Studies on the Mechanisms of the Activation of Peptic Ulcer After Non Specific Trauma *

Effect of Cortisone on Gastric Secretion

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IN 1953 [2] and again in 1954 [3] we reported a group of patients who developed activation of quiescent peptic ulcers with subsequent perforation or hemorrhage within a week after either accidental or surgical trauma. There have been many similar reports by others.[5, 7, 13] It has become evident that this is an important and frequent postoperative complication in patients who have quiescent peptic ulcers.

The edict of Edkins—no acid, no ulcer—and the well established correlation between hypersecretion and ulcer activity led us to study the effects of trauma on gastric secretions.

In previous papers [2, 3] we reported our observation that the stomach began to secrete within 8 to 12 hours after trauma (Fig. 1) and in many cases the concentration of hydrochloric acid in both non-ulcer and known ulcer patients rose after trauma. In a few of the non-ulcer patients and in most of the ulcer patients, this concentration reached levels comparable to that found in patients with active duodenal ulcers within 12 to 24 hours. These findings rather surprised us, since normal stimuli of vagal and hormonal mechanisms, such as hunger or the presence of food in the stomach were presumed to be absent in the immediate post-traumatic patient. Therefore, we began a search for some stimulus other than the normal physiological ones.

The increased production of adrenal steroids after trauma has been well established. Many reports [1, 8, 10] of the appearance of peptic ulcer frequently associated with hemorrhage or perforation in patients under steroid therapy were appearing. Seymoure Grey [6] reported increased gastric secretion in patients under steroid therapy. Because of these observations, we investigated the possibility that increased steroid activity after trauma was stimulating gastric secretion and that the secretion was responsible for the post-traumatic activation of these quiescent peptic ulcers.

Isolated gastric pouches were made in 19 dogs. Because of lack of experience we obtained only three dogs with suitable pouches. Two had intact vagi to the pouch. The antrum was intact in Dog 1 and removed in Dog 2. The isolated pouch drained to the outside and intestinal continuity was established by esophagojejunostomy. After recovery of the two animals, gastric secretion was measured for several days and then laparotomies were performed. Studies in the immediate postoperative period in these dogs failed to show any increase in gastric secretion (Fig. 2 and Table 1). Thus we could not produce

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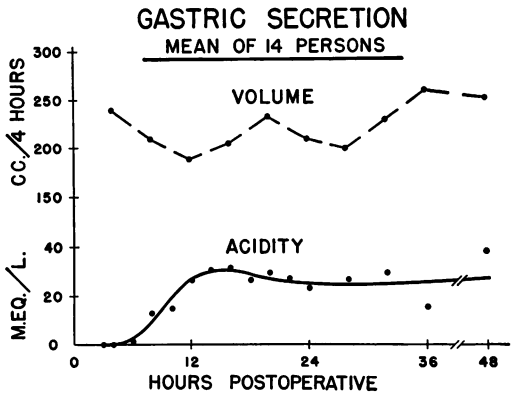


FIGURE 1

TABLE 1. *Effect of Trauma on Gastric Secretion in the Dog*

	Values During 48-Hour Preoperative Period	Values During 48-Hour Postoperative Period
mEq free HCl/hr.	1.076	0.618
Total volume	702 cc.	476 cc.
Total mEq free HCl	51.67	29.62
Serum chlorides	89–102 mEq/L	105–107 mEq/L

Dog #1. Isolated gastric pouch with vagi and antrum intact.

in dogs the post-traumatic hypersecretion that we had found to be present in man.

Since there might be a species difference in the effect of cortisone on the gastric secretory activity in man and dog, we tested the effect of cortisone in the dog. Two pouch dogs were studied. The antrum was absent in both. One pouch dog had intact vagi and the other had the vagi severed. After a control period the dogs were given cortisone acetate 25 mg. intramuscularly daily for more than a month. Statistical analysis of the acid values before and after cortisone failed to show any effect on gastric secretion in either dog (Fig. 3, 4).

We then returned to the study of gastric secretions in man.

