgery* 75(6):842-846, June 1985.
- CRIGUI, M.H., COWAN, L.D., HEISS, G., HASKELL, W.L., LASKARZEWSKI, P.M., CHAMBLESS, L.E. Frequency and clustering of nonlipid coronary risk factors in dyslipoproteinemia. The Lipid Research Clinics Program Prevalence Study. *Circulation* 73(1, Part 2):I-40-I-50, January 1986.
- CRYER, P.E., HAYMOND, M.W., SANTIAGO, J.V., SHAH, S.D. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. *New England Journal of Medicine* 295(11):573-577, September 1976.
- CSONKA, E., SOMOGYI, A., AUGUSTIN, J., HABERBOSCH, W., SCHETTLER, G., JELLINEK, H. The effect of nicotine on cultured cells of vascular origin. *Virchows Archiv A. Pathological Anatomy and Histology* 407(4):441-447, 1985.
- DAVIS, J.W., SHELTON, L., EIGENBERG, D.A., HIGNITE, C.E., WATANABE, I.S. Effects of tobacco and non-tobacco cigarette smoking on endothelium and platelets. *Clinical Pharmacology and Therapeutics* 37(5):529-533, May 1985.
- DIVERS, W.A. Jr., WILKES, M.M., BABAKNIA, A., YEN, S.S.C. Maternal smoking and elevation of catecholamines and metabolites in the amniotic fluid. *American Journal of Obstetrics and Gynecology* 141(6):625-628, November 1981.

- DOUSSET, J.C., GUTIERRES, J.B., DOUSSET, N. Hypercholesterolaemia after administration of nicotine chewing gum. (Letter.) *Lancet* 2(8520):1393-1394, December 13, 1986.
- DOWNEY, H.F., CRYSTAL, G.J., BASHOUR, F.A. Regional renal and splanchnic blood flows during nicotine infusion: Effects of beta adrenergic blockade. *Journal of Pharmacology and Experimental Therapeutics* 216(2):363-367, February 1981.
- EVANS, D.R., NEWCOMBE, R.G., CAMPBELL, H. Maternal smoking habits and congenital malformations: A population study. *British Medical Journal* 2(6183):171-173, July 21, 1979.
- FAULKNER, J.M. Nicotine poisoning by absorption through the skin. *Journal of the American Medical Association* 100(21):1664-1665, May 27, 1933.
- FEDRICK, J. Factors associated with low birth weight of infants delivered at term. *British Journal of Obstetrics and Gynaecology* 85(1):1-7, January 1978.
- FLORIN, I., RUTBERG, L., CURVALL, M., ENZELL, C.R. Screening of tobacco smoke constituents for mutagenicity using the Ame's test. *Toxicology* 18:219-232, 1980.
- FRANKE, F.E., THOMAS, J.E. The treatment of acute nicotine poisoning. *Journal of the American Medical Association* 106(1):507-512, January 4, 1936.
- FREDHOLM, B., SÅWE, U. Effects of Nicorette chewing and cigarette smoking on skin capillary blood flow. (Abstract.) *Clinical Physiology* 1(1):604-605, 1981.
- FREEDLANDER, B.L., FRENCH, F.A. Absence of co-carcinogenic action of oxidation products of nicotine in initiation of pulmonary adenomas in mice with urethan. (Abstract.) *Proceedings of the American Association for Cancer Research* 2(2):109, April 1956.
- GARG, M. Variation in effects of nicotine in four strains of rats. *Psychopharmacologia* 14:432-438, 1969.
- GEHLBACH, S.H., WILLIAMS, W.A., FREEMAN, J.I. Protective clothing as a means of reducing nicotine absorption in tobacco harvesters. *Archives of Environmental Health* 34(2):111-114, March-April 1979.
- GEHLBACH, S.H., WILLIAMS, W.A., PERRY, L.D., FREEMAN, J.I., LANGONE, J.J., PETA, L.V., VAN VUNAKIS, H. Nicotine absorption by workers harvesting green tobacco. *Lancet* 1(7905):478-480, March 1, 1975.
- GEHLBACH, S.H., WILLIAMS, W.A., PERRY, L.D., WOODALL, J.S. Green-tobacco sickness. An illness of tobacco harvesters. *Journal of the American Medical Association* 229(14):1880-1883, September 30, 1974.
