

Influence of Epinephrine, Cortisone Acetate and Adrenocorticotrophic Hormone on Gastric Secretion¹

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The adrenal glands play an important role in the defense mechanism when an organism is exposed to stress. That this endocrine gland is involved in gastrointestinal ulceration has been reported (Mann, 1916; Rogoff and Stewart, 1926). They observed a high incidence of ulcer formation of the stomach and small intestine in bilateral adrenalectomy.

Both clinically (Dragstedt et al., 1950) and experimentally (Cummins et al., 1940), gastric hypersecretion seems to play an important role in the genesis of peptic ulcer. Several workers who investigated the relationship between adrenalectomy and gastric secretion have reported conflicting results in this regard. Madden and Ramsburg (1951) and McLaughlin (1933) reported the gastric acidity to be unchanged or even decreased after adrenalectomy, while Mann (1916) maintained that gastric acidity was at least partly responsible in the formation of these ulcers.

It appears certain that there is a close relationship between the activity of adrenocortical steroids and peptic ulceration of the gastroduodenal tract. The availability of cortisone and ACTH for clinical

uses has been followed by many reports on the incidental ulceration of the gastrointestinal tract during or following the use of these drugs (Habif et al., 1950; Halsted, 1952; Smyth, 1951). Gray et al. (1951) maintained that hypersecretion of gastric juice was responsible for these ulcers while Dragstedt et al. (1956) and Drye et al. (1953) discounted such hypersecretion with the use of cortisone and ACTH.

On the other hand, epinephrine as a product of stress has been well documented. That this agent may be used to produce ulceration of the stomach and duodenum has been shown by Baronofsky and Wangenstein (1945).

What influence this hormone has on gastric secretion, however, has been largely unknown.

An investigation on the influence of epinephrine, cortisone acetate and ACTH on gastric secretion in animals and in operative stress in man, form the basis of this thesis.

MATERIALS AND METHODS

Adult mongrel dogs of both sexes, weighing between 11 and 15 kg were used in these experiments. Before the initiation of the experiment, the animals were kept in the cage for at least two weeks to accommodate them to the new surroundings and, during this period, the intestinal parasites were removed. In order to remove the influence of the vagus nerves in these experiments, a Heidenhain pouch was used. This was constructed

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under sodium pentothal anesthesia, care being taken to construct the pouch only as large as was compatible with the function of the remaining stomach.

Studies of the gastric secretion and eosinophile changes were started approximately 2 weeks following the operation when the swelling and hyperemia of the operative site had subsided and the 24 hour gastric secretion had stabilized. Animals were given nothing by mouth, except water, for 18 to 24 hours before the experiments. Before each experiment, one or two hourly collections of gastric juice and eosinophile counts were performed before the injection of drugs to obtain a baseline value for that experiment. The hourly gastric secretions before and after the injections were collected through a modified Dragstedt cannula into a glass bottle or rubber bag and, after measuring the volume, these were analyzed for free and total acids using Toepfer's reagent and 0.01-N NaOH.

Eosinophile counts were used as an index of the activity of the blood adrenocorticosteroid hormones. Fuch-Rosenthal counting chambers were used and the average value of four countings was taken for each count. Depression of more than 50% of the control figures was considered significant. Injections were made through three different routes: subcutaneous, intramuscular and intravenous. The intravenous route was subdivided into two: one in which the drug was given in undiluted form, and the other in which it was given in 30 cc of 5% dextrose in water in 30 minutes to avoid the undesirable effects of sudden elevation of the drug concentration in the blood.

In a patient with esophageal atresia due to lye burn and a gastric fistula, 100 mg of cortisone acetate was injected daily following a 4 day control period. Twelve-hour nocturnal gastric secretions were collected through the gastric fistula, and these were analyzed for acid output.

Gastric acidity and eosinophile counts were performed in patients who underwent various surgical procedures. Twelve-hour gastric secretions were collected through a mercury-weighted gastric tube

once before the operation and on the first, third, fifth and seventh postoperative days.

Eosinophile counts were performed on the days of gastric analysis.