Methods

In order to get more accurate values for the volume of gastric juice secreted, the

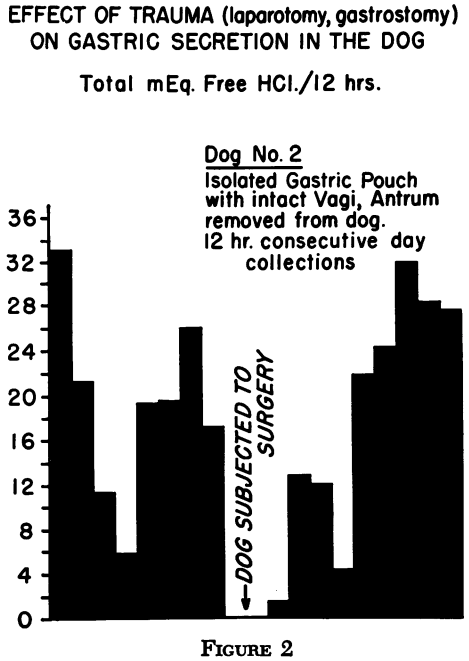


FIGURE 2

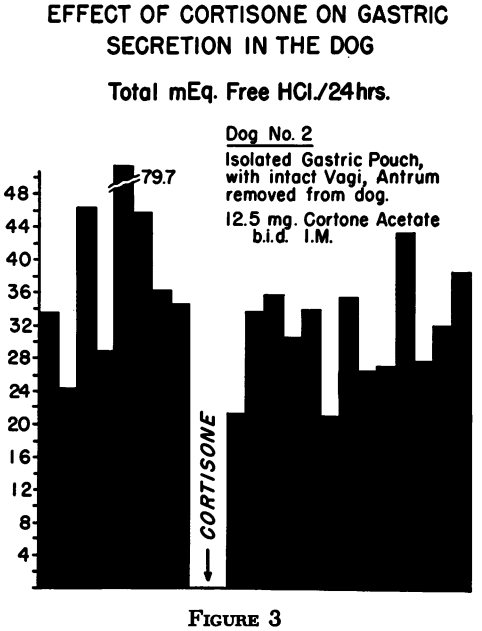


FIGURE 3

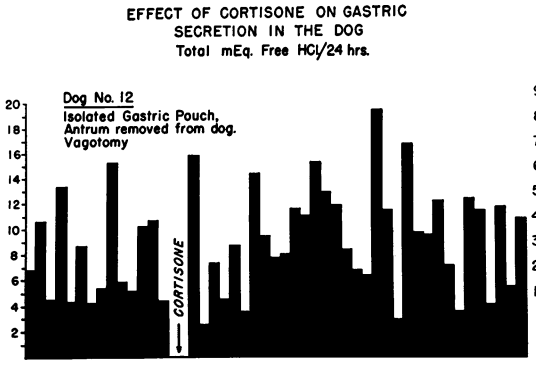


FIGURE 4

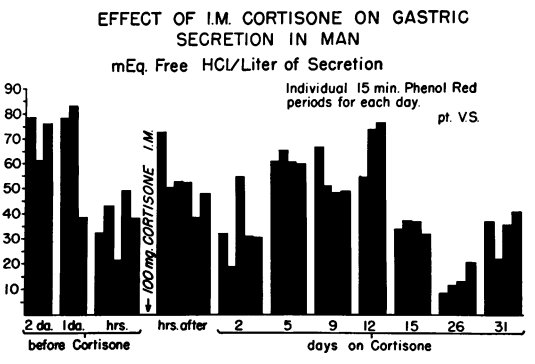


FIGURE 5

method of Schoen and Knoefel [11] was used. This is similar to the Fick Principle and detects any dilution of gastric juice. Observed values of acid and pepsin were corrected for the dilution detected by this method. A solution containing 5 mg. of phenol red in a liter of normal saline is injected through a Levine tube into the empty stomach; the amount injected was equal to the volume of residual gastric contents removed. Fifteen minutes later the stomach is completely emptied and the volume aspirated is measured. Repeated determinations every 15 minutes are done for a period of an hour, or an hour and a half. The concentration of phenol red in each specimen was determined spectrophotometrically. Gastric secretory and emptying rates are calculated from the concentration and volume of phenol red injected and aspirated.

Free acid was measured by pH meter with values converted to mEq. by conversion tables.