- GENNSER, G., MARSAL, K., BRANTMARK, B. Maternal smoking and fetal breathing movements. *American Journal of Obstetrics and Gynecology* 123(8):861-867, December 15, 1975.
- GHOSH, S.K., PARIKH, J.R., GOKANI, V.N., KASHYAP, S.K., CHATTERJEE, S.K. Studies on occupational health problems during agricultural operation of Indian tobacco workers. A preliminary survey report. *Journal of Occupational Medicine* 21(1):45-47, January 1979.
- GNASSO, A., HABERBOSCH, W., SCHETTLER, G., SCHMITZ, G., AUGUSTIN, J. Acute influence of smoking on plasma lipoproteins. *Proceedings of the Society for Experimental Biology and Medicine* 182:414-418, 1986.
- GOLDFRANK, L., MELINEK, M., BLUM, A. Nicotine. *Hospital Physician* 16(4):22-35, 1980.
- GOUJARD, J., RUMEAU, C., SCHWARTZ, D. Smoking during pregnancy, stillbirth and abruptio placentae. *Biomedicine* 23(1):20-22, February 10, 1975.
- GVOZDJÁKOVÁ, A., BADA, V., SÁNY, L., KUCHARSKÁ, J., KRUTÝ, F., BOZEK, P., TRYSTANSKÝ, L., GVOZDJÁK, J. Smoke cardiomyopathy: Disturbance of oxidative processes in myocardial mitochondria. *Cardiovascular Research* 18:229-232, 1984.
- GREEN, M.S., JUCHA, E., LUZ, Y. Blood pressure in smokers and nonsmokers: Epidemiologic findings. *American Heart Journal* 3(5):932-940, May 1986.

- HADDOW, J.E., KNIGHT, G.J., PALOMAKI, G.E., KLOZA, E.M., WALD, N.J. Cigarette consumption and serum cotinine in relation to birthweight. *British Journal of Obstetrics and Gynaecology* 94(7):678-681, July 1987.
- HAMMER, R.E., MITCHELL, J.A. Nicotine reduces embryo growth, delays implantation, and retards parturition in rats. *Proceedings of the Society for Experimental Biology and Medicine* 162(2):333-336, November 1979.
- HAMOSH, M., SIMON, M.R., HAMOSH, P. Effect of nicotine on the development of fetal and suckling rats. *Biology of the Neonate* 35(5/6):290-297, 1979.
- HARTIALA, J.J., MAPP, C., MITCHELL, R.A., GOLD, W.M. Nicotine-induced respiratory effects of cigarette smoke in dogs. *Journal of Applied Physiology* 59(1):64-71, July 1985.
- HARZ, A.J., ANDERSON, A.J., BROOKS, H.L., MANLEY, J.C., PARENT, G.T., BARBORIAK, J.J. The association of smoking with cardiomyopathy. *The New England Journal of Medicine* 311(19):1201-1206, November 8, 1984.
- HEMMINKI, K., MUTANEN, P., SALONIEMI, I. Smoking and the occurrence of congenital malformations and spontaneous abortions: Multivariate analysis. *American Journal of Obstetrics and Gynecology* 145(1):61-66, January 1, 1983.
- HIMMELBERGER, D.U., BROWN, B.W. Jr., COHEN, E.N. Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. *American Journal of Epidemiology* 108(6):470-479, December 1978.
- HLADOVEC, J. Endothelial injury by nicotine and its prevention. *Experientia* 34(12):1585-1586, December 15, 1978.
- HOFFMANN, D., ADAMS, J.D. Carcinogenic tobacco-specific N-nitrosamines in snuff and in the saliva of snuff dippers. *Cancer Research* 41:4305-4308, November 1981.
- HOFFMANN, D., BRUNNEMANN, K.D. Endogenous formation of N-nitrosoproline in cigarette smokers. *Cancer Research* 43(11):5570-5574, November 1983.
- HOFFMANN, D., HECHT, S.S. Nicotine-derived N-nitrosamines and tobacco-related cancer: Current status and future directions. *Cancer Research* 45(3):935-944, March 1985.
- HOFFMANN, D., LaVOIE, E.J., HECHT, S.S. Nicotine: A precursor for carcinogens. *Cancer Letters* 26(1):67-75, February 1985.