RESULTS

1) Control Studies

In order to establish a baseline in these studies, control values were established in the following manner:

- A) Animals given no injection and those that received 30 cc of 5% dextrose in water showed no remarkable change in gastric secretion and eosinophile counts. There was some tendency for the gastric acidity to decrease with the passage of time, but this was not considered significant.
- B) The gastric secretion and eosinophile counts during the one or two hours immediately preceding the injection were taken as the baseline value of the animal for that experiment. Animals showing high free acid values during the fasting phase were removed from the experiment.
- C) Histamine diphosphate, 0.03 mg/kg of body weight, was injected into the experimental animals from time to time in order to ascertain the response of the gastric secretory glands to stimulation and also to compare the hypersecretion produced by histamine injection and that produced by ACTH or cortisone. Animals that did not show response to histamine were considered to have a defective secretory mechanism and were, consequently removed from these experiments. Histamine injection in responsive animals produced a prompt and pronounced increase in both the volume and the acidity of the gastric juice during the initial hour (maximum 0.9 mEq/hr), and this increase tended to continue for two to three hours after the injection. There was a sustained depression of circulating eosinophiles (27% to 48% of the controls).

2) Epinephrine and Gastric Secretion

- A) Subcutaneous injection of epinephrine, 0.03 mg/kg, produced a definite decrease in the acid output of the gastric glands immediately following the injection, and this decrease was sustained. There was a gradual decrease of circulating co-

sinophiles, becoming less than 50% of the control value 4 hours after the injection.

B) Intravenous injection of epinephrine, in doses of 0.03 mg/kg and 0.06 mg/kg in 30 cc of 5% dextrose in water, showed no appreciable effect on either the volume or the acidity of the gastric juice. There was a significant decrease of circulating eosinophiles 4 and 7 hours, respectively, after the injection.

3) Cortisone acetate and Gastric Secretion

A) Intramuscular injection of cortisone acetate in doses of 50 mg, 100 mg, 150 mg, 200 mg, showed no apparent influence on gastric secretion. The eosinophile counts started to fall significantly three to four hours after the injection.

B) When cortisone acetate, 15 mg/kg, was injected intravenously diluted in 30 cc of 5% dextrose in water, there was a moderate increase in both the volume and the acidity of the gastric juice. This increase was pronounced during the first and second hours after injection, reaching a maximum value of 0.2 mEq/hr during the first hour. In general, the eosinophile counts fell immediately following the injection and this lowered value was maintained during the entire course of the experiment (Fig. 1).

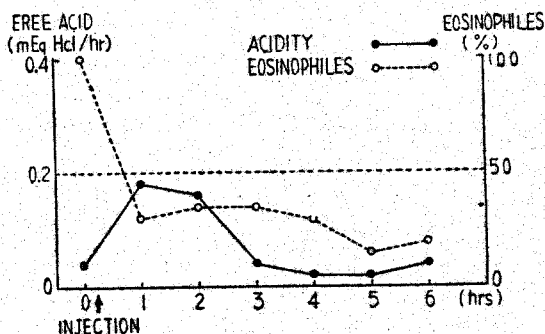


Fig. 1. Changes in gastric secretion & eosinophile counts following intravenous injection of 15 mg/kg of cortisone acetate (5% D/W, 20 cc) (Average of 6 experiments).

C) When cortisone acetate 15 mg/kg, undiluted, was injected intravenously, there was a prompt and significant increase of gastric secretion which

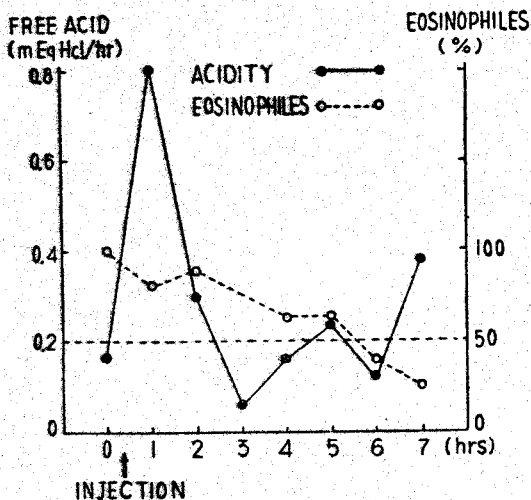


Fig. 2. Gastric secretion & eosinophile counts following intravenous injection of 15 mg/kg of cortisone acetate (Average of 5 experiments).

was very similar to the hypersecretion produced by histamine injection (Fig. 2).