Gastric pepsin was determined at pH 2.0 by digestion of coagulated egg albu-

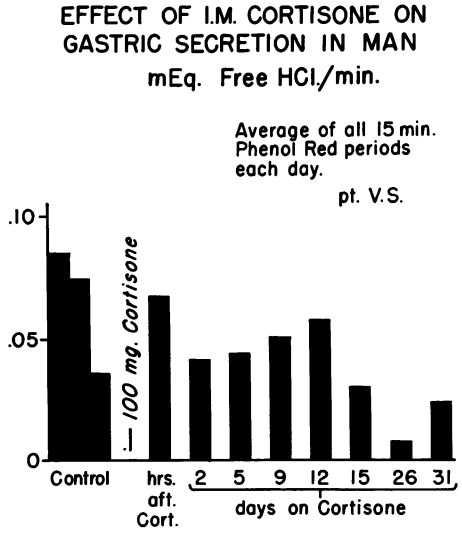


FIGURE 6

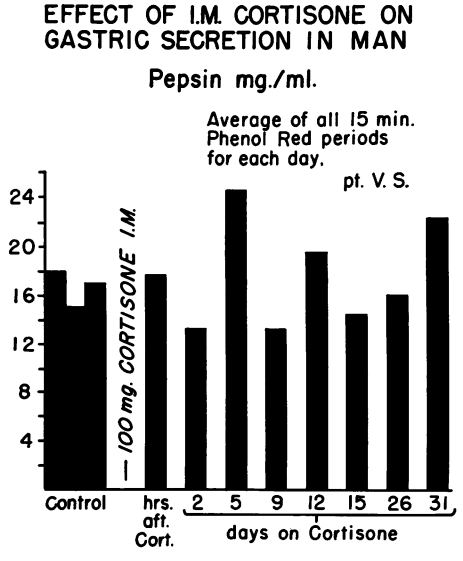
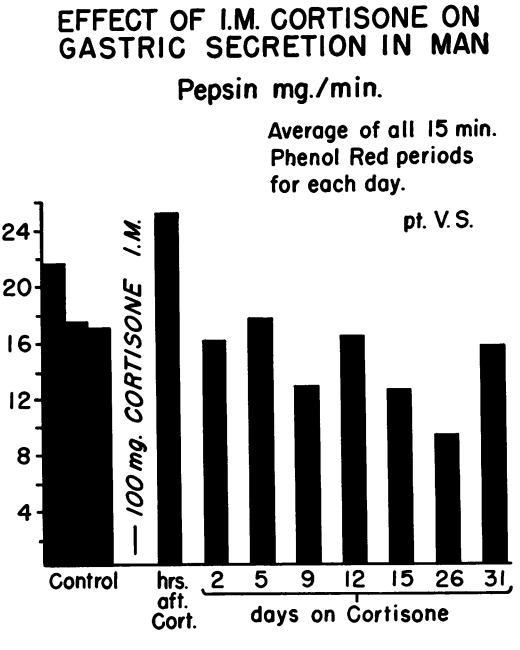


FIGURE 7

men, standardized against a known purified pepsin solution.

Uropepsin was measured by a modification of the method of West.[12] Normal range is 15 to 40 units per hour.

Using this method, we studied the effects of cortisone. In two patients hydrochloric acid in mEq. per liter and mEq. per minute, gastric secretory rate, pepsin in milligrams per ml and milligrams per minute were determined daily for three days before cortisone and on five different days between the fifth and thirtieth day during administration of 100 mgm of cortisone intramuscularly per day. There was no increase in the secretion of hydrochloric acid or pepsin or in the secretory rate. In fact, there was a marked and progressive decrease in hydrochloric acid (Figs. 5–14). In a third patient there was an absence of free acid before cortisone and none appeared during a month's administration of cortisone. These findings do not support the observations of Grey. Others [4, 9] also have failed to reproduce his results.



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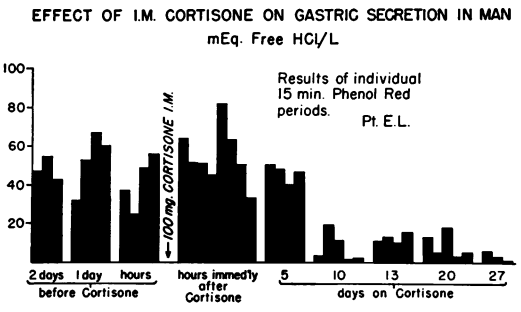


FIGURE 9

In our original studies, as reported in 1953 [2] and 1954,[3] we had been chiefly interested in the effect of trauma on the concentration of hydrochloric acid in the gastric secretion. We decided to study the effect of trauma on gastric secretion in much more detail. These studies were to include the effect of trauma on the secretory rate, the concentration of hydrochloric acid, the rate of secretion of hydrochloric acid, the concentration and rate of secretion of pepsin and uropepsin levels; in addition, since histamine is a potent gastric stimulant and is known to arise from injured tissue, we measured pre and postoperative arterial histamine levels.

