4 T. Mikawa, T. Toyo-oka, Y. Nonomura and S. Ebashi, J. Biochem. Tokyo *81*, 273 (1977).
5 A. Sobieszek and J.V. Small, J. molec. Biol. *101*, 75 (1976).
6 A. Sobieszek, Eur. J. Biochem. *73*, 477 (1977).
7 N. Nakahata, Experientia *34*, 362 (1978).
8 N. Nakahata, Pflügers Arch. *382*, 133 (1979).
9 S. Imai and K. Takeda, J. Pharmac. exp. Ther. *156*, 557 (1967).
10 W.J. O'sullivan and D.D. Perrin, Biochemistry *3*, 18 (1964).
11 F.J. Julian, J. Physiol., Lond. *218*, 117 (1971).
12 M. Endo, S. Kitazawa, M. Yagi, M. Iino and Y. Kakuta, in: Excitation-contraction coupling in smooth muscle, p. 199. Ed. R. Casteels, T. Godfraind and J.C. Rüegg. North-Holland Publishing Co., Amsterdam 1977.
13 K. Saida and Y. Nonomura, J. gen. Physiol. *72*, 1 (1978).
14 A.R. Gordon, Proc. natl Acad. Sci. USA *75*, 3527 (1978).
15 M. Aizu and Y. Ogawa, Jap. J. Pharmac. *28*, 131p (1978).
16 P. Hellstrand and A. Arner, Acta physiol. scand. *110*, 59 (1980).

The effect of hexamethonium on the secretion induced by sodium deoxycholate in the rat jejunum[1]

L. Karlström, J. Cassuto, M. Jodal and O. Lundgren

Department of Physiology, University of Göteborg, Box 33031, S-400 33 Göteborg, (Sweden), 15 October 1980

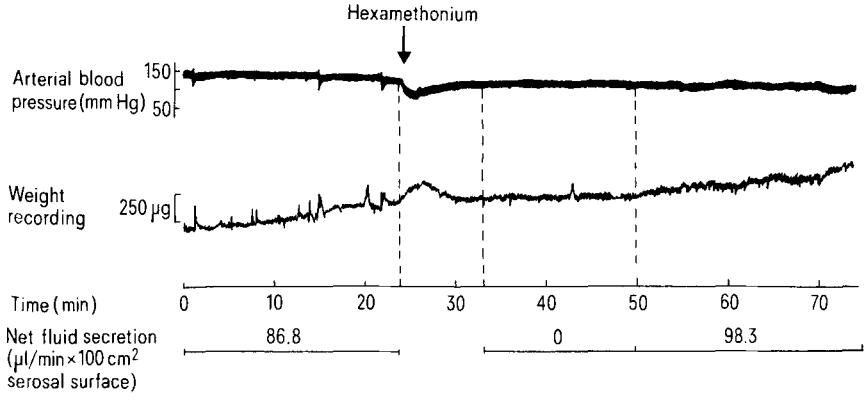
Summary. The i.v. administration of hexamethonium reduces or abolishes net water secretion induced by sodium deoxycholate in the denervated rat jejunum. The findings suggest that a local nervous reflex may be involved in bile salt-induced intestinal secretion.

The mucosa of the gastrointestinal tract is heavily innervated by the 'enteric nervous system'[2], but little is known about its functional importance for the control of intestinal fluid transport. Vasoactive intestinal polypeptide, considered by most authors to be localized only in nervous tissue in the gut[3] and thus probably a transmitter of the enteric nervous system[3], has been found in the stools of cholera patients[4]. Furthermore, Cassuto et al.[5] recently provided experimental evidence for the proposal that cholera toxin induces intestinal secretion in part via intramural nervous reflexes. One of the drugs used by Cassuto and co-workers was hexamethonium, a cholinergic ganglionic blocking agent, which proved to be very efficient in inhibiting choleraic secretion in rats. It was, therefore, considered to be of interest to study if the well-known bile salt-induced intestinal secretion might also be influenced by the administration of hexamethonium.

Methods. Male Sprague-Dawley rats, weighing 250–350 g, were used. Anesthesia was induced with nembutal 50 mg/kg i.p. and maintained by repeated small i.v. injections (5 mg every 2 h). Arterial blood pressure was recorded from the right femoral artery by a pressure transducer (Statham P 23DC). The nerves surrounding the superior mesenteric artery were divided. In all experiments a 10 cm segment of the proximal jejunum with an intact vascular supply was perfused in a recirculating system with a modified Krebs-Henseleit solution containing per l 30 mmoles mannitol and 8 mmoles Na-deoxycholate. The perfusion rate was 0.2 ml/min. Net intestinal transport of fluid was continuously recorded in 4 experiments with the method described by Jodal et al.[7] for the cat, adapted for rats. In the remaining experiments a weight method was used, continuously monitoring weight changes of the intestinal segment. This method made it possible to measure net fluid transport rates in the face of intestinal peristaltic movements[5,8,9]. All recordings were made on a Grass polygraph. Hexamethonium (20 mg/kg) was given i.v. after 30 min of constant intestinal secretion. This hexamethonium dose has in other experiments been shown to abolish the vagal influence on heart rate[9].

