

TABLE 6.—Relative risk of congenital malformation for infants of cigarette smokers and nonsmokers, comparing available studies with regard to study design, study population, sample size, number of infants with malformations, and definition of malformation

Author, reference	Study design	Study population	Sample size	Infants with malformations	Relative risk SM/NS	Definition of malformations
Lowe (16)	Retrospective	Stillborn plus 24-hour deaths.	2,042	23	1.36	Major.
Comstock, et al. (17)	do	Neonatal deaths	236	37	.31	Major, cause of death.
Yerushalmy (112)	Prospective	Infants less than 2,500 g.	695	59	.67	Major.
Ontario Department of Health (67)	Retrospective	Stillborn plus 1st-week deaths plus surviving infants.	51,490	1,744	.97	
Butler and Alberman (14)	do	Stillborn plus neonatal deaths.	7,123	1,382	1.19	Major, cause of death.
Kullander and Eklen (4)	Prospective	(a) Stillborn plus neonatal deaths plus remainder of deaths to age 1.	137	43	1.25	Major and minor malformations.
		(b) Surviving infants to age 1.	4,903	700	1.06	
Fedrick, et al. (24)	Retrospective	(a) ¹ Stillborn plus neonatal deaths ¹ and deaths to age 7, ² survivors ² to age 7.	17,418	86	1.55	(1).
		(b) Neonatal deaths ¹ (3-month study).	7,822	204	1.07	(2).

¹ Autopsy-proven congenital cardiac malformation.

² Clinically determined congenital heart disease.

Congenital Malformation Summary

Given the considerable variation in study design, study population, sample size, number of affected infants, definition of malformation, and results, no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformation at the present time.

Lactation

Introduction

The following section is a review of available evidence which bears upon any interaction between cigarette smoking and lactation. Emphasis is placed upon the relationship of cigarette smoking to the quantity of milk produced, to the presence of constituents of cigarette smoke within the milk, and to effects upon the nursing infant mediated through changes in either the quantity of milk available or the substances within the milk.

Epidemiological Studies

Underwood, et al. (99), in a study of 2,000 women from various social and economic strata, observed a definite but statistically insignificant trend toward more frequent inadequacy of breast milk production among those smoking mothers who attempted to nurse compared to nonsmokers.

Mills (52), in a study of 520 women, found that among women who indicated either a desire to nurse or no desire to nurse yet continued to nurse beyond 10 days, and who had delivered their first live-born infant, the average period of nursing for mothers who smoked was significantly shorter than for nonsmokers. Moreover, among the 24 mothers who had given up smoking during at least the final 3 months of their pregnancies, the average length of nursing was identical to that of the nonsmokers. There was no significant difference between smokers and nonsmokers with regard to complete inability to nurse their offspring. This study is difficult to interpret because the author did not determine the reason(s) for the discontinuation of nursing among the women.

Experimental Studies

STUDIES IN ANIMALS

Nicotine

Influence on the Lactation Process

Blake and Sawyer (11) studied the influence of subcutaneously injected nicotine (4 mg. total over a 5-minute period) upon lactation in the rat. They found that nicotine inhibited the suckling-induced

rise in prolactin. No effect of injected nicotine was demonstrated for oxytocin secretion since milk release was not blocked.

Wilson (110) examined the effects of nicotine supplied through drinking water (0.5, 1.0, and 2.0 mg. daily) on the weight gain of nursing rats. Apparently, the nicotine had been available throughout gestation as well, because the author commented on a reduction in litter size among the experimental groups, more or less proportionate to the dose of nicotine; hence, a prenatal effect could not have been distinguished from a postnatal one. Average birth weight was similar for experimental and control groups. No difference in weight gain was seen for any of the groups. The lack of impact on birth weight suggests that dose was lower than that used in other studies.

Presence of Nicotine in the Milk

Hatcher and Crosby (32), using a frog bioassay, reported traces of nicotine in cow's milk 24 hours after the intramuscular injection of 5.0 mg./kg. and 5 hours after the injection of 0.5 mg./kg.

Evidence for an Effect Upon the Nursing Offspring

Hatcher and Crosby (32) found that 0.5 mg./kg. nicotine injected into nursing cats had no apparent harmful effect upon the kittens. Apparently 4.0 mg./kg. suppressed lactation. Kittens fed the milk from the cow which had been injected with 5.0 mg./kg. nicotine were also apparently unaffected.