- HOJNACKI, J., MULLIGAN, J., CLUETTE-BROWN, J., IGOE, F., OSMOLSKI, T. Oral nicotine impairs clearance of plasma low density lipoproteins. *Proceedings of the Society for Experimental Biology and Medicine* 182:414-418, 1986.
- HUDSON, D.B., MEISAMI, E., TIMIRAS, P.S. Brain development in offspring of rats treated with nicotine during pregnancy. *Experientia* 29(3):286-288, March 15, 1973.
- HUDSON, D.B., TIMIRAS, P.S. Nicotine ingestion during gestation: Impairment of reproduction, fetal viability and development. *Biology of Reproduction* 7(2):247-253, 1972.
- HURST, D.J., GILBERT, G.L. Acute change in lung collagen synthesis produced by cigarette smoke components. (Abstract.) *American Review of Respiratory Disease* 119(4, Supplement):222, April 1979.
- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. *Tobacco Smoking*. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Volume 38. World Health Organization, International Agency for Research on Cancer, 1986.
- ISLES, C., BROWN, J.J., CUMMING, A.M.M., LEVER, A.F., McAREAVEY, D., ROBERTSON, J.I.S., HAWTHORNE, V.M., STEWART, G.M., ROBERTSON, J.W.K., WAPSHAW, J. Excess smoking in malignant-phase hypertension. *British Medical Journal* 1(6163):579-581, March 3, 1979.
- JAIN, A.C., BOWYER, A.F., MARSHALL, R.J., ASATO, H. Left ventricular function after cigarette smoking by chronic smokers: Comparison of normal subjects and patients with coronary artery disease. *American Journal of Cardiology* 39(1):27-31, January 1977.

- JANOFF, A. Biochemical links between cigarette smoking and pulmonary emphysema. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* 55(2):285-293, August 1983.
- JANOFF, A. Elastases and emphysema: Current assessment of the protease-antiprotease hypothesis. *American Review of Respiratory Disease* 132(2):417-433, August 1985.
- JAY, M., KOJIMA, S., GILLESPIE, M.N. Nicotine potentiates superoxide anion generation by human neutrophils. *Toxicology and Applied Pharmacology* 86:484-487, December 1986.
- JONASON, T., BERGSTRÖM, R. Cessation of smoking in patients with intermittent claudication. *Acta Medica Scandinavica* 221(3):253-260, 1987.
- KAIJSER, L., BERGLUND, B. Effect of nicotine on coronary blood-flow in man. *Clinical Physiology* 5(6):541-552, December 1985.
- KAUFMAN, T., EICHENLAUB, E.H., LEVIN, M., HURWITZ, D.J., KLAIN, M. Tobacco smoking: Impairment of experimental flap survival. *Annals of Plastic Surgery* 13(6):468-472, 1984.
- KAWANO, S., SATO, N., FUKUDA, M., SHICHIRI, M., KAMADA, T., ABE, H. Inenmaku ketsuryu ni eikyo o oyobuso shoinshi no kento - (dai ippo) naishikyoka hansha supekutoryu kaiseki ni yory kitsuen no eiko no kento. [Effect of cigarette smoking on gastric hemodynamics. Analysis by reflectance spectrophotometry.] *Japanese Journal of Gastroenterology* 79:187-192, 1982.
- KELSEY, J.L., DWYER, T., HOLFORD, T.R., BRACKEN, M.B. Maternal smoking and congenital malformations. An epidemiological study. *Journal of Epidemiology and Community Health* 32(2):102-107, June 1978.
- KHAN, M.A., PROVENZA, D.V., OLSON, N.O., OVERMAN, D.O. Nicotine toxicity in chick vertebral chondrocytes in vitro. *Chemico-Biological Interactions* 35(3):363-367, 1981.
- KIKENDALL, J.W., EVAUL, J., JOHNSON, L.F. Effect of cigarette smoking on gastrointestinal physiology and non-neoplastic digestive disease. *Journal of Clinical Gastroenterology* 6(1):65-79, February 1984.
- KLEIN, L.W., AMBROSE, J., PICHARD, A., HOLT, J., GORLIN, R., TEICHHOLZ, L.E. Acute coronary hemodynamic response to cigarette smoking in patients with coronary artery disease. *Journal of the American College of Cardiology* 3(4):879-886, April 1984.