4) Influence of Atropine Sulfate on the Cortisone Effect on Gastric Secretion

When the intravenous injection of cortisone was accompanied by the simultaneous injection of 0.14 mg of atropine sulfate or was preceded 30 minutes and 60 minutes by the injection of atropine, there was either no increase or only a slight increase of gastric secretion one to two hours following the injection (Fig. 3).

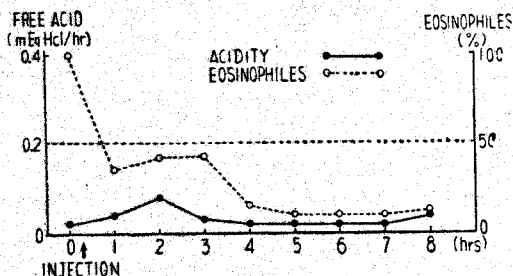


Fig. 3. Gastric secretion and eosinophile counts following intravenous injection of 15 mg/kg of cortisone acetate (5% D/W, 30 cc) simultaneous with subcutaneous injection of 0.14 mg of atropine sulfate (Average of 3 experiments).

5) Adrenocorticotrophic Hormone and Gastric Secretion

A) The intramuscular injection of 10 mg of ACTH produced essentially no change in gastric secretion. There was a significant decrease in eosinophile count within 6 hours after the injection.

B) When 10mg of ACTH in 30 cc of 5% dextrose in water was injected intravenously, there was a moderate increase in gastric secretion 5 to 6 hours after the injection. This increase was comparable to that produced by cortisone acetate given intravenously (Fig. 4). There was a gradual fall in the eosinophile counts, reaching significant levels 3 hours after the injection.

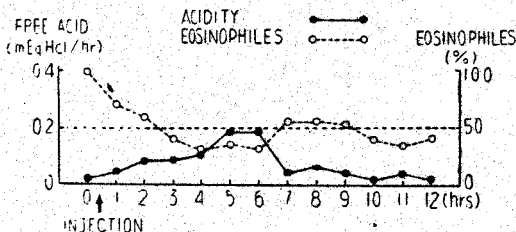


Fig. 4. Gastric secretion and eosinophile counts following intravenous injection of 10 mg ACTH (5% D/W, 30 cc) (Average of 8 experiments).

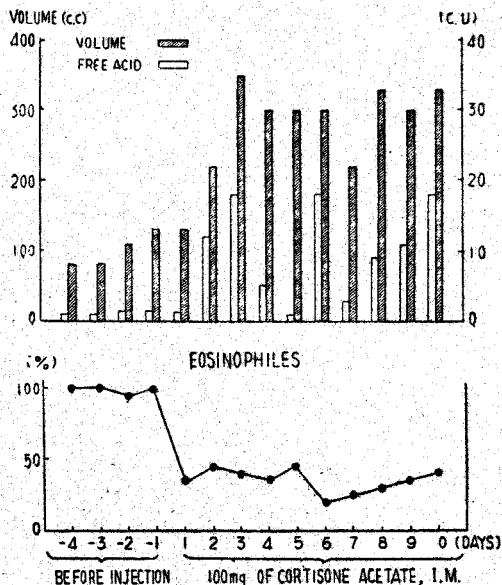


Fig. 5. Changes in gastric secretion & eosinophile counts following intramuscular injection of 100 mg of cortisone acetate in man.

6) Cortisone Acetate and Gastric Secretion in Man

When 100 mg of cortisone acetate was injected in a human subject, there was a moderate increase in both the volume and free acid value following the injection and a prompt and sustained decrease in the eosinophile counts (Fig. 5).

7) Operative Stress and Gastric Secretion in Man

There was only a slight increase of gastric secretions during the immediate postoperative period (24 to 48 hours). There was, however, a significant increase in the HCl output 2 to 5 days after the operation (Fig. 6). This was considered significant, because this period the volume of gastric juice tended to be markedly reduced as compared to postoperative levels and this increase in HCl output was largely in concentrated free acid. Gastric secretions tended to return to normal 5 to 7 days after the operation.

