ing of an apparently otherwise unaltered steroid compound is a method of inactivation peculiar to progesterone has not been determined.

No explanation can be offered at present for the apparent plateau in bound and total progesterone beginning eight days after implantation of the intrasplenic pellets. Obviously, the rate of absorption may have stabilized or declined, or the rate of removal of bound progesterone from the circulation by excretion or chemical alteration may have increased. Another possibility is that of increasing hepatic inactivation of the progesterone as absorbed by means other than binding.

The apparently linear relation of free and total plasma progesterone to time after the implantation of subcutaneous pellets also raises problems. One of the more interesting of these is the increase in the level of bound progesterone in these animals, possibly suggesting eventual hepatic inactivation of part of the absorbed material by binding. Although it may prove to be of no significance, it is interesting that the maximal level of bound progesterone was almost identical in the two groups of animals.

An interesting fact that emerges is that the minimal physiologically effective plasma level of progesterone with respect to the endometrium appears to be of the order of 1.0 μg per ml of the free fraction. Every animal with this or a higher level exhibited progestational changes in the stromal nuclei. All animals with lower plasma levels showed no endometrial response, irrespective of the level of bound progesterone.

Summary. Pellets of crystalline progesterone implanted into the spleens of ovariectomized mice had no effect upon the endometrium despite the presence of relatively high levels of bound progesterone in the plasma; the highest level of free progesterone in these animals was 0.7 μg per ml. Subcutaneous pellets of progesterone produced characteristic progestational changes in the endometrium when the level of free plasma progesterone exceeded 1.0 μg per ml. Binding appears to be a mechanism of hepatic inactivation of progesterone in the mouse.

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Effect of Dialyzed Enterogastrone Upon Twelve-Hour Nocturnal Gastric Secretion in Man.*

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Previous studies[1] have demonstrated occasional decreases in the 12-hour (nocturnal) and 24-hour gastric secretion in man following the intramuscular injection of 1000 to 3000 mg of an enterogastrone concentrate. This effect was variable in degree and temporary in duration. The administration of 400 to 2000 mg did not alter significantly the secretory response of the human stomach to the single standard dose of histamine or to the repeated injection of small amounts of histamine.[2] Insulin-stimulated secretion likewise was not affected, although the response possibly was modified by doses of 2000 or 3000 mg. Ferayorni, Code, and Morlock[3] similarly noted no change in gastric secretion during a double histamine test in 10 human subjects given 200 mg of enterogastrone intramuscularly. In 14 volunteers, quantities up to 400 mg intramuscularly and 18 g orally

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1 Kirsner, J. B., Levin, E., and Palmer, W. L., *Gastroenterology*, 1948, **10**, 256.

2 Levin, E., Kirsner, J. B., and Palmer, W. L., *Gastroenterology*, 1948, **10**, 274.

3 Ferayorni, R., Code, C. K., and Morlock, C. G., *Gastroenterology*, 1948, **11**, 730.

did not diminish the response to a modified Ewald test meal. Pollard and his associates[4] administered 8 to 16 g of the concentrate by mouth daily to 12 patients with peptic ulcer for as long as 11 months; 16 individuals received intramuscular injections of 200 mg daily for intervals up to 9 months. There were no changes in the volume of fasting gastric secretion, output of hydrochloric acid, concentration of pepsin or gastric motility.

The enterogastrone utilized in the initial experiments, although less crude than earlier products, consisted of a mixture of proteins of varying molecular size; its chemical composition is not known, and its physiologic characteristics are obscure. The most recent preparation of enterogastrone† is described[5] as free of inactive protein by dialysis through a cellophane membrane. Inhibition of gastric secretion in the rat and the dog approximated twice the degree obtained with the standard preparation. Neither this product nor other samples of enterogastrone have manifested anti-secretory activity in the guinea pig. Tests for toxicity are reported as satisfactory at 500 mg/kg and for vasodepressor activity as meeting present requirements.

The present study was undertaken to determine the effect of this concentrate upon the nocturnal gastric secretion of patients with peptic ulcer.

Method of study. The procedure was the same as that described in previous papers.[6-8] Ten male patients, 9 with active duodenal ulcer and one with a benign gastric ulcer, were studied. Constant suction of the gastric content was maintained by a Gomco aspirator. The volume and free acidity of each hourly collection were measured and the output of hydrochloric acid in milligrams calculated from these data. In 8 patients, the stomach was aspirated continuously for 60 hours, beginning at 9:30 P.M. After 48 hours had elapsed the enterogastrone was administered at 9:30 P.M. in single total doses of 200 to 5000 mg. The initial 12 hours (9:30 P.M. to 9:30 A.M.) constituted the control nocturnal period; the 12 hours (9:30 P.M. to 9:30 A.M.) after the injection of the concentrate represented the test period. In one case the control interval extended during the night and morning (11:30 P.M. to 11:30 A.M.); 2000 mg of enterogastrone then were given and the hourly secretion measured for the subsequent 12 hours (11:30 A.M. to 11:30 P.M.). A similar procedure was followed in the tenth patient; the control period was of 10 hours duration (11:30 P.M. to 9:30 A.M.); 5000 mg of enterogastrone then were administered and the gastric aspirations continued for the succeeding 10 hours (9:30 A.M. to 7:30 P.M.).

The patients were not given food or liquid by mouth. Normal electrolyte and fluid balances were maintained by the intravenous administration of 5% glucose in isotonic saline solution. The enterogastrone was injected intramuscularly into the glutei in a single dose. Pain developed locally almost at once, and usually was so intense as to prevent sleep. The body temperature remained normal in 7 cases; a slight elevation to 37.6 or 37.8°C occurred in 3 individuals (A.H., W.W., and C.M.) during the final one or two hours of the test period. No other untoward effects were observed.