- KONTUREK, S.J., RADECKI, T., THOR, P., DEMBINSKI, A., JACOBSON, E.D. Effects of nicotine on gastric secretion and ulcer formation in cats. *Proceedings of the Society for Experimental Biology and Medicine* 138(2):674-677, November 1971.
- LAI, Y.-L., DIAMOND, L. Effects of high or low nicotine cigarette smoke exposure on elastase induced emphysema. (Abstract). *American Review of Respiratory Disease* 135(Supplement):150, 1987.
- LANDAUER, W. Nicotine-induced malformations of chicken embryos and their bearing on the phenocopy problems. *Journal of Experimental Zoology* 143(1):107-122, February 1960.
- LARSON, P.S., HAAG, H.S., SILVETTE, H. *Tobacco: Experimental and Clinical Studies. A Comprehensive Account of the World Literature*. Baltimore: Williams and Wilkins, 1961.
- LaVOIE, E.J., SHIGEMATSU, A., RIVENSON, A., MU, B., HOFFMANN, D. Evaluation of the effects of cotinine and nicotine-N'-oxides on the development of tumors in rats initiated with N-[4-(5-nitro-2 furyl)-2-thiazolyl] formamide. *Journal of the National Cancer Institute* 75(6):1075-1081, December 1985.
- LAWRENCE, W.T., MURPHY, R.C., ROBSON, M.C., HEGGERS, J.P. The detrimental effect of cigarette smoking on flap survival: An experimental study in the rat. *British Journal of Plastic Surgery* 37(2):216-219, April 1984.

- LEE, K.S., GRUBER, C.M. Jr. The effect of nicotine on the production of peptic ulcers in histamine treated dogs. *Archives of Internationales de Pharmacodynamie et de Therapie* 90(4):462-465, August 1952.
- LEE, L.-Y., MORTON, R.F., HORD, A.H., FRAZIER, D.T. Reflex control of breathing following inhalation of cigarette smoke in conscious dogs. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* 54(2):562-570, February 1983.
- LEHTOVIRTA, P., FORSS, M., RAURAMO, I., KARINIEMI, V. Acute effects of nicotine on fetal heart rate variability. *British Journal of Obstetrics and Gynaecology* 90(8):710-715, August 1983.
- LELCUK, S., THRELFALL, L., VALERIE, R., SHEPRO, D., HECHTMAN, H.B. Nicotine stimulates pulmonary parenchymal thromboxane synthesis. *Surgery* 100(5):836-840, November 1986.
- LINDNER, E. Untersuchungen/ber das Verhalten des N-(3'-phenyl-propyl-(2'))-1,1-diphenyl-propyl-(3)-amins (Segontin (<sup>1</sup>)) gegen/ber der Wirkungen des Noradrenalins. *Archives Internationales de Pharmacodynamie et de Therapie* 146:475-484, December 1963.
- LOCKHART, L.P. Nicotine poisoning. (Letter.) *British Medical Journal* 1:246-247, February 11, 1933.
- LONGO, L.D. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *American Journal of Obstetrics and Gynecology* 129(1):69-103, September 1, 1977.
- LUNDBERG, J.M., MARTLING, C.-R., SARIA, A., FOLKERS, K., ROSELL, S. Cigarette smoke-induced airway oedema due to activation of capsaicin-sensitive vagal afferents and substance P release. *Neuroscience* 10(4):1361-1368, 1983.
- LUNDBERG, J.M., SARIA, A., MARTLING, C.R. Capsaicin pretreatment abolishes cigarette smoke-induced edema in rat tracheo-bronchial mucosa. *European Journal of Pharmacology* 86(2):317-318, December 24, 1982.
- MALIZIA, E., ANDREUCCI, G., ALFANI, F., SMERIGLIO, M., NICHOLAI, P. Acute intoxication with nicotine alkaloids and cannabinoids in children from ingestion of cigarettes. *Human Toxicology* 2(2):315-316, 1983.
- MANNING, F.A., FEYERABEND, C. Cigarette smoking and fetal breathing movements. *British Journal of Obstetrics and Gynaecology* 83(4):262-270, April 1976.