Nitrosamines

Mohr (53) found that diethylnitrosamine and dibutylnitrosamine, when administered to lactating hamsters, were associated with the development of typical tracheal papillary tumors in the young, suggesting passage of these compounds in the milk. Although diethylnitrosamine and dibutylnitrosamine have not been identified in cigarette smoke, many N-nitrosamines are potent carcinogens, and some of them are present in cigarette smoke (37, 79).

STUDIES IN HUMANS

Nicotine and/or Tobacco Smoke

Influence on the Lactation Process

Emanuel (22) noted no reduction in milk production among 10 wet nurses who were encouraged to smoke seven to 15 cigarettes daily;

some were observed to inhale the smoke. Hatcher and Crosby (32) noted that after a mother smoked seven cigarettes within 2 hours, it was difficult to obtain a specimen of breast milk. Perlman, et al. (71) found that of 55 women smokers with an adequate milk supply at the beginning of his study, 11 (20 percent) of the women had an inadequate supply at the time of discharge from the hospital. No relationship was reported between the number of cigarettes smoked and the likelihood of developing an inadequate milk supply. The authors' impression was that there was no greater proportion with an inadequate milk supply among smokers than among nonsmokers, but no corroborating data were supplied.

Presence of Nicotine in the Milk

Hatcher and Crosby (32) found, using a frog bioassay, that the milk of a woman collected after she had smoked seven cigarettes in 2 hours contained approximately 0.6 mg./liter nicotine. Emanuel (22), using a leech bioassay, studied excretion of nicotine in the milk of wet nurses who were encouraged to smoke for the experiment. After the subjects had smoked six to 15 cigarettes over a 1- to 2-hour period, the author found nicotine in their milk 4 to 5 hours after smoking, with a maximum concentration of 0.03 mg./liter. Bisdom (10) demonstrated nicotine in the milk of a mother who smoked 20 cigarettes a day. Thompson (97) found approximately 0.1 mg./liter of nicotine in the milk of a mother who smoked nine cigarettes a day (plus three pipefuls). Perlman, et al. (71), using a *Daphnia* bioassay, demonstrated nicotine in the milk of all women who smoked in their study. Moreover, they found a direct dose-relationship between concentration of nicotine and the number of cigarettes smoked. No comment is made by the authors on the possible inaccuracy introduced by examining only the residual milk following nursing, but it is well known that the composition of the fore milk and hind milk is different and perhaps the concentration of nicotine also differs.

Evidence for a Clinical Effect Upon the Offspring

Emanuel (22) noted that among the infants in his study, loose stools were observed only in the one whose wet nurse had smoked 20 cigarettes in the previous 4 hours. Bisdom (10) observed a case of "nicotine poisoning" in a 6-week-old infant whose mother smoked 20 cigarettes a day. The symptoms included: restlessness, vomiting, diarrhea, and tachycardia. Nicotine was demonstrated in the milk, and the symptoms abated when smoking was stopped. Greiner (30) also described a case of possible nicotine poisoning in a 3-week-old nursing

whose mother smoked 35 to 40 cigarettes a day. The symptoms included vomiting and loose stools. Following the curtailment of smoking, the symptoms gradually abated over a 3-day period. Perlman, et al. (71) noted no effect of smoking on the weight gain of the infants of the smokers in their study. Furthermore, no untoward symptoms were observed. They therefore doubted an effect of smoking on lactation. They noted that the dose received by the infants was beneath the toxic level as computed from adult experience, and this accorded with their clinical observations. The fact that they admitted to the study only women with an apparently adequate milk supply may have affected their results. The authors suggested that perhaps the lack of effect of smoking upon lactation might represent the development of tolerance to nicotine, as both the mother and the offspring had been exposed throughout the pregnancy.

VITAMIN C

Venulet (105, 106, 107), in a series of studies, demonstrated that the level of vitamin C was reduced in the milk of smoking mothers as compared with nonsmokers. The clinical significance of this observation has not been evaluated.

Lactation Summary

1. The two pertinent epidemiological studies suggest a possible influence of smoking upon the adequacy of milk supply. However, with only limited numbers of women and without control of other potentially significant variables, no conclusions can be drawn.
2. Studies in rats have demonstrated that nicotine can interfere with suckling-induced rise in prolactin. The relevance for humans is uncertain.
3. Evidence exists that nicotine passes into breast milk. No clear evidence for an acute effect upon the nursing infant is available. Potential chronic effects have not been studied.
4. New evidence from experiments with mice suggests that nitrosamines, known carcinogens, pass through the milk to suckling young.

