Potentiation, by Nicotine, of Duodenal Ulcers in the Rat (36134)

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Epidemiological studies indicate an association between cigarette smoking and peptic ulcer (1). Unlike the association between smoking and lung cancer, in which the tar content of cigarettes has been directly implicated, the reason for the smoking–ulcer relationship is unknown. Recently, Konturek and co-workers (2) demonstrated that administration of nicotine in dogs blocked secretion of pancreatic juice normally stimulated by secretin. Nicotine also reduced bile secretion. Since pancreatic juice is largely responsible for neutralization, within the duodenum, of acid coming from the stomach, it was postulated that the inhibition of secretin action on pancreatic secretion by nicotine might play an important role in the higher incidence of peptic ulcer among smokers.

We recently developed a model to produce duodenal ulcers in rats (3). It consists of administering by continuous subcutaneous infusion a combination of two gastric secretogogues, such as pentagastrin + carbachol. The ulcers reach maximal incidence within 24 hr, they appear only in the duodenum, and their incidence and severity are dependent on the doses of secretogogues. In the present experiment, we examined the effect of graded doses of nicotine on the development of duodenal ulcers in rats receiving small doses of pentagastrin + carbachol, that is, doses known to induce ulcers in only one-third of the animals.

Methods. Female Upjohn rats (derived from the Sprague-Dawley strain) (weighing 210–220 g) were fasted overnight. On the next morning, they were infused subcutaneously with a combination of pentagastrin (2 μg/kg/min) + carbachol (0.1 μg/kg/min) diluted in saline. During infusion, the animals were placed in tubular cages, which partially restricted their movements so that they could not chew the infusion tubing. Pentagastrin + carbachol were infused from a constant infusion machine at a rate of 13 ml/24 hr. Control animals received the two secretogogues only. Five other groups received, in addition, graded doses of nicotine sulfate, from 5 μg/kg/min up to 40 μg/kg/min, as indicated in Table I. The

TABLE I. Potentiation by Nicotine of Duodenal Ulcers Produced by Pentagastrin + Carbachol.

	Pentagastrin, 2 μg/kg/min + Carbachol, 0.1 μg/kg/min					Nicotine alone	
Group:	I	II	III	IV	V	VI	VII
Dose of nicotine sulfate (μg/kg/min)	0	5	10	20	40	20	40
No. of animals	11	8	10	10	10	12	12
Ulcers							
Gastric (corpus)							
Incidence (%)				20	70		
Duodenal							
Incidence (%)	36	75	80	90	90	0	0
Severity 0–3+	0.3	0.5	0.7	1.4	1.5		
Ulcers/duodenum	0.5	1.3	1.3	1.9	2.2		
Ulcer index[a]	4.4	9.3	10.0	12.3	12.7	0	0
Mortality (%)				10	10		

[a] Ulcer index: Sum of incidence divided by 10, severity in pluses (from a scale of 0 to 3+), and number of ulcers per duodenum.

nicotine was mixed in the same syringe with pentagastrin and carbachol. Two additional groups of animals recieved nicotine alone, at the rate of 20 and 40 μg/kg/min, respectively. After 24 hr of infusion, the animals were killed, and the stomach and duodenum were dissected. They were coded and mixed to prevent identification by the examiner, and inspected for the presence of ulcerations.

Results. As shown in Table I, nicotine markedly increased the incidence of duodenal ulcers, their severity and their number per animal; and the effect was dose dependent for the last two parameters. At 20 and 40 μg/kg/min of nicotine, gastric (corpus) ulcers were also found in some of the animals; whereas, at 5 and 10 μg/kg/min, only the duodenum was ulcerated. Figure 1 shows du-