- MAOUAD, J., FERNANDEZ, F., BARRILLON, A., GERBAUX, A., GAY, J. Diffuse or segmental narrowing (spasm) of the coronary arteries during smoking demonstrated on angiography. *American Journal of Cardiology* 53(2):354-355, January 15, 1984.
- MARITZ, G. Pre- and postnatal carbohydrate metabolism of rat lung tissue: The effect of maternal nicotine exposure. *Archives of Toxicology* 59(2):89-93, July 1986.
- MARKS, M.H., BURCH, J.B., COLLINS, A.C. Genetics of nicotine response in four inbred strains of mice. *Journal of Pharmacology and Experimental Therapeutics* 226(1):291-302, 1983.
- MARTIN, J.C., BECKER, R.F. The effects of maternal nicotine absorption or hypoxic episodes upon appetitive behavior of rat offspring. *Developmental Psychobiology* 4(2):133-147, 1971.
- MARTIN, J.C., MARTIN, D.D., RADOW, B., DAY, H.E. Life span and pathology in offspring following nicotine and methamphetamine exposure. *Experimental Aging Research* 5(4):509-522, August 1979.
- MARTIN, J.L., WILSON, J.R., FERRARO, N., LASKEY, W.K., KLEAVELAND, J.P., HIRSHFELD, J.W. Jr. Acute coronary vasoconstrictive effects of cigarette smoking in coronary heart disease. *American Journal of Cardiology* 54(1):56-60, July 1, 1984.
- MASON, G.R., USZLER, J.M., EFFROS, R.M., REID, E. Rapidly reversible alterations of pulmonary epithelial permeability induced by smoking. *Chest* 83(1):6-11, January 1983.

- MAU, G., NETTER, P. Die auswirkungen des viaterlichen zigaretten kongums aug die perintale sterblichkeit und lie missbildungshaufigkeit. [The effects of paternal cigarette smoking on perinatal mortality and on incidence of malformations.] *Deutsche Medizinische Wochenschrift* 99:1113-1118, 1974.
- McNALLY, W.D. A report of seven cases of nicotine poisoning. *Journal of Laboratory and Clinical Medicine* 8:83-85, 1923.
- McPHAUL, M., PUNZI, H.A., SANDY, A., BORGANELLI, M., RUDE, R., KAPLAN, N.M. Snuff-induced hypertension in pheochromocytoma. *Journal of the American Medical Association* 252(23/30):2860-2862, 1984.
- MEHTA, J., MEHTA, P. Role of blood platelets and prostaglandins in coronary artery disease. *American Journal of Cardiology* 48:366-373, August 1981.
- MENSCH, A.R., HOLDEN, M. Nicotine overdose after a single piece of nicotine gum. (Letter.) *Chest* 86(5):801-802, November 1984.
- MEYER, M.B., TONASCIA, J.A. Maternal smoking, pregnancy complications, and perinatal mortality. *American Journal of Obstetrics and Gynecology* 128(5):494-502, July 1, 1977.
- MEYERS, M.G., BENOWITZ, N.L., DUBBIN, J.D., HAYNES, R.B., SOLE, M.J. Cardiovascular effects of smoking in patients with ischemic heart disease. *Chest* 93(1):14-19, 1988.
- MINER, L.L., MARKS, M.H., COLLINS, A.C. Classical genetic analysis of nicotine-induced seizures and nicotine receptors. *Journal of Pharmacology and Experimental Therapeutics* 231(3):545-554, December 1984.
- MOROSCO, G.J., NIGHTINGALE, T.E., FRASINEL, C., GOERINGER, G.C. Pancreatic elastase activation as a possible indicator of the relative hazard of different cigarettes. *Journal of Toxicology and Environmental Health* 8:89-94, 1981.
- MURTHY, S.N.S., DINOSO, V.P. Jr., CLEARFIELD, H.R., CHEY, W.Y. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretin during smoking. *Gastroenterology* 73(4):758-761, 1977.
- MUSTARD, J.F., MURPHY, E.A. Effect of smoking on blood coagulation and platelet survival in man. *British Medical Journal* 1(5330):846-849, March 2, 1963.
- NAEYE, R.L. Effects of maternal cigarette smoking on the fetus and placenta. *British Journal of Obstetrics and Gynaecology* 85(10):732-737, October 1978.