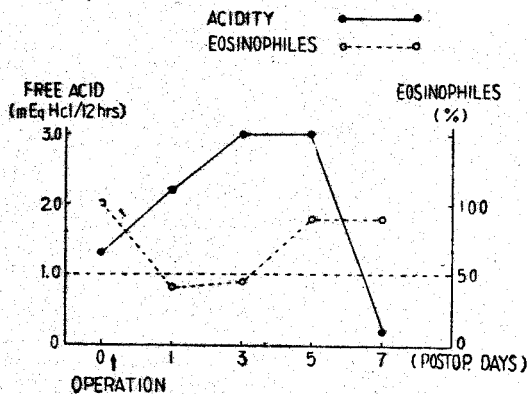


Fig. 6. Changes in gastric secretion & eosinophile counts following operation (Average of 3 experiments).

DISCUSSION

There was no evidence that the injection of epinephrine was followed by an increase in gastric secretion. It confirms the findings of Baranofsky and Wangenstein (1945) who reported that there

was no increase in gastric secretion with the injection of epinephrine. This may be explained on the basis of the inhibitory action of the sympathetic nervous system on gastric secretion. Shape and Kittle(1951) reported that they were able to produce hypersecretion of the stomach by denervating the sympathetic supply of the stomach wall.

The action of cortisone acetate on gastric secretion was more complex. When this was administered intramuscularly, it showed no apparent effect on the gastric secretion, even in relatively large doses. However, when it was injected intravenously, there was a definite increase in gastric secretion, and this hypersecretion was inhibited by the preliminary injection of atropine sulfate. The gastric pouch in these experimental animals was devoid of vagus supply and, consequently, it may be concluded that the stimulating effect of cortisone acetate on gastric glands is mediated through a humoral pathway. That such a humoral pathway exists has been demonstrated by Ivy and Farrell(1925) experimentally. This, together with the fact that this hypersecretion is inhibited by atropine sulfate, seems to indicate that the action of cortisone acetate is directly on the parietal cells of the stomach through a humoral pathway.

It is note-worthy that Dragstedt et al.(1956) were unable to produce gastric hypersecretion in experimental animals with Heidenhain pouches by the administration of cortisone acetate. It should be noted that all the injections were carried out subcutaneously. Dry and Schoen(1958) reported that they were unable to produce gastric hypersecretion by the intramuscular injection of cortisone acetate. These findings are in agreement with the results of author's experiment. The finding that the intravenous injection of cortisone acetate in the same doses was able to produce definite hypersecretion of the gastric glands seems to indicate that cortisone acetate can stimulate the gastric glands when this is given in such a way that the blood concentration of this hormone can be raised in a relatively short time. The lack of response when it was given intramuscularly or subcutaneously may be due to the fact that the delayed absorption may not produce

a high enough concentration of this hormone in the blood to stimulate the parietal cells of the stomach. It should be noted that the intravenous injection of cortisone acetate in an undiluted form produces an even more pronounced gastric hypersecretion.

A similar phenomenon was observed in the administration of ACTH. The intramuscular injection of this hormone showed no apparent effect on gastric secretion. On the other hand, the intravenous injection of ACTH was followed by a moderate increase in gastric secretion. Dragstedt et al.(1956) were unable to produce gastric hypersecretion with the intramuscular injection of this hormone, and their findings corroborate the author's. The fact that the intravenous injection of ACTH followed by a moderate increase in gastric secretion seemed to indicate that the sudden elevation of the blood concentration of this hormone was an important factor in producing gastric hypersecretion.