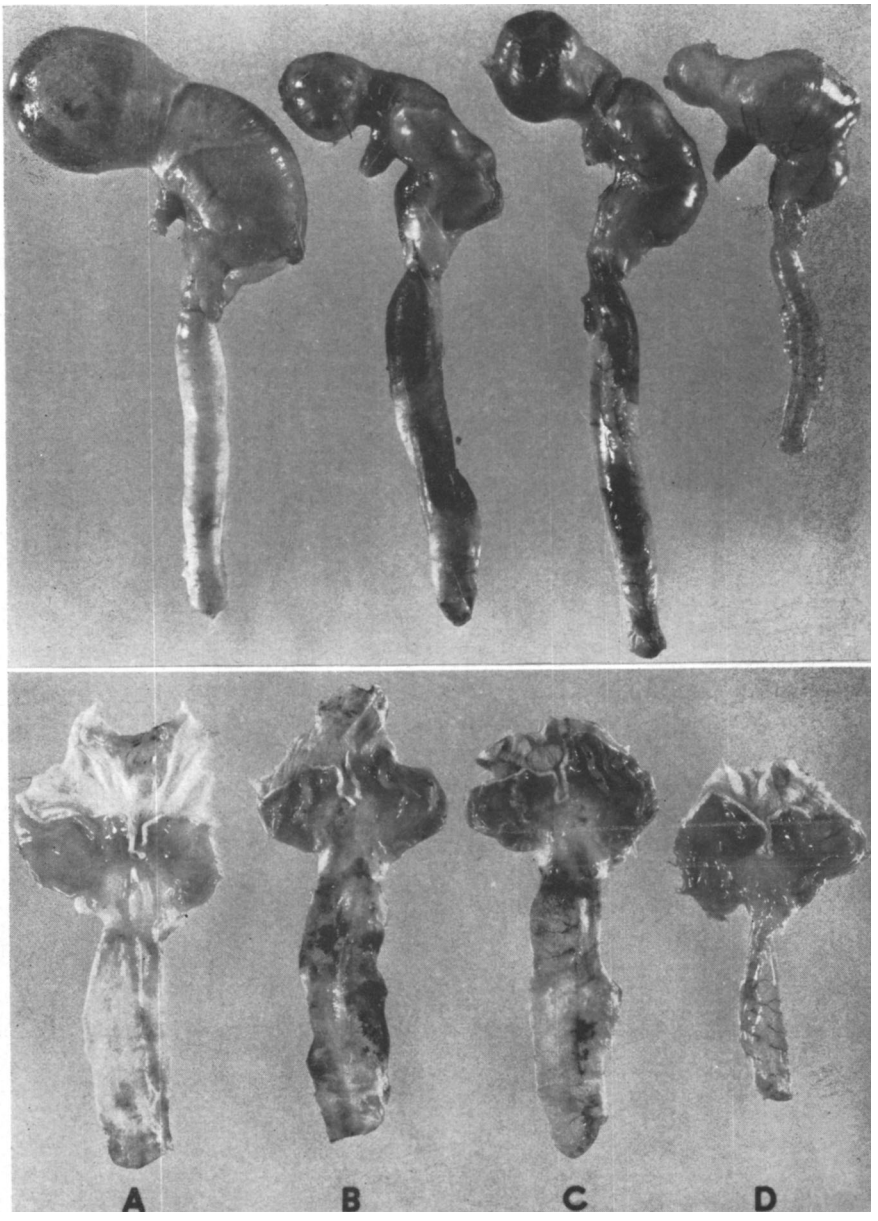

FIG. 1. Duodenal ulcers produced by a combination of pentagastrin, carbachol and nicotine: (top) external view of stomach and duodenum; (bottom) same stomach and duodenum after open-

ing along mesenteric attachment (duodenum) and greater curvature (stomach). (A) Pentagastrin + carbachol: small erosion of duodenum. (B) Pentagastrin + carbachol + nicotine sulfate (20 μg/kg/min): multiple and extensive duodenal ulcers. (C) Pentagastrin + carbachol + nicotine sulfate (40 μg/kg/min): same lesions as in (B). (D) Nicotine sulfate alone (40 μg/kg/min): intact duodenum.

odenal ulcers produced by the combined treatment of nicotine and secretogogues.

Discussion. It is significant that no ulcers were produced by nicotine alone. It appears, therefore, that the effect of nicotine is to sensitize the duodenum to the ulcerogenic effect of pentagastrin + carbachol rather than to act in a synergistic manner. The mechanism by which nicotine exerts a pro-ulcer effect is still unclear. Konturek *et al.* (2) showed that nicotine, given to dogs, inhibited the stimulating effect of secretin on bicarbonate content of pancreatic juice and bile. It is possible that, in our experiments, the high incidence and severity of duodenal ulcers in the nicotine-treated animals was due to reduction of pancreatic juice and bile secretion, via inhibition by nicotine of the action of secretin. Such a reduction of alkaline fluid in the duodenum would allow hyperacid juice, flowing from the duodenum, to remain unneutralized and thus injure the duodenal mucosa. This explanation is conjectural at this time, since similar studies on pancreatic and biliary secretion have not been performed in the rat. Toon, *et al.* (4) demonstrated that cigarette smoke abets the ulcerogenic property of histamine in beeswax in dogs, and attributed this effect to nicotine.

Stimulation of gastric secretion itself by nicotine is not a valid explanation in view of the reports from Thompson and Brückner (4, 5) that, in rats, acute treatment with nicotine (single administration or hourly injections) did not stimulate acid secretion, although an increase in gastric secretion was seen following administration, for 2 weeks, of 100 μg of nicotine three times a day (6). Similarly, Konturek *et al.* (2) found that nicotine did not stimulate gastric secretion in dogs.

It is plausible that the inhibition of secretin action by nicotine favors ulcer formation not only by preventing secretion of pancreatic juice, but also by removing the inhibition of gastric secretion normally exhibited by secretin. Such antigastric secretory effect has previously been demonstrated in rat (7), dog (8), and man (9, 10). The formation of gastric (corpus) ulcers in animals receiving pentagastrin, carbachol, and a high dose (40 μg/kg/min) of nicotine is more difficult to interpret. At that dose, the animals showed some tremor, and the gastric ulcers may have been due to the stress induced by the toxicity of nicotine. In the rat, it is well known that exposure to even short periods of stress can produce gastric (but never duodenal) ulcers.

One cigarette yields 15–30 mg of nicotine, and it is estimated that 90% of the nicotine in inhaled smoke is absorbed through the lungs (11). Although it remains to be seen whether in man the gastrointestinal tract responds to nicotine as in rats, the present results, coupled with those obtained by Konturek *et al.* (2), throw some light on the possible cause for the relatively high incidence of ulcers among smokers.

Summary. Discrete duodenal ulcers were produced in a small percentage of rats by continuous infusion of two gastric secretogogues, pentagastrin + carbachol. When nicotine sulfate was added to the mixture, nearly all rats developed duodenal ulcers, and the latter were up to five times more severe and up to four times more numerous, depending on the dose of nicotine. Nicotine alone was not ulcerogenic. It is suggested that nicotine sensitizes to ulcer formation by reducing secretion of pancreatic juice (by inhibiting the action of secretin). The lack of pancreatic juice, which is alkaline, prevents neutralization of acid flowing from the stomach, and thus permits acid to attack the duodenal mucosa. Nicotine may be responsible for the higher incidence of peptic ulcer among smokers.

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