- NAEYE, R.L., PETERS, E.C. Mental development of children whose mothers smoked during pregnancy. *Obstetrics and Gynecology* 64(5):601-607, November 1984.
- NAKAMURA, M., HAGA, T., MIYANO, M., SASAKI, H., TAKISHIMA, T. Dose-response curves of central and peripheral airways to nicotine injections in dogs. *Journal of Applied Physiology* 61(5):1677-1685, 1986.
- NAKAMURA, M., HAGA, T., SASAKI, H., TAKISHIMA, T. Acute effects of cigarette smoke inhalation on peripheral airways in dogs. *Journal of Applied Physiology* 58(1):27-33, 1985.
- NICOD, P., REHR, R., WINNIFORD, M.D., CAMPBELL, W.B., FIRTH, B.G., HILLIS, L.D. Acute systemic and coronary hemodynamic and serologic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease. *Journal of the American College of Cardiology* 4(5):964-971, November 1984.
- NIEBURG, P., MARKS, J.S., McLAREN, N.M., REMINGTON, P.L. The fetal tobacco syndrome. *Journal of the American Medical Association* 253(20):2998-2999, May 24-31, 1985.
- NISHIMURA, H., NAKAI, K. Developmental anomalies in offspring of pregnant mice treated with nicotine. *Science* 127:877-878, 1958.
- PACKHAM, M.S., MUSTARD, J.F. The role of platelets in the development and complications of atherosclerosis. *Seminars in Hematology* 23(1):8-26, January 1986.

- PALLADINO, G., BRUNNEMANN, K.D., ADAMS, J.D., HALEY, N.J., HOFFMANN, D. Snuff-dipping in college students: A clinical profile. *Military Medicine* 151:342-346, June 1986.
- PETERS, M.A., NGAN, L.L.E. The effects of totigestational exposure to nicotine on pre- and postnatal development in the rat. *Archives Internationales et de Pharmacodynamie* 257(1):155-167, May 1982.
- PETERS, R.W., BENOWITZ, N.L., VALENTI, S., MODIN, G., FISHER, M.L. Electrophysiologic effects of cigarette smoking in patients with and without chronic beta-blocker therapy. *American Journal of Cardiology* 60:1078-1082, 1987.
- PETITTI, D.B., KLATSKY, A.L. Malignant hypertension in women aged 15 to 44 years and its relation to cigarette smoking and oral contraceptives. *American Journal of Cardiology* 52(3):297-298, August 1983.
- PHILIPP, K., PATEISKY, N., ENDLER, M. Effects of smoking on uteroplacental blood flow. *Gynecologic and Obstetric Investigation* 17(4):179-182, April 1984.
- QUICK, C.R.G., COTTON, L.T. The measured effect of stopping smoking on intermittent claudication. *British Journal of Surgery* 69(Supplement): S24-S26, 1982.
- QUIMBY, G.F., BONNICE, C.A., BURSTEIN, S.H., EASTWOOD, G.L. Active smoking depresses prostaglandin synthesis in human gastric mucosa. *Annals of Internal Medicine* 104(5):616-619, May 1986.
- RATTAN, S., GOYAL, R.K. Effect of nicotine on the lower esophageal sphincter. Studies on the mechanism of action. *Gastroenterology* 69(1):154-159, July 1975.
- REES, P.J., CHOWIENCZYK, P.J., CLARK, T.J.H. Immediate response to cigarette smoke. *Thorax* 37(6):417-422, June 1982.
- REES, T.D., LIVERETT, D.M., GUY, C.L. The effect of cigarette smoking on skin-flap survival in the face lift patient. *Plastic Reconstructive Surgery* 73(8):911-914, June 1984.
- RENAUD, S., BLACHE, D., DUMONT, E., THEVENON, C., WISSENDANGER, T. Platelet function after cigarette smoking in relation to nicotine and carbon monoxide. *Clinical Pharmacology and Therapeutics* 36(3):389-395, September 1984.
- RESNICK, R., BRINK, G.W., WILKES, M. Catecholamine-mediated reduction in uterine blood flow after nicotine infusion in the pregnant ewe. *Journal of Clinical Investigation* 63(6):1133-1136, June 1979.
- RIEBE, M., WESTPHAL, K. Studies of the induction of sister-chromatid exchanges in Chinese hamster ovary cells by various tobacco alkaloids. *Mutation Research* 124(3/4):281-286, December 1983.