It is interesting to note the appearance time of the gastric hypersecretion and eosinophile depression following the intravenous injection of cortisone acetate and ACTH. There was a prompt initiation of the gastric hypersecretion following the injection of cortisone acetate, whereas in ACTH, this was not observed until 5 to 6 hours after the injection

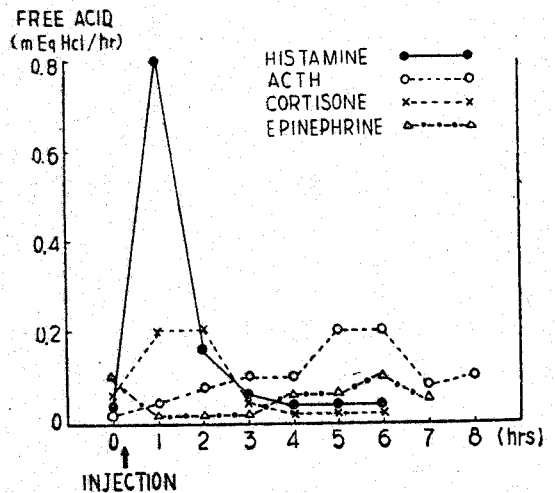


Fig.7. Comparison of changes in gastric acidity produced by administration of Histamine, ACTH, Cortison acetate and Epinephrine.

(Fig. 7). Porter et al. (1953) observed a similar phenomenon and concluded that gastric hypersecretion which is mediated through the pituitary axis is slower in response. It is speculated that adrenal gastric hypersecretion following the injection ACTH is delayed because this has to be mediated through the adrenal cortex.

The gastric hypersecretion which was observed during the postoperative period in this experiment is contrary to the observation of others. Hartman (1945) questioned the occurrence of gastric hypersecretion in burn patients, and Howard (1955) stated that in patients with war wound gastric and salivary secretions were diminished. On the other hand, Drye and Schoen (1953, 1958) reported that there was definite hypersecretion following operative trauma. In analyzing these conflicting data, it may be significant to consider the importance of the fluid and electrolyte balance of these patients. Ncheles and Olson (1942) reported that following experimental burn, gastric hypersecretion was observed only in the animals which received intravenous injections of electrolytes. Also, Madden and Ramberg (1951) maintained that the influence of the adrenals on gastric secretion is mediated through the changes in water and electrolyte balance.

Then what is the specific role of gastric hypersecretion following the administration of cortisone and ACTH or that produced by nonspecific trauma upon the formation of gastroduodenal ulcer? One of the most reliable methods of producing gastroduodenal ulcer is to produce sustained hypersecretion of gastric juice with histamine. The fact that gastric hypersecretion, ulceration or perforation of an ulcer could be produced by the sustained action of intramuscularly injected histamine in bees-wax has been reported by numerous investigators (Barofsky et al., 1946; Code and Varco, 1940; Friessen and Wangenstein, 1946; Hay et al. 1942; Varco et al. 1941; Walpole et al., 1940). Iams (1946) reported that the injection of histamine was followed by the formation of peptic ulcer in man. Comparison of the levels of gastric hypersecretion produced by cortisone acetate or ACTH and that produced by histamine injection in these experimental animals

is interesting. With cortisone acetate or ACTH administration, the peak hourly gastric secretion was 0.2 mEq HCl, whereas with histamine this was 0.9 mEq; that is, histamine injection produced four and one half times as much secretion as did either cortisone or ACTH alone. It is possible that with large doses of cortisone or ACTH this hourly gastric hypersecretion could be increased to the level produced by histamine injection, as indicated when undiluted cortisone was injected intravenously. Cortisone not only has this primary effect on gastric secretion, but it also has a secondary effect which is related to its action as a catalyzer on gastric secretion. That such a secondary effect may exist has been shown by Stempen (1954), who reported that in patients with Addison's disease the administration of histamine alone did not produce gastric hypersecretion and that, in order for hypersecretion to occur, it required a simultaneous injection of cortisone. From these findings it appears reasonable to postulate that gastric hypersecretion following cortisone or ACTH administration is at least partly responsible for producing gastroduodenal ulcers following nonspecific trauma.

At the same time, it should be remembered that cortisone possesses other important biological function, one of these being its powerful influence on wound healing. It has been established that cortisone and ACTH delay wound healing by inhibiting connective tissue growth and the formation of granulation tissue (Ragen, 1949; 1950; Ragen et al., 1949; Creditor et al., 1950; Spain et al., 1950). This factor may also play an important role in the formation of gastroduodenal ulcer following the administration of cortisone or ACTH.