Eight individual patients were studied. Studies of all the above factors were not completed on each patient.

In six patients studied, there was an increase in the concentration of hydrochloric acid after trauma (Table 2). Statistical analysis shows this increase to be significant. In these same six patients, four of them showed an increase in the total amount of acid secreted and two showed a decrease (Table 3). The decreased amount of acid accompanied by an increased concentration is explained by a decrease in the secretory rate (Table 4).

There was a definite increase in the gastric pepsin after trauma, (Table 5) in the eight patients studied. The determinations of uropepsin in five patients showed a

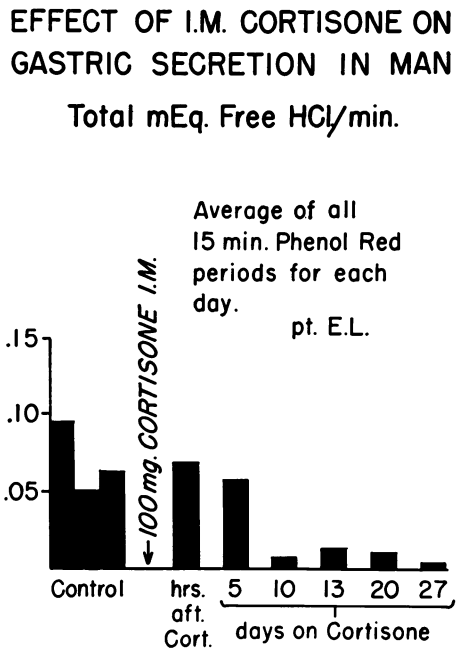


FIGURE 10

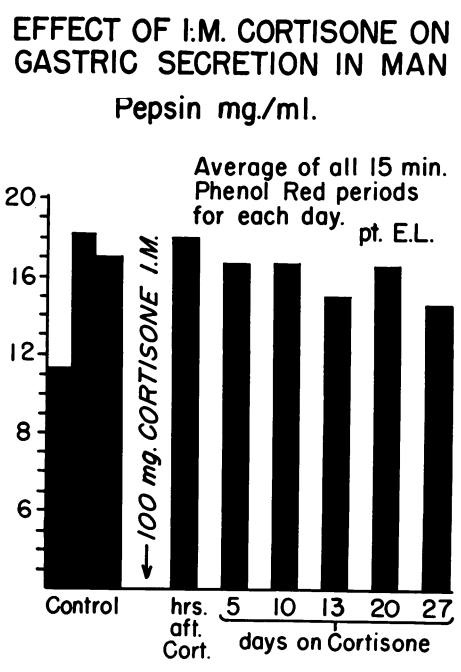


FIGURE 11

tendency to increase in the postoperative period (Table 6). The average values in five patients for concentrations of hydrochloric acid, pepsin, and uropepsin showed a good correlation between pepsin and uropepsin but a rather poor one between uropepsin and the concentration of hydrochloric acid (Fig. 15). Further, there was frequently a poor correlation between uropepsin and concentration of hydrochloric acid or pepsin in the individual patient as shown for one patient (Fig. 16).

Studies of arterial histamine in four patients before and after surgical trauma showed no significant changes, and all values, both before and after trauma, were within the normal range (Table 7).