- RIEBE, M., WESTPHAL, K., FORTNAGEL, P. Mutagenicity testing in bacterial test systems, of some constituents of tobacco. *Mutation Research* 101(1):39-43, March 1982.
- RIGOTTI, N.A., EAGLE, K.A. Atrial fibrillation while chewing nicotine gum. (Letter.) *Journal of the American Medical Association* 255(8):1018, February 28, 1986.
- ROGERS, D.F., WILLIAMS, D.A., JEFFERY, P.K. Nicotine does not cause "bronchitis" in the rat. *Clinical Science* 70(5):427-433, May 1986.
- SAXENA, K., SCHEMAN, A. Suicide plan by nicotine poisoning: A review of nicotine toxicity. *Veterinary and Human Toxicology* 27(6):495-497, December 1985.
- SCHMAHL, D., OSSWALD, H. Fehlen einer carcinogenen Wirkung von cotinin bei Ratten. [The absence of a carcinogenic action of cotinine on rats.] *Zeitschrift f/r Krebsforschung* 71:198, 1968.
- SHEPHERD, R.J., COLLINS, R., SILVERMAN, F. Responses of exercising subjects to acute "passive" cigarette smoke exposure. *Environmental Research* 19:279-291, 1979.
- SHIONO, P.H., KLEBANOFF, M.A., BERENDES, H.W. Congenital malformations and maternal smoking during pregnancy. *Teratology* 34(1):65-71, August 1986.

- SIESS, W., LORENZ, R., ROTH, P., WEBER, P.C. Plasma catecholamines, platelet aggregation and associated thromboxane formation after physical exercise, smoking or norepinephrine infusion. *Circulation* 66(1):44-48, July 1982.
- SOLOMON, T.E., SOLOMON, N., SHANBOUR, L.L., JACOBSON, E.D. Direct and indirect effects of nicotine on rabbit pancreatic secretion. *Gastroenterology* 67(2):276-283, August 1974.
- SONNENFELD, T., WENNMALM, A. Inhibition by nicotine of the formation of prostacyclin-like activity in rabbit and human vascular tissue. *British Journal of Pharmacology* 71:609-613, 1980.
- SRIDHARAN, M.R., FLOWERS, N.C., HAND, R.C., HAND, J.W., HORAN, L.G. Effect of various regimens of chronic and acute nicotine exposure on myocardial infarct size in the dog. *American Journal of Cardiology* 55(1):1407-1411, May 1, 1985.
- STANCIU, C., BENNETT, J.R. Smoking and gastroesophageal reflux. *British Medical Journal* 3(5830):793-795, September 30, 1972.
- STEWART, P.M., CATTERALL, J.R. Chronic nicotine ingestion and atrial fibrillation. *British Heart Journal* 54(2):222-223, August 1985.
- STONE, P.J., CALORE, J.D., MCGOWAN, S.E., BERNARDO, J., SNIDER, G.L., FRANZBLAU, C. Functional  $\alpha_1$ -protease inhibitor in the lower respiratory tract of cigarette smokers is not decreased. *Science* 221:1187-1189, 1983.
- SUZUKI, K., HORIGUCHI, T., COMAS-URRUTIA, A.C., MUELLER-HEUBACH, E., MORISHIMA, H.O., ADAMSONS, K. Placental transfer and distribution of nicotine in the pregnant rhesus monkey. *American Journal of Obstetrics and Gynecology* 119(2):253-262, May 15, 1974.
- SZUTS, T., OLSSON, S., LINDQUIST, N.G., ULLBERG, S., PICOTTI, A., ENZELL, C. Long term fate of 14 C-nicotine in the mouse: Retention in the bronchi, melanin-containing tissues and urinary bladder wall. *Toxicology* 10(3):207-220, July 1978.
- THOMPSON, J.H., GEORGE, R. Chronic effects of nicotine on gastric secretion in rats with hypothalamic lesions. *American Journal of Digestive Diseases* 17(6):513-518, June 1972.
- THYBERG, J. Effects of nicotine on phenotypic modulation and initiation of DNA synthesis in cultured arterial smooth muscle cells. *Virchows Archiv* 52(1):25-32, 1986.