Trauma is associated with other important physiological phenomena besides the elevation of the level of ACTH and cortisone in the blood. From the standpoint of ulcer formation of the stomach and duodenum, derangement of the blood supply to the stomach wall and septicemia may be very significant. It has been reported that trauma is attended with hemoconcentration (Beard and Blalock, 1931), and it was suggested by Friesen (1950) that this may contribute to the formation of ulcer. Thrombosis of

small vessels of the stomach from the increase in the number of circulating platelets (Warren and Belke, 1953) and increase in the clotting mechanism of blood from hypoheparinemia is as the result of ACTH activation (McGraw et al., 1952) could explain such ulcers. Venous stasis may also play a role in the genesis of post-traumatic ulceration of the stomach and duodenum (Baranofsky and Wangenstein, 1946).

The possible role of septicemia in the production of gastroduodenal ulceration in trauma has been emphasized. Hartman (1945, 1946) was able to produce ulcers of the stomach and intestine in 77.7% of the experimental animals which sustained 3rd degree burns over 50–60% of the body surface, but when these animals were treated with penicillin, the incidence was only 23%. This finding seems to indicate that there is a definite relationship between septicemia and the formation of gastroduodenal ulcers following trauma. It is possible that the gastric hypersecretion seen in trauma is related to gastrointestinal ulcers in general and that secondary influence such as thrombosis of vessels and septicemia may also contribute to ulcer formation.

CONCLUSION

Heidenhain gastric pouches were constructed in dogs, and the effect of epinephrine, cortisone acetate and ACTH on gastric secretion mediated through humoral pathway was investigated. In man, the influence of operative trauma on gastric secretion was investigated to evaluate its possible role in the pathogenesis of gastroduodenal ulcer following trauma.

- 1) There was no evidence that epinephrine produces gastric hypersecretion.
- 2) Cortisone acetate and ACTH when administered intravenously produced moderate hypersecretion of the gastric glands. Cortisone acetate seems to act on the parietal cells of the stomach through a humoral pathway. The possible mechanism of this was discussed.
- 3) There is gastric hypersecretion following operative trauma in man. Such hypersecretion may be an important factor in the formation of

ulcers following trauma.

REFERENCES

- Baranofsky, I.D. and Wangenstein, O.H.: *Role of nitroglycerin in accelerating occurrence of the histamine provoked ulcer. Proc. Soc. Exp. Biol. Med.* 62:127, 1946.
- Baranofsky, I.D. and Wangenstein, O.H.: *Cited by Baranofsky and Wangenstein.*
- Baranofsky, I.D. Friesen, S., Sanchez-Palomera, E., Code, F. and Wangenstein, O.H.: *Vagotomy fails to protect against histamine-provoked ulcer. Proc. Soc. Exp. Biol. Med.* 62:114, 1946.
- Beard, J.W. and Blalock, A.: *Experimental shock. VII Arch. Surg.* 22:617, 1951.
- Code, O.F. and Varco, R.L.: *Chronic histamine action. Proc. Soc. Exp. Biol. Med.* 44:475, 1940.
- Creditor, M.C., Evans, M., Mundy, W.L. and Ragen C.: *Effect of ACTH on wound healing in human. Proc. Soc. Exp. Biol. Med.* 74:245, 1950.
- Cummins, G.M., Groseman, M.I. and A.C. Ivy: *An experimental study of the acid factor in ulceration of the gastrointestinal tract in dogs. Gastroenterology.* 10: 714, 1948.
- Dragstedt, L.R., Ragin, J., Dragstedt L.R., II. and Evans, S.C., Jr.: *Stress and duodenal ulcer. Annal. Surg.* 144: 450, 1956.
- Drye, J.C. and Schoen, A.M.: *Studies on the mechanisms of the activation of peptic ulcer non-specific trauma. Effect of cortisone on gastric secretion. Ann. Surg.* 67:469, 1953.
- Drye, J.C. and Schoen, A.M.: *Schuster, G.: Gastric secretion in the immediate postoperative period. Arch. Surg.* 67:469, 1953.
- Friesen, S. and Wangenstein, O.H.: *Experimental burns accompanied by histamine administration abets the ulcer diathesis. Proc. Soc. Exp. Biol. Med.* 63:245, 1946.
- Friesen, S.: *The genesis of gastroduodenal ulcer following burns. An experimental study. Surgery.* 28:123, 1950.
- Gray, S.J., Benson, J.A. Jr., Spiro, H.M. and Reifenshtein, R.W.: *Effect of ACTH and cortisone upon the the stomach its significance in the normal and in peptic ulcer. Gastroenterology.* 19:658, 1951.
- Habif, D.V., Hare, C.C. and Glasser, G.H.: *perforated duodenal ulcer associated with pituitary adrenocorticotrophic hormone (ACTH) therapy. J. A. M. A.* 144:996, 1950.