Preeclampsia

Previous epidemiological studies of the relationship between cigarette smoking and preeclampsia were reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) and form the basis of the following statements:

The results of several large prospective and retrospective studies indicate a statistically significant lower incidence of preeclampsia among smoking women (14, 43, 100). The results of one large retrospective study demonstrated a significant inverse relationship between the incidence of preeclampsia and the number of cigarettes smoked (100). When other risk factors, such as parity, social class, maternal weight before the pregnancy, and maternal weight gain during the pregnancy were controlled, smoking women retained a significantly decreased risk of preeclampsia (21). The lower risk of preeclampsia for cigarette smoking women has been demonstrated in Britain and Scotland (14, 21, 46, 83), The United States (100, 118), Venezuela (42), and Sweden (43). If a maternal smoker does develop preeclampsia, however, available data suggest that her infant has a higher mortality risk than does the infant of a nonsmoker with preeclampsia (21, 83).

Summary

1. Available evidence indicates that maternal cigarette smokers have a significantly lower risk of developing preeclampsia as compared to nonsmokers.
2. If a woman who smokes cigarettes during pregnancy does develop preeclampsia, her infant has a higher mortality risk than the infant of a nonsmoker with preeclampsia.

Pregnancy References

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Chapter 6
Peptic Ulcer Disease

Source: 1973 Report, Chapter 5, pages 151 - 164.

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Introduction

Previous epidemiological and experimental studies of the relationship between cigarette smoking and peptic ulcer disease were reviewed in the 1971 and 1972 reports on the health consequences of smoking (17, 18) and form the basis of the following summary:

The results of epidemiological studies indicate that cigarette smoking males have an increased prevalence of peptic ulcer disease and a greater mortality from peptic ulcer as compared to nonsmoking males. Among males, the association between cigarette smoking and peptic ulcer disease is stronger for gastric than for duodenal ulcer, but significant for both. For males, cigarette smoking appears to reduce the effectiveness of standard peptic ulcer treatment and to slow the rate of peptic ulcer healing. The relationship between cigarette smoking and the prevalence of and mortality from peptic ulcer disease is less clear for females than for males.

Experimental studies of the effect of cigarette smoking in man, and of the effect of injection and infusion of nicotine in animals, on gastric secretion and motility have produced conflicting results. In dogs, an infusion of nicotine has been found to inhibit pancreatic and hepatic bicarbonate secretion, thus demonstrating a possible link between cigarette smoking and duodenal ulcer.

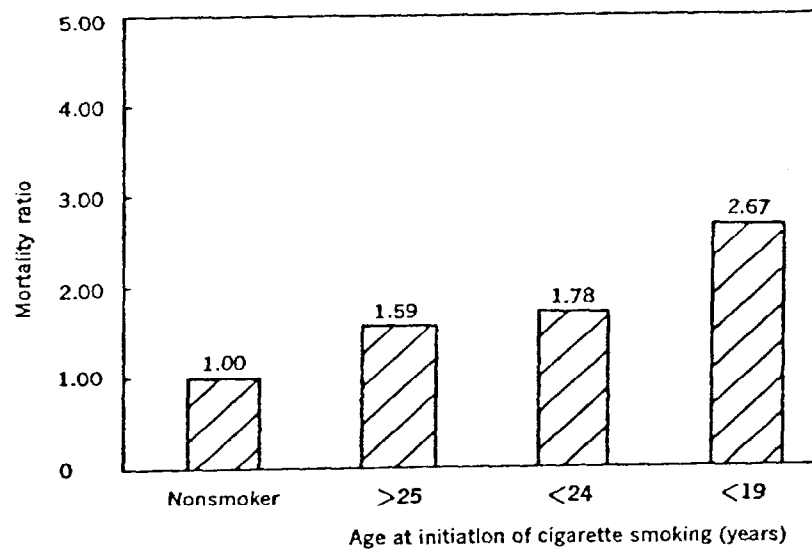
Recently, additional epidemiological, clinical, autopsy, and experimental studies have confirmed the association between cigarette smoking and gastric ulcer mortality and have clarified a mechanism through which cigarette smoking might be linked to duodenal ulcer.

