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Inhibitory Effect of Urine Extracts on Gastric Secretion.

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It was found by Sandweiss, Saltzstein and Farbman[1, 2] that extracts prepared from the urine of pregnant women as well as from the urine of normal non-pregnant women exerted striking protection against Mann-Williamson ulcers when administered subcutaneously. The association of this type of experimental ulcer with an unneutralized gastric secretion naturally raised the question of what effect these extracts have on normal gastric secretion. These workers[2] had observed that daily subcutaneous injections in dogs of 1 or 5 cc of these extracts of urine (the daily dosage found effective in their Mann-Williamson dogs) had no effect on the acidity of the gastric secretion stimulated by a meal. In the case of pregnancy urine extracts this ineffectiveness of small subcutaneous doses was confirmed by Culmer, Atkinson and Ivy[3] who further found that daily subcutaneous injections of 10 to 20 cc depressed the volume of secretion of dogs with total gastric pouches.

At the request of one of us (D. J. S.) Professor Ivy kindly tested the effect on gastric secretion of *intravenous* administration of extracts of normal female urine. In dogs with entire gastric pouches there was a marked inhibition of gastric secretion stimulated by histamine.[4] Since then, on extending this work to extracts of urine from other sources, Ivy and his co-workers[5] have found a gastric secretory depressant in the urine of the normal human male and of the dog. Necheles[6] recently reported a similar extract differing from the above in that it also inhibited gastric motility.

The present paper is a report on the effect on gastric secretion of

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1 Sandweiss, D. J., Saltzstein, H. C., and Farbman, A., *Am. J. Digest. Dis.*, 1938, **5**, 24.

2 Sandweiss, D. J., Saltzstein, H. C., and Farbman, A., Detroit Physiological Society, March 3, 1938; also *Am. J. Digest. Dis.*, 1939, **6**, 6.

3 Ivy, A. C., personal communication; also Culmer, C. U., Atkinson, A. J., and Ivy, A. C., *Proc. Am. Physiol. Soc.*, 51st meet., 1939, p. 56.

4 Ivy, A. C., personal communication.

5 Gray, J. C., Wieczorowski, E., and Ivy, A. C., *Proc. Am. Physiol. Soc.*, 51st meet., 1939, p. 91.

6 Necheles, H., personal communication.

intravenous administration of urine from normal (non-pregnant) females and from peptic ulcer patients. Such a study was believed to be of interest since it was found[2] that extracts of urine from ulcer patients did not have the protecting action on the Mann-Williamson ulcer that normal urine extracts had.

The procedure of Katzman and Doisy[7] for obtaining the A. P. L. hormone in pregnancy urine (Antuitrin-S) was employed in preparing the extracts used in our study.* Assays were made on 47 vagotomized dogs under nembutal anaesthesia, the animals having been previously fasted for 24 hours. Gastric juice was obtained by fistula from the whole stomach, the pylorus and oesophagus being tied off to exclude contamination by regurgitated intestinal contents and oesophageal mucus. Gastric secretion was stimulated by hourly subcutaneous injections of histamine phosphate (0.1 mg per kilo per hour). Urine extracts were administered by femoral vein in doses of 1 mg per 5 kilo body weight.

Results. 1. The profuse secretion of acid gastric juice which is stimulated by histamine injection (see "control experiments," Fig. 1) was prevented if normal urine extract was administered before the histamine. Although hourly subcutaneous injections of histamine were repeated for as long as 6 hours, there persisted throughout this time a complete inhibition of gastric secretion. 2. When given 2 or 3 hours after the initial hourly injection of histamine, extracts of normal urine exerted a profound inhibition of the gastric secretion. This inhibitory effect commenced within 30 to 45 minutes and lasted for a period of 3 to 4 hours (Fig. 1). 3. Normal urine extracts abolished completely the secretion induced by histamine if they were administered 7 to 9 hours after the initial hourly histamine injection. However, by this time the rate of secretion in the control animals was declining so that it can not be said that a greater depressing effect was exerted when the extract was given on the 7th to 9th hour than when given earlier. 4. Extracts prepared from the urine of duodenal ulcer patients also exerted a marked depressing effect on gastric secretion (Fig. 1). 5. The principle in the normal urine responsible for depressing gastric secretion was only slightly, if at all, inactivated by heating the extract at 99°C for 30 or 60 minutes. However, heating at this temperature for 4 hours inactivated the extract completely (Fig. 1).

Conclusions. From the urine of normal individuals there can be

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[7] Katzman, P. A., and Doisy, E. A., *J. Biol. Chem.*, 1932, **98**, 745.

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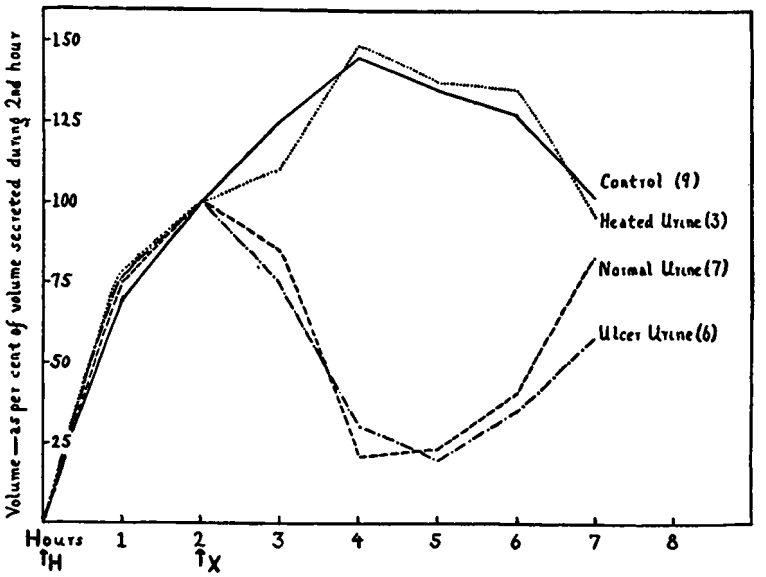

FIG. 1.

Of the 47 experiments, 25 are represented by the above series. The hourly rate of gastric secretion is expressed in terms of per cent of the volume secreted during the second hour. Histamine phosphate (0.1 mg per kilo) was given subcutaneously every hour, commencing at the point H. Urine extracts were given intravenously at the end of the second hour, at the point X. The nature of the experiment and the number of animals used are indicated.

extracted a substance which when given intravenously inhibits gastric secretion stimulated by histamine. This gastric secretory depressant is inactivated by heating for 4 hours at 99°C. When given subcutaneously, the daily amount found effective for protection against the Mann-Williamson ulcer is too small a dosage to reduce gastric secretion.[2] Extracts of urine from ulcer patients do not protect against the experimental ulcer but do reduce gastric secretion. From this and other data it would seem probable that the apparent beneficial effect on Mann-Williamson ulcers previously reported may be due to some factor in the urine extract other than the one which inhibits gastric secretion. We do not as yet know the nature of the substances nor what organ or mechanism of the body is responsible for their elaboration.