Results. During bile salt perfusion, there was a net intestinal secretion in all experiments (n = 8). After giving hexamethonium, the secretion was reduced to about 16% of the initial value (see table). In one experiment the secretion turned into absorption and in 3 other experiments the secretion was totally abolished. The effect lasted for 15–50 min after which secretion gradually returned. A representative experiment is illustrated in the figure.

Discussion. The results of this study indicate a possible nervous reflex involvement in bile acid-induced intestinal secretion by showing that hexamethonium, a cholinergic ganglionic receptor blocker, markedly inhibited the intestinal secretion produced by sodium deoxycholate. The nervous reflex is probably confined to the intestinal wall since the extrinsic nerves of the intestine, surrounding the superior mesenteric artery, had been sectioned in all ex-



The effect of hexamethonium on blood pressure and sodium deoxycholate induced intestinal secretion. Secretion was deduced from the continuous recording of the intestinal weight.

Arterial blood pressure and net fluid secretion in the small intestine of rats before and after giving hexamethonium, 20 $mg \times kg^{-1}$ b.wt i.v. Fluid secretion was induced by perfusing the intestinal lumen with an isotonic electrolyte solution containing 8 mmoles sodium deoxycholate. Mean ± SE, n = 8

	Before hexamethonium	After hexamethonium			
		0–15 min	15–30 min	30–45 min	45–60 min
Arterial blood pressure, mm Hg	105.0 ± 5.0	74.3 ± 4.6	82.1 ± 5.4	85.7 ± 5.4	89.3 ± 5.2
Net fluid secretion, $\mu l \times min^{-1} \times 100\ cm^{-2}$ serosal surface	− 186.8 ± 30.6	− 30.6 ± 16.9*	− 26.0 ± 19.5*	− 39.6 ± 17.8*	− 77.1 ± 33.2*

* Statistically significant from control ($p < 0.05$, Wilcoxon non-parametric test).

periments. Several studies indicate that bile salts induce intestinal secretion by acting directly on the enterocyte via the cell membrane-bound adenylate cyclase system[10]. However, other studies have not confirmed this hypothesis[11], and there may well be several different mechanisms involved in the regulation of intestinal fluid transport.

It has recently been shown that bile salts enhance colonic motility via a nervous reflex[12], implying that bile salts may in some way stimulate enteric nerves. In this context, it is interesting to note that bile has been reported to release motilin in man[13]. Since motilin has been claimed to be located in the enterochromaffin (EC)[14] cells of the gut, one may propose a functional interplay between the bile acids, the EC cells and the enteric nervous system in the regulation of intestinal fluid transport. Such a mechanism has already been proposed for cholera toxin-induced secretion by Cassuto et al.[5]. According to that study cholera toxin triggers the release of 5-HT from the EC cells which in turn activates nervous reflex(es) via the adjacent dendritic nerve endings in the mucosa. The net effect on the intestinal epithelium of this nervous activation is a secretion of fluid into the intestinal lumen. It is proposed that bile salt produces this secretion in part via a similar mechanism.

Net fluid secretion in the colon has been claimed to be caused by the cathartic effects of bile salts on the colonic mucosa in bile salt malabsorption as seen in patients after e.g. ileal resection. Since EC cells and enteric nerves are present throughout the gastro-intestinal tract the nervous mechanism outlined above for the small intestine may also be functioning in the colon. This is supported by preliminary experiments in which hexamethonium was shown to inhibit the bile salt-induced secretion in the colon also.

1 This research was sponsored by grants from the Swedish Medical Research Council (14X-2855), from the Swedish Society for Medical Sciences, from Magnus Bergvalls Stiftelse and from the Medical Faculty, University of Göteborg.

2 J.B. Furness and M. Costa, Neuroscience *5*, 1 (1980).
3 J. Fahrenkrug, Digestion *19*, 149 (1979).
4 S.R. Bloom, D.R. Nalin, S.J. Mitchell and M.G. Bryant, Proc. 1st Int. Symp. Gastrointestinal Hormones. Asilomar, Ca. 1976.
5 J. Cassuto, M. Jodal, R. Tuttle and O. Lundgren, Scand. J. Gastroenterol. *16*, 377 (1981).
6 M. Jodal, D.-A. Hallbäck and O. Lundgren, Acta physiol. scand. *102*, 94 (1978).
7 M. Jodal, D.-A. Hallbäck, J. Svanvik and O. Lundgren, Acta physiol. scand. *95*, 441 (1975).
8 J. Cassuto, J. Fahrenkrug, M. Jodal, R. Tuttle and O. Lundgren, Gut, in press (1981).
9 J. Cassuto, M. Jodal and O. Lundgren, submitted.
10 D. Conley, M. Coyne, A. Chung, G. Bonorris and L. Schoenfield, Gastroenterology *71*, 72 (1976).
11 T.S. Gaginella, S.F. Phillips, R.R. Dozios and V.L.W. Go, Gastroenterology *74*, 11 (1978).
12 S.J. Shiff, R.D. Soloway and W.J. Snape, Gastroenterology *78*, 1258 (1980).
13 W. Domschke, G. Lux, P. Mitznegg, S. Neeb, U. Strunz and S. Domschke, Gastroenterology *78*, 1123 (1980).
14 W.Y. Chey, R. Escoffery, F. Roth, T.M. Chang and H. Yajima, Gastroenterology *78*, 1150 (1980).