TABLE 2. *Effect of Trauma on Gastric Secretion in Man*
mEq Free HCl/Liter

Patient	24–0-Hr. Preop.	24–48-Hr. Postop.	Change
B. A. (hernia)	38.45	79.50	+41.05
J. J. (expl. chest)	0.00	22.40	+22.40
M. W. (colon resect.)	0.00	13.86	+13.86
E. B. (colon resect.)	34.50	55.90	+21.40
M. N. (hernia)	41.60	43.90	+ 2.30
A. G. (hernia)	35.20	69.50	+34.30

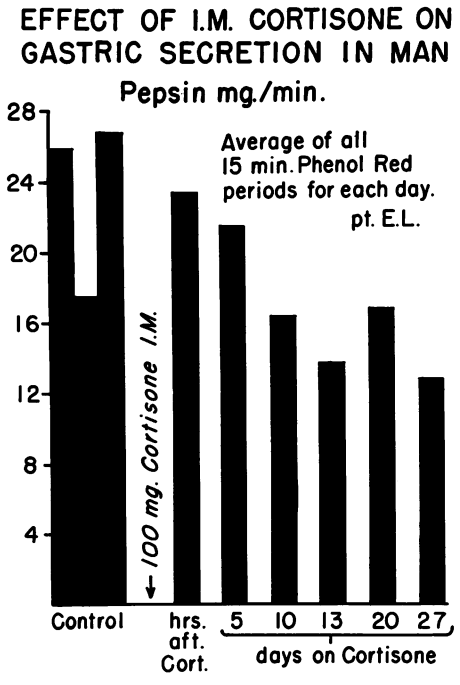
Based on Phenol Red Method.[11]

Discussion

The hazards of the activation of a quiescent peptic ulcer with the possibility of hemorrhage or perforation after major op-

TABLE 3. *Effect of Trauma on Gastric Secretion in Man*
mEq Free Hcl./24 Hrs.

Patient	Preoperative	Postoperative
B. A.	154.9	166.8
J. J.	0.0	13.9
M. E. W.	0.0	4.8
E. B.	35.5	37.2
M. N.	146.3	138.4
A. G.	34.6	24.2



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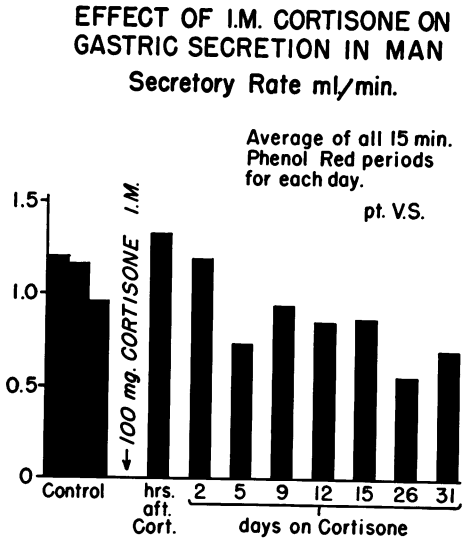

FIGURE 13

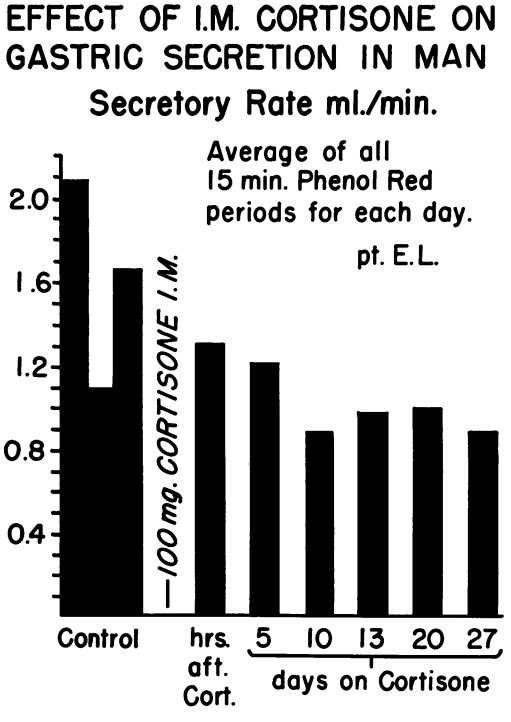

FIGURE 14

eration or after accidental trauma is a real one. This has been well documented by us as well as by others.[2, 3, 5, 7, 13] Similarly, the appearance of peptic ulcer and the all too frequent associated hemorrhage and perforation in patients under steroid therapy is too well documented to be denied. However, as attractive and as logical as the relationship between these two occurrences seems to be, we have been unable to demonstrate any true relationship between them.