Epidemiological and Clinical Studies

Previous studies of the relationship between peptic ulcer disease and cigarette smoking have been conducted in predominantly white, Western populations. A large prospective epidemiological study is currently being conducted in Japan. From this study, Hirayama (6) reported 5-year followup data on 265,118 men and women, aged 40 years and older, representing 91 to 99 percent of the total population in the area of the 29 health districts in which the study was conducted. Both male

and female cigarette smokers experienced higher death rates from gastric ulcer as compared with nonsmokers. The mortality ratio for cigarette smokers was 1.81 for males ($P < 0.001$) and 2.15 for females ($P < 0.05$). The mortality ratio for smokers (males and females combined) was dose-dependent as measured by age at initiation of smoking (fig. 1). The results of this study, in the context of the genetic and cultural differences between Japanese and Western populations, provide a significant confirmation of the association between cigarette smoking and gastric ulcer mortality.

Figure 1.—Gastric ulcer mortality ratios of Japanese (men and women combined) by age at initiation of cigarette smoking (1966–1970).



SOURCE: Hirayama, T. (6).

Alp, et al. (1) conducted a retrospective survey of 638 patients, admitted to two Australian teaching hospitals between 1954 and 1963, with chronic gastric ulcer confirmed by roentgenographic, endoscopic, or surgical examination. The findings in the patients were compared with information available about the South Australian population obtained at census in 1954 and 1961, and with a control group of 233 subjects matched for age and sex with the ulcer patients. Cigarette use, a family history of peptic ulcer, domestic stress, and aspirin and alcohol intake occurred significantly more frequently among ulcer patients. Alp, et al. (2) found that after surgical treatment, recurrence of the ulcer was significantly more likely to recur among those patients who continued to smoke, drink, and use aspirin ($P < 0.001$).

Fingerland, et al. (5) compared the autopsy findings from 765 males with their smoking history. The autopsies were performed without selection during 1965 and 1966 at the University of Hradec Králové, Czechoslovakia. Peptic ulcer was significantly more frequent among male ex-smokers and male lifelong smokers than among male non-smokers ($P < 0.02$). Among males, a dose-response relationship was found between estimated total cigarette consumption and the presence of peptic ulcer at autopsy.

Cooper and Tolins (4) reported results from a retrospective study of the relationship between cigarette smoking and postoperative complications among 2,988 males, admitted to 19 Veterans Administration hospitals, for the surgical treatment of duodenal ulcer. Smoking history was obtained for 1,441 of the men, and of these 273 were non-smokers, 1,018 smoked cigarettes only, and 93 smoked cigarettes plus a pipe and/or cigars. The authors found no evidence of an association between either the number of cigarettes smoked per day, or the number of years of cigarette smoking, and postoperative complications, operative mortality, or length of hospital stay. They emphasized that their results must be viewed with considerable caution and listed several potential sources of bias. In addition, they noted, " * * * that these results apply only to the immediate postoperative findings and do not apply to the long-range effects of smoking upon the patient after surgery for duodenal ulcer disease."

Experimental Studies

Gastric Secretion

STUDIES IN HUMANS

Morales, et al. (10, 11) studied the effect of cigarette smoking on gastric secretion in a group of 312 patients. The patients included 138

with duodenal ulcer, 93 with gastric ulcer, and 81 with other gastrointestinal disorders, who served as controls. Cigarette smoking was significantly more frequent among the patients with peptic ulcer than among the controls.

The chronic effect of smoking on gastric secretion was quite variable. Male smokers among the controls and in the group with duodenal ulcers had a significantly increased baseline acid output as compared with nonsmokers in the same groups ($P < 0.05$). After a subcutaneous injection of histamine, only the group of male smokers with gastric ulcers had a significant increase in acid output over the values obtained for nonsmokers in the same group ($P < 0.05$). Among the smokers in the control group, the relationship between gastric acid output and the number of cigarettes smoked daily was dose dependent. No such relationship was obtained for either of the two groups with peptic ulcers.

