In fact, this effect was neither enhanced by epinephrine nor antagonized by dibenzyline, a potent adrenergic blocking agent, when these drugs were used in doses effective in rabbits(8). Similarly, the observation that Benadryl, an antihistaminic agent, did not significantly antagonize the effects of the extract on S-180 suggests that histamine does not play a critical role in the pathogenesis of the tumor necrosis studied. The antagonistic effect of cortisone, although difficult to explain at present, is consistent with results obtained by others in different systems and suggests possible interference with the effects of endotoxins by this hormone(1).

The observations described herein on the effects of an extract from *Staphylococcus aureus* on S-180 provides additional evidence that gram-positive bacteria may contain a substance with biological activities similar to those of endotoxins of gram-negative microorganisms.

Summary. 1) A trichloracetic acid extract of *Staphylococcus aureus,* strain D (5 to 40 μg/mouse), in 24 hours caused extensive hemorrhagic necrosis of Sarcoma 180 in HaICR Swiss mice when injected intraperitoneally 7 days after tumor implantation. The extract was ineffective against tumors 1 to 4 days after implantation. 2) The effect was also produced in Sarcoma 180 grown in C57Bl/6, C3H, AKR and DBA_2 mice. 3) Epinephrine, dibenzyline and the antihistaminic drug Benadryl, in the doses used, did not alter the necrotizing activity of the extract. Cortisone, however, reduced the incidence of the effect.

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Role of the Sex Hormones in Peptic Ulcer.* (26250)

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Recent clinical observations have stimulated interest in the relationship of abnormalities of the various endocrine organs and occurrence of acid-peptic ulceration. It has been well established clinically that duodenal ulcer occurs much more frequently in males than in females. A recent report of peptic ulcer occuring in 2 brothers with primary testicular atrophy(1) is of unusual interest. Peptic ulceration is observed frequently in patients with hepatic cirrhosis(2). During pregnancy progressive decrease in gastric secretory volume is followed by a lower incidence of peptic ulcer(3). Pregnancy and cirrhosis are associated with an increase of circulating estrogens.

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TABLE I.

Group	Rx	No. of dogs	Sex	No. showing ulceration at time of death or sacrifice	Duration of treatment until death or ulceration (days)	% of group ulcerating
I	H	12	7 ♂ 5 ♀	6 dogs had duodenal ulcer(s) of which 1 had perforated (5 male, 1 female)	20.3	50.0
II	H T	12	7 ♂ 5 ♀	9 dogs had duodenal ulcer(s) of which 1 had perforated; one had a gastric ulcer (6 male, 4 female)	12.6	83
III	H Stil	12	6 ♂ 6 ♀	10 dogs had duodenal ulcers (4 male, 6 female)	9.3	83

H—histamine, T—testosterone, Stil—stilbestrol.

These clinical observations do not provide a satisfactory indication of what role, if any, the sex hormones play in originating or perpetuating acid-peptic ulceration. The greater frequency of duodenal ulcers in male human subjects, the equal incidence of ulcer in both sexes prior to puberty(4) and recent reports of endocrine abnormalities concommitant with fulminating peptic ulcer(5) have prompted the following experiments. In this study, the effects of testosterone and diethyl stilbestrol upon histamine induced ulceration and gastric secretion are evaluated. The study is divided into two sections. The first concerns the effect of testosterone and diethyl stilbestrol on histamine induced ulceration.

Methods and materials. Adult mongrel dogs of both sexes were divided into 3 groups. All dogs received daily intramuscular injections of 30 mg of histamine in beeswax until death or termination of experiment(6). Group I (12 dogs, 6 males and 6 females) received no additional medication. Group II (12 dogs, 7 males and 5 females) received a daily injection of 100 mg of testosterone cyclopentyl-proprionate in oil in addition to the histamine. Group III (12 dogs, 6 males and 6 females) were given 5 mg of diethyl stilbestrol daily in addition to histamine.

All dogs were maintained in individual cages and received a standard kennel diet and water *ad libitum*. Injections were made daily at the same time in the afternoon. The 4 dogs that did not die while receiving 30 mg of histamine in beeswax alone were sacrificed, one after 45 days, the other 3 after 90 days. In all dogs, the stomach and duodenum were examined grossly for evidence of peptic ulcers; when doubt as to their presence existed, microscopic sections were made of any suspicious area.

Results. In Group I (histamine), 6 of the 12 dogs (5 males, 1 female) showed duodenal ulcers at time of death (Table I). The interval required to cause death from ulcers or to produce peptic ulceration in dogs averaged 20.3 days. One dog died after 28 days and another after 29 days without developing ulcers and the remaining 4 had no ulcers upon sacrifice, at 45 or 90 days. This incidence of ulceration is somewhat lower than that previously reported and may be the result of allowing the dogs to eat following histamine injection.

Of the 12 dogs in Group II (histamine and testosterone), 10 had ulcers at time of death (6 males and 4 females), the occurrence of which averaged only 12.6 days from onset of treatment (Table I). The other 2 dogs died prior to 45 days without ulceration (one at 3 days and the other at 36 days.) In Group III (histamine and stilbestrol), 10 of the 12 dogs (4 males, 6 females), died with well developed duodenal ulceration in an average of 9.3 days (Table I). Of the remaining 2 dogs, one died in 3 days and the other in 10 days without developing an ulcer.

The second portion of the study concerns the effect of stilbestrol and testosterone on gastric secretion.

Methods and materials. Five adult female and 4 adult male mongrel dogs weighing 8-12

TABLE II. Stilbestrol. Change in Heidenhain Pouch Secretion.