- TOTH, B. Effects of long term administration of nicotine hydrochloride and nicotinic acid in mice. *AntiCancer Research* 2(1/2):71-73, January-April 1982.
- TOTTI, N., McCUSKER, K.T., CAMPBELL, E.J., GRIFFIN, G.L., SENIOR, R.M. Nicotine is chemotactic for neutrophils and enhances neutrophil responsiveness to chemotactic peptides. *Science* 223(4632):169-171, January 13, 1984.
- TRUHAUT, R., DE CLERCQ, M., LOISILLIER, F. Sur les toxicités, aiguë et chronique de la cotinine, et sur son effet cancérigène chez le rat. *Pathologie-Biologie* 12:39-42, January 1964.
- TSUDA, M., NIITSUMA, J., SATO, S., HIRAYAMA, T., KAKIZOE, T., SUGIMURA, T. Increase in the levels of N-nitrosoproline, N-nitrosothiopropine, and N-nitroso-2-methylthiopropine in human urine by cigarette smoking. *Cancer Letters* 30(2):117-124, 1986.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking for Women. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1980.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, DHHS Publication No. (PHS) 82-50179, 1982.

- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health. DHHS Publication No. (PHS) 84-50204, 1983.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Chronic Obstructive Lung Disease. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health. DHHS Publication No. (PHS) 84-50205, 1984.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Cancer and Chronic Lung Disease in the Workplace. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health. DHHS Publication No. (PHS) 85-50207, 1985.
- U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Office on Smoking and Health. DHHS Publication No. (CDC) 87-8398, 1986.
- VALENZUELA, J.E., DEFILIPPI, C., CSENDES, A. Manometric studies on the human pyloric sphincter. Effect of cigarette smoking, metoclopramide, and atropine. *Gastroenterology* 70(4):481-483, April 1976.
- WADDELL, W.J., MARLOWE, C. Localization of nicotine-<sup>14</sup>C, cotinine-<sup>14</sup>C, and nicotine-1'-N-oxide-<sup>14</sup>C in tissues of the mouse. *Drug Metabolism and Disposition* 4(6):530-539, November-December 1976.
- WALD, N.J., IDLE, M., BOREHAM, J., BAILEY, A., VAN VUNAKIS, H. Serum cotinine levels in pipe smokers: Evidence against nicotine as cause of coronary heart disease. *Lancet* 2(8250):775-777, October 10, 1981.
- WANG, N., CHEN, M., SCHRAUFNAGEL, D.E., YAO, Y. The cumulative scanning electron microscopic changes in baby mouse lungs following prenatal and postnatal exposures to nicotine. *Journal of Pathology* 144(2):89-100, October 1984.
- WELLS, D.G., RUSTICK, J.M. Hypertension from smokeless tobacco. (Letter.) *Anesthesiology* 65:339, 1986.
- WEIZENECKER, R., DEAL, W.B. Tobacco cropper's sickness. *Journal of the Florida Medical Association* 57(12):13-14, December 1970.
- WERNER, B. Interviews with parents of 595 children with poisoning accidents. *International Conference of Poison Control*, June 4, 1969.
- WINNIFORD, M.D., WHEELAN, K.R., KREMERS, M.S., UGOLINI, V., VAN DEN BERG, E. Jr., NIGGEMANN, E.H., JANSEN, D.E., HILLIS, L.D. Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: Evidence for adrenergically mediated alterations in coronary artery tone. *Circulation* 73(4):662-667, April 1986.
- WIRTH, W., GOSSWALD, R. Pharmacologische Untersuchungen in der Reihe der Diphenylcarbamidsaure-thioester: II Mitteilung. *Arch. Int. Pharmacodyn.* 155:393-417, 1965. (Cited in Larson, P.S., Silvette, H. *Tobacco: Experimental and Clinical Studies, Supplement II.* Baltimore, Maryland: Williams and Wilkins Co., 1971, p. 198.)
- YAMATAKE, Y., SASAGAWA, S., YANAURA, S. Drug responses of canine trachea, bronchus and bronchiole. *Chemical and Pharmaceutical Bulletin* 26:318-320, January 1978.
- YOSHINAGA, K., RICE, C., KRENN, J., PILOT, R.L. Effects of nicotine on early pregnancy in the rat. *Biology of Reproduction* 20(2):294-303, March 1979.