Our findings do not indicate that the cortisone ulcer is due to gastric hypersecretion. We would like to make the suggestion that these ulcers are the result of a much simpler process. Since cortisone is known to have a depressing effect on fibroplasia and healing in general, is it not possible that simple erosions that occur quite frequently in normal people and almost always heal spontaneously progress under steroid therapy to real ulcers because of the depressing effect on normal healing by

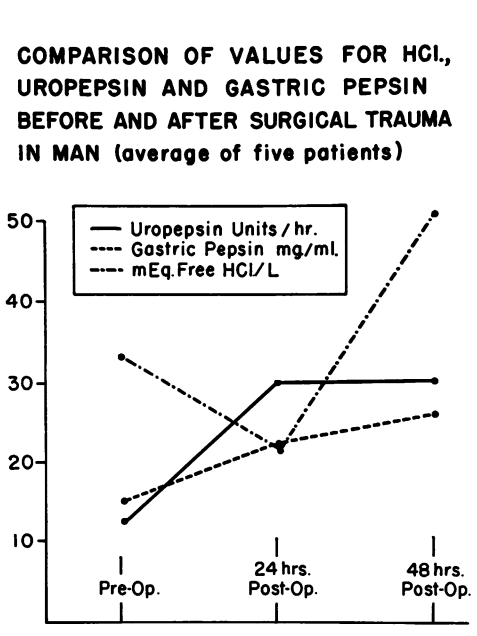

FIGURE 15

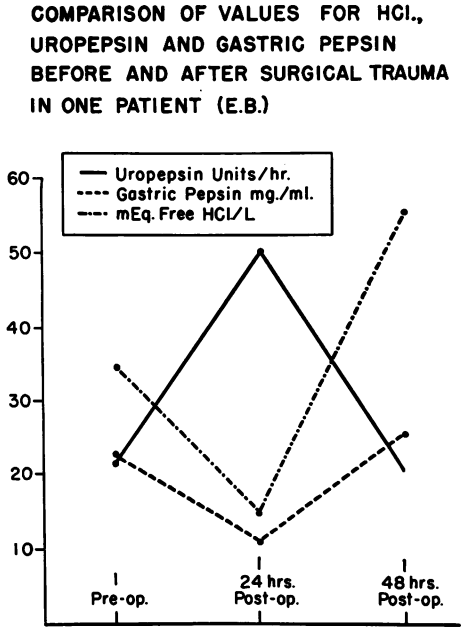

FIGURE 16

these steroids? Is it not possible that the quiescent peptic ulcer in patients under steroid therapy is unable to "stay even" with the ulcergenic process already present and become deeper and thus perforate or cause hemorrhage by erosion into a blood vessel?

We believe we have demonstrated a gastric hypersecretion in man starting within 12 to 24 hours after trauma. We have not been able to discover or demonstrate the stimulus which is responsible for this. Our work makes it seem unlikely that it is due to the Selye stress mechanism. Histamine does not seem to be involved. This leaves as an explanation, except for unknown and remote possibilities, hyperactivity of the cephalic phase mediated by the vagus nerve as the remaining possibility. The anxiety, distress and worry of the posttraumatic patient may well cause vagal stimulation. As soon as some one has the opportunity to study the occasional post-

TABLE 4. *Effect of Trauma on Gastric Secretion in Man Secretory Rate (ml./min.)*

Patient	24-Hr. Preoperative	48-Hr. Postoperative
B. A.	2.90	1.46
J. J.	0.68	0.51
E. B.	0.83	0.48
M. N.	2.39	2.42
M. E. W.	0.38	0.29
A. G.	0.82	0.25

Based on Phenol Red Method.

TABLE 5. *Effect of Trauma on Gastric Secretion in Man Pepsin mg./ml.*

Patient	Preoperative	48-Hr. Postop.	Difference
Alvey	9.03	25.63	+16.63
Wilkerson	10.60	24.10	+13.50
Fykes	17.09	21.25	+ 4.18
Johnson	16.10	27.20	+11.10
Wilson	16.00	24.40	+ 8.40
Briscoe	22.80	26.90	+ 4.10
Newman	7.95	12.60	+ 4.65
Gilbert	23.80	48.90	+25.10

Digestion of coagulated egg albumen, Method of Mett

TABLE 6. *Effect of Trauma on Gastric Secretion in Man*
Uropepsin Units/hr.