In these experiments, the acute effect of smoking on gastric secretion was slight. In one set of experiments, a group of eight smokers served as its own control. The smoking of two cigarettes prior to collection of gastric juice had no significant effect on acid output as compared to baseline values. After smoking two cigarettes and also receiving a subcutaneous injection of histamine, the patients experienced no significant change in gastric acid output as compared to baseline values; 21 male patients, including members from the groups with ulcers and controls, smoked one cigarette 1 hour after an intravenous infusion of histamine. A transient depression of gastric acid output was noted as compared with the values obtained from nine patients who did not smoke.

STUDIES IN ANIMALS

Konturek, et al. (8) studied the effect of intravenous infusion of nicotine on the formation of acute, experimental duodenal ulcers in cats. The authors infused nicotine intravenously in doses comparable to the smoking of four, eight, and 16 cigarettes per hour into cats in whom near maximal gastric acid output had been stimulated with intravenous pentagastrin. The investigators found that nicotine in the two lower doses had no effect upon the gastric acid output stimulated by pentagastrin, but that the highest dose produced a significant decrease in response, due to a fall in both volume and acid concentration. Nicotine alone failed to alter a negligible basal gastric secretion. In control animals (pentagastrin alone), duodenal ulcers were found in eight of 10 animals. Nicotine at the two lower doses, in combination with pentagastrin, produced ulcers in all 26 animals. At the intermediate dose of nicotine, the mean ulcer area was twice that found in

the control group. At the highest dose of nicotine, peptic ulcers appeared in only two of six animals and the area of ulcer was reduced compared to controls.

Shaikh, et al. (14) studied the acute and chronic effects of subcutaneously injected nicotine on gastric secretion in rats. Under basal conditions, the volume of gastric secretion was initially depressed, then stimulated, and depressed again as the dose of nicotine was increased. Acid output was decreased over the entire range of nicotine dosage. Pepsin output reflected a similar triphasic response to increasing nicotine doses as did gastric secretory volume. In the absence of nicotine, pentagastrin stimulated gastric volume, acid, and pepsin output. The injection of nicotine, in increasing doses, administered simultaneously with pentagastrin, resulted in a gradual decrease in response for all parameters. Volume of gastric juice, acid output, and pepsin output were all increased significantly by chronic exposure to nicotine alone. Based on an average smoking dose of nicotine, the dose of nicotine employed in the chronic experiments corresponded to the smoking of three to five cigarettes per day.

Thompson, et al. (16) extended the study of rats described above by studying the effects of chronic nicotine injections in vagotomized rats and rats with discrete lesions in the hypothalamus. In sham-operated animals, chronic nicotine injections significantly increased baseline volume of gastric juice, acid output, and pepsin output. Following vagotomy, the nicotine response was completely suppressed. Caudal hypothalamic lesions did not influence the response to nicotine in the presence of intact vagus nerves. Anterior hypothalamic lesions, ranging from the anterior hypothalamic area to the ventromedial hypothalamus, blocked the nicotine-induced gastric secretory stimulation in the presence of intact vagi. The authors concluded that chronic nicotine-induced gastric secretory stimulation is mediated via anterior hypothalamic activation and intact vagus nerves. The importance of local effects remained uncertain.

Pancreatic Secretion

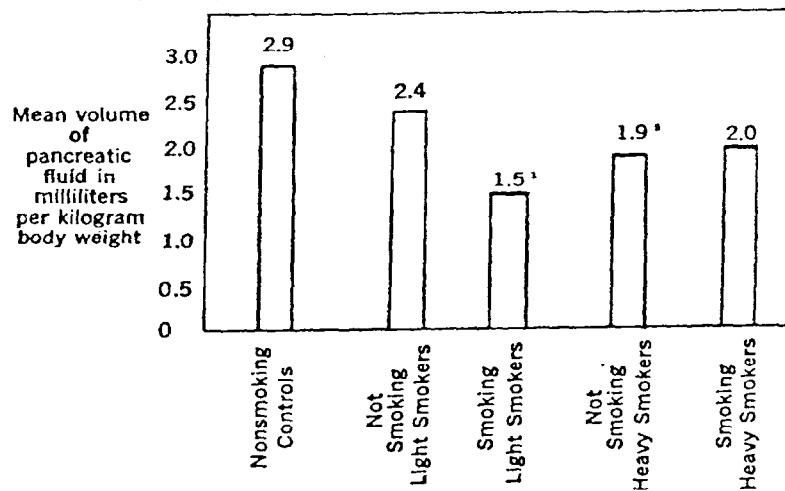
STUDIES IN HUMANS

Bynum, et al. (3) studied the effect of cigarette smoking upon pancreatic secretion in 23 healthy young males and females. Five control male nonsmokers were compared with seven male and two female light smokers (less than one pack of cigarettes per day for less than 3 years) and eight male and one female heavy smokers (more than one pack of