Results. The data are recorded in Table I. The 12-hour gastric secretion was not reduced significantly in the four patients receiving 200 to 2000 mg of enterogastrone. The output of acid was decreased in each of the 6 individuals given 5000 mg of the preparation. The inhibition was slight in one and moderate or pronounced in 5. Depression of gastric secretion became apparent immediately in one case and within 2 or 3 hours in the remaining 5 patients. Anacidity for periods of 5 to 9

[4] (a) Pollard, H. M., Block, M., and Bachrach, W. H., *Proc. Central Society Clinical Research*, 1946, **19**, 34. (b) Pollard, H. M., Block, M., Bachrach, W. H., and Mason, J., *Arch. Surg.*, 1948, **56**, 372.

[5] Hailman, H. F., and Visscher, F., personal communication.

† Supplied by Dr. H. F. Hailman, Upjohn Co., Kalamazoo, Mich.

[6] Levin, E., Kirsner, J. B., Palmer, W. L., and Butler, C., *Arch. Surg.*, 1948, **56**, 345.

[7] Kirsner, J. B., Levin, E., and Palmer, W. L., PROC. SOC. EXP. BIOL. AND MED., 1948, **69**, 108.

[8] Levin, E., Kirsner, J. B., and Palmer, W. L., PROC. SOC. EXP. BIOL. AND MED., 1948, **69**, 153.

TABLE I.
Effect of Dialyzed Enterogastrone on 12-Hour Nocturnal Gastric Secretion of 10 Patients with Peptic Ulcer.

	Control				After enterogastrone			
Case	Vol. (cc)	Free HCl (Cl. units)	Total output HCl (mg)	Amt enterogastrone intramusc. (mg)	Vol. (cc)	Free HCl (Cl. units)	Total output HCl (mg)	Comment
♂—27 D.U.	976	79	2815	200	1114	77	3138	No effect
♂—42 D.U.	1033	49	1829	500	1047	38	1449	No significant effect
♂—39 D.U.	923	81	2719	1000	1130	85	3492	No effect
♂—51 D.U.	814	73	2487	2000	1054	70	3088	No effect
♂—57 D.U.	1056	87	3340	5000	1099	56	2646	Slight decr. 2 hr after inj.; reduced acid 2 hr., anacidity 2 hr
♂—34 D.U.	822	74	2218	5000	762	39	1071	Marked decr.; anacidity 3 hr after inj., continued for 7 hr
♂—72 D.U.	1647	48	2974	5000	1151	2	107	Marked decr. apparent immed.; anacidity 11 of 12 hr
♂—54 D.U.	1494	95	4874	5000	725	22	1251	Marked decr. after 3 hr.; anacidity 7 to 12 hr
♂—64 D.U.	1684	101	6220	5000	703	31	1501	Marked decr. after 3 hr.; anacidity 5 hr
♂—43 G.U.	519	12 (10 hr)	260	5000	332	6 (10 hr)	108	Moderate decr.; anacidity after 2 hr

consecutive hours was noted in 5 instances; in one case there was no free acid in 11 of the 12 specimens. However, hydrochloric acid usually reappeared towards the conclusion of the nocturnal period. Free acid had been present continuously during the control periods in the 9 patients with duodenal ulcer. The inhibition of secretion consisted usually of a pronounced decrease in the concentration of acid. However, the volume of gastric content also diminished markedly in 3 patients.

Comment. The present data indicate that the fasting gastric secretion may decrease greatly, albeit temporarily, following the intramuscular administration of 5000 mg of a dialyzed preparation of enterogastrone. This finding is in contrast to a single previous experiment in which gastric secretion was unaffected by the injection of 5000 mg of an apparently less concentrated product. Although the injections produced severe pain immediately, the decrease in acid usually did not become apparent until two or three hours had elapsed. As in preceding studies, the effect consisted chiefly of a lowered concentration of acid; the volume of secretion also diminished significantly in three of the present series. The mechanism of this reduction and its significance remain obscure. It may be noted that the intramuscular administration of a non-specific protein, sterile lactalbumin, did not reduce the nocturnal gastric secretion in 10 patients with peptic ulcer; indeed, an increased output of acid was noted in 6.[9] The inhibition is not attributable to an elevation in body temperature, since the temperature increased in only three patients and then very slightly; the reduction in acid in one of this group was slight. The temporary duration of the inhibition, the tremendous quantities required, the accompanying severe pain, and the uncertainty as to the nature of the material and the mechanisms involved do not warrant further clinical trial of the present dialyzed preparation of enterogastrone. Nevertheless, the data would appear to justify the continued search for a much more effective and safely administered product, whose chemical nature and physiological behavior may be studied more precisely.

Conclusions. 1. The output of hydrochloric acid in the 12-hour nocturnal gastric secretion of 4 patients with peptic ulcer was unchanged following the intramuscular administration of 200 to 2000 mg of a dialyzed preparation of enterogastrone. 2. Gastric secretion was reduced slightly in one and markedly in five of six patients with peptic ulcer, given 5000 mg. The transitory inhibition consisted chiefly of a decrease in the concentration of acid and, to a lesser extent, of the volume of secretion.

[9] Kirsner, J. B., Levin, E., and Palmer, W. L., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 90.

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Thiosemicarbazide: A New Toxic Derivative of Thiourea.*

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Previous papers from this laboratory[1-4] have described the acute toxicity of thiourea and a number of its singly substituted derivatives, notably alpha-naphthyl thiourea (ANTU), which has proved to be an effective rodenticide for the field control of Norway rats.[1] The subject of the present paper is thiosemicarbazide ($NH_2NHCSNH_2$), in

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