- Halsted, J. A.: *The effects of ACTH and cortisone in diseases of the digestive system. Med. Cl. N. Am.* 36:1069, 1952.
- Hay, L. J., Varco, R. L., Code, C. F. and Wangenstein, O. H.: *The experimental production of gastric and duodenal ulcers in laboratory animals by the intramuscular injection of histamine in beeswax. Surg. Gyn. Obst.* 75:1942.
- Iams, A. M.: *An ulcer which appeared in the stomach of man receiving histamine intravenously. Gastroenterology.* 6:449, 1946.
- Ivy, A.C. and Farrell, J.I.: *Contributions to the physiology of gastric secretion. VIII. The proof of a humoral mechanism. Am. J. Physiol.* 74:639, 1925.
- Madden, R. J. and Ramsburg, H. H.: *Gastric secretion in the adrenalectomized rat. Endocrinology.* 46:82, 1951.
- Mann, F. C.: *A future study of the gastric ulcers following adrenalectomy. J. Exp. Med.* 24:329, 1916.
- McLadghlin, C. W.: *The Curling's ulcer. Study of intestinal ulceration associated with supurarenal damage. Arch. Surg.* 27:490, 1933.
- Necheles, H. and Olson, W. H.: *Experimental investigation of gastrointestinal secretion and motility following burns and their relation to ulcer. Surgery.* 11:751, 1942.
- Porter, R. W., Movius, H. J. and French, J. D.: *Hypothalamic influences on HCl secretion of the stomach. Surgery.* 33:875, 1953.
- Ragen, C.: *Effect of ACTH and cortisone on connetive tissue in "Connective tissue", New York, Joseiah Macy Jr. Foundation, p. 137, 1950.*
- Rogoff, J.M. and Stewart, C.N.: *Studies on adrenal insufficiency in dogs. Control animals not subjected to any treatment. Am. J. Physiol.* 78:684, 1926.
- Shape, P.W. and Kittle, C.F.: *The relation of the autonomic nervous system to gastric secretion with particular reference to the sympathetic nerves. Surgery.* 29:1951.
- Smyth, C. A.: *Activation of peptic ulcer during pituitary adrenocorticotrophic hormone (ACTH) therapy. Report of 3 cases. J. A. M. A.* 145:574, 1951.
- Spain, D. W., Molemut, N. and Haber, A.: *The effect of cortisone on formation of granulation tissue in mice. A. J. Path.* 26:710, 1950.
- Stempen, S. J. and Dragradi, A.: *The histamine response of the gastromucosa in a patient with adrenal insufficiency. Effect of cortisone administration. Gastroenterology.* 27:358, 1954.
- Varco, R.L., Code, C.F., Walpole, S.H. and Wangenstein, O. H.: *Duodenal ulcer formation in the dog by intramuscular injection in beeswax mixture. Am. J. Physiol.* 133:475, 1941.
- Walpole, S.H., Varco, R.L., Code, C.F. and Wangenstein, O. H.: *Production of gastric and duodenal ulcers in the cat by intramuscular implantation of histamine. Proc. Soc. Exp. Biol. Med.* 44:619, 1953.
- Warren, R. and Sokdo, J. S.: *Alternation in numbers of circulating platelet following surgical operation and administration of adrenocorticotrophic hormone. Circulation* 7:481, 1953—*Year Book* p. 37, 1953.