Dog	Sex	Volume, %	Free acid, %
366	♀	+18	−14
124	"	+13	0
582	♂	−11	−11
589	♀	−27	−41
827	"	−12	0
616	♂	−50	−51
	Avg	−10	−19.5

kg were used. Twenty-four hour secretions from the Heidenhain pouch in each animal were collected for at least 20 days prior to administration of stilbestrol or testosterone. All animals were given a diet of 300 g of lean cooked meat and 100 g of dried kennel rations daily. Water was given *ad libitum*. Following initiation of injections, 24 hour secretions were again collected for a period of 20 days. An interval of 10 days was allowed when the hormone administered was changed. All specimens were analyzed for volume, pH, free acid, and pepsin.

Six dogs (2 males and 4 females) received 5 mg of diethyl stilbestrol daily and 5 dogs (2 males and 3 females) received 100 mg of testosterone cyclopentylpropionate in oil daily. Two dogs received diethyl stilbestrol for 20 days and after a 10-day rest period, received 100 mg of testosterone cyclopentylpropionate for an additional 20 days. All injections during this portion of the study were given at 7:30 a. m. daily.

Results. The dogs receiving stilbestrol showed very little change in amount and character of pouch secretion (Table II). The volume dropped an average of 10% and average free acid decreased by 19.5%. No change occurred in pepsin secretion. Dogs in the testosterone series showed similar results (Table III). Average volume decreased 11.6%, and free acid 6.4%. Again, there was no difference in pepsin secretion.

TABLE III. Testosterone. Change in Heidenhain Pouch Secretion.

Dog	Sex	Volume, %	Free acid, %
366	♀	− 9	+27
124	"	+13	+38
1811	"	−24	− 7
1503	♂	−49	−42
1183	"	+11	−48
	Avg	−11.6	− 6.4

Grouping the dogs by sex, the 4 female dogs that received stilbestrol showed no change in volume of secretion and average decrease of free acid was 14%. The 3 female dogs that received testosterone showed an average decrease in volume of 10%, and average increase of free acid of 13%. The 2 male dogs receiving testosterone showed an average decrease in volume of 19% and a decrease in free acid of 45%. These changes in secretion obviously are small and do not appear to be significant.

Discussion. Both testosterone and stilbestrol show obvious abetment of peptic ulcer provocation by histamine. It has been shown previously that other drugs such as pitressin (7), nitroglycerin(8), and caffein(9) can potentiate the effect of histamine on the duodenal mucosa. The effectivenes of the aforementioned drugs has generally been attributed to changes induced on the local vascular system producing mucosal ischemia and therefore enhanced susceptibility to the gastric juice. Since the effect of testosterone and stilbestrol on gastric pouch secretion is not significant, hypersecretion is probably not the important factor in the observed abetment of the histamine provoked ulcer noted in these experiments. The underlying mechanism for potentiation of the histamine ulcer by these 2 hormones remains obscure. Kowalewski *et al.*(10) have quantitated the production of mucopolysaccharides in the stomach of rats by a radioactive sulfur technic and have shown a decrease in production of these substances following administration of testosterone.

Summary. Histamine induced ulceration in the dog is enhanced by daily administration of 5 mg of diethyl stilbestrol or 100 mg of testosterone cyclopentylpropionate. Secretion from Heidenhain pouches in dogs is not significantly changed by daily administration of these drugs.

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Induction of Mammary Secretion in Rats by Electrical Stimulation.* (26251)

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This laboratory has recently demonstrated that many agents can induce mammary growth and/or secretion in estrogen-primed rats, including adrenergic and cholinergic drugs(1,2), tranquilizers(3,4), morphine(5), carcinogens(2), rat hypothalamic tissue(6), electrical stimulation of the uterine cervix (5) and several nonspecific stresses(7). Most of these agents are believed to act through the CNS but others may directly stimulate the anterior pituitary to release prolactin and ACTH. Most of these agents have produced adrenal cortical stimulation as indicated by reduced thymus weight, and both prolactin and ACTH have been shown to be essential for initiating mammary secretion in intact, estrogen-primed rats(7). It was of interest to see whether direct electrical stimulation of the head, nasal mucosa, lumbar region and nipples could also release sufficient prolactin and ACTH to induce mammary secretion in estrogen-primed rats.

Methods. Virgin female rats (Carworth) weighing between 200-300 g were injected subcutaneously with 10 μg estradiol per day for 10 days to produce mammary lobule-alveolar development(4). For the next 5 days, 4 groups of 5 rats each were electrically stimulated for 30 seconds twice daily in the regions of the head, nasal mucosa, lumbar area and nipples, respectively. Ten control rats received injections of physiological saline twice daily. An electrodyne stimulator with fine needle point electrodes, set at a frequency of 20 cycles/second, was used. The electrodes used for different groups were the same. The alternating current was just detectable on the finger tips and produced only slight struggling by the rats. Electrical stimulation of the head was effected by piercing the 2 electrodes through the skin over the frontal bones; of the lumbar region by piercing the electrodes through the skin of the 2nd and 3rd lumbar vertebrae; of the nasal mucosa by placing the electrodes in the nasal openings; of the nipples by inserting one electrode in the dermis of the teat and the other in the skin surrounding the nipple. On the 16th day, all rats were killed and the right inguinal mammary glands were removed, fixed in Bouin's fluid, sectioned at 6-7 μ and stained with H and E stain. The sections were examined microscopically and assigned ratings of 0 to 3.00 in units of 0.25, depending on amount of mammary secretion observed. Adrenals, thymus, ovaries and uterus were also removed and weighed.

Results. The mammary glands of the saline-injected controls (Group 1) regressed from a lobule-alveolar system at 10 days to practically a bare duct system by the 16th day, with no evidence of secretion (Table I).

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