cigarettes per day for more than 3 years). Pancreatic secretion was measured by the double secretin test, using Boots secretin. The experiment was divided into two parts for the smokers: A basal collection period and an experimental period during which the subjects smoked seven nonfiltered cigarettes at the rate of four per hour. Light smokers had basal values for pancreatic secretory volume and bicarbonate output in response to secretin which were not significantly different from controls. After the subjects had smoked, significant depression of both pancreatic volume and bicarbonate output was noted ($P < .001$). Heavy smokers had basal values that were significantly less than in the control subjects ($P < 0.01$). Smoking, however, did not further depress the response to secretin (figs. 2 and 3).

Solomon and Jacobsen (15) reviewed some possible mechanisms whereby the increased prevalence and mortality from duodenal ulcer among cigarette smokers might be produced. They concluded that evidence from studies in animals, coupled with the findings of Bynum, et al. (3), supported the hypothesis that the mechanism active in humans involves impaired neutralization of acid secondary to the inhibition of pancreatic bicarbonate secretion.

Figure 2.—Effect of cigarette smoking on volume of secretin-stimulated pancreatic secretion in humans.

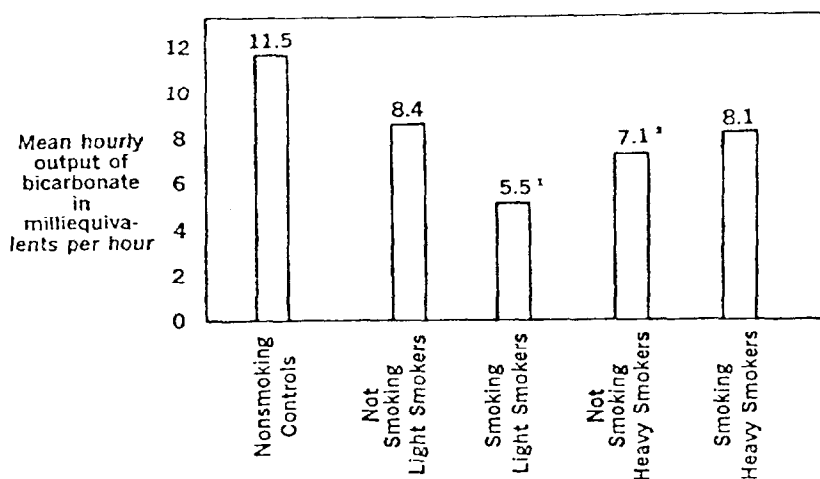


[†] Significantly different from nonsmoking test within group of light smokers ($P < 0.001$).

^{*} Significantly different from nonsmoking controls ($P < 0.01$).

SOURCE: Bynum, et al. (3).

Figure 3.—Effect of cigarette smoking on secretin-stimulated pancreatic bicarbonate output in humans.



¹ Significantly different from nonsmoking test within group of light smokers ($P < 0.001$).

² Significantly different from nonsmoking controls ($P < 0.01$).

SOURCE: Bynum, et al. (3).

STUDIES IN ANIMALS

Konturek, et al. (7) extended his research on the mechanism of nicotine-induced inhibition of pancreatic secretion in the dog, using the design previously employed (9). Infused secretin alone led to a sustained increase in pancreatic bicarbonate output. Intravenous nicotine, at all four doses of infused secretin, produced a significant inhibition of pancreatic volume and bicarbonate output ($P < 0.05$). Infused nicotine appeared to inhibit competitively the effect of secretin on pancreatic secretion of fluid and bicarbonate. Topical (intraduodenal) nicotine failed to affect significantly the response to infused secretin. Stimulation of endogenous secretin by an acid infusion into the duodenum produced the expected pancreatic secretory response. Nicotine either applied to the duodenal mucosa or injected intravenously significantly inhibited the pancreatic secretory response to endogenous secretin. Nicotine had no significant effect on total pancreatic protein output. Nicotine did not alter the cholecystokinin-induced stimulation of pancreatic secretion. The authors concluded that nicotine may inhibit pancreatic secretion of fluid and bicarbonate both