Patient	Pre-operative	24-Hr. Postop.	48-Hr. Postop.
Alvey	17.14	36.80	50.00
Wilkerson	1.94	3.06	9.00
Briscoe	24.20	50.80	21.70
Newman	9.00	17.70	Lost
Gilbert	11.70	41.40	37.50

Modified from the method of West *et al.*
Normal range 15 to 40 Units/hr.

TABLE 7. *Effect of Trauma on Gastric Secretion in Man*
Arterial Histamine (γ%)

Patient	Pre-operative	24-Hr. Postop.	48-Hr. Postop.
Alvey	7.29	8.04	12.78
Wilkerson	2.65	1.45	1.90
Briscoe	0.00	1.50	1.10
Newman	1.60	4.20	3.90

Modified bioassay of Code, using guinea pig ileum.
Normal range: 1 to 10γ%.

vagotomy patient in the post-traumatic state, we may be able to answer or confirm this.

While it seems that hypersecretion occurs after trauma, this hypersecretion per se may not necessarily be the critical factor in the post-traumatic activation of the quiescent peptic ulcer, but rather the central factor may be the presence of a much more moderate gastric secretion, which occurs in most all patients within 12 to 24 hours after trauma. Under ordinary living conditions, gastric secretion is buffered by food, saliva and duodenal regurgitation. However, the post-traumatic patient exists under a much different environment. Even with low or normal gastric secretory activity, his duodenal mucosa may actually be subjected to the activity of a highly effective digestive juice because it is completely unbuffered rather than because there is hypersecretion present.

Conclusions

1. Following trauma, there is a hypersecretion of hydrochloric acid and pepsin.
2. Post-trauma hypersecretion is not due to the increased elaboration of adrenal corticoids.
3. Cortisone does not cause hypersecretion of hydrochloric acid or pepsin.
4. In the individual patient uropepsin levels do not accurately reflect the secretory activity of the stomach.
5. "Cortisone ulcers" are not the result of hypersecretion.
6. Peptic ulcer following trauma may be due, not to hypersecretion, but to the unbuffered normal or elevated concentration of digestive juices acting on the gastric or duodenal mucosa.
7. "Cortisone ulcers" may be caused by cortisone depression of the normal healing process.

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Bibliography

1. Brush, Brock E., M. A. Black, T. Geohegan, D. C. Ensign and J. W. Sigler: The Steroid-Induced Peptic Ulcer. A. M. A. Archives of Surgery, **74**:675, 1957.
2. Drye, James C., A. M. Schoen and G. Schuster: Gastric Secretion in the Immediate Postoperative Period. A. M. A. Archives of Surgery, **67**:469, 1953.
3. Drye, James C. and A. M. Schoen: Effect of Nonspecific Trauma on Gastric Secretion. A. M. A. Archives of Surgery, **69**:450, 1954.
4. Farmer, Douglas A., P. M. Burke and R. H. Smithwick: Observations on Peptic Activity of the Gastric Contents in Normal Individuals and in Patients with Peptic Ulceration. Surgical Forum, **4**:316, 1953.
5. Fletcher, Donald G. and H. W. Harkins: Acute Peptic Ulcer as a Complication of Major Surgery, Stress, or Trauma. Surgery, **36**:212, 1954.
6. Gray, Seymour J., J. A. Benson and R. W. Reifenstein: Effect of Corticotropin and Cortisone on Gastric Secretion. J. A. M. A., **147**:1529, 1951.

7. Herbut, P. A.: Acute Peptic Ulcers Following Distant Operations. Surg., Gynec. & Obst., **80**:410, 1945.
8. Kern, Jud, Jr., G. M. Clark and J. G. Lukins: Peptic Ulceration During Therapy for Rheumatoid Arthritis. Gastroenterology, **33**:25, 1957.
9. Meena, Albert L., J. H. Conn, H. Nauman and J. D. Hardy: Pepsin in Gastric Physiology: Effect of Ulcer Diathesis, ACTH, Histamine, Anesthesia-Operation, Banthine, Pilocarpine, Epinephrine, and Sedation Upon Blood and Urine Pepsin Levels and Upon Gastric Acidity. Surgical Forum, **7**:366, 1956.
10. Sandweiss, David J.: Effects of Adrenocorticotrophic Hormone (ACTH) and of Cortisone on Peptic Ulcers. Gastroenterology, **27**:604, 1954.
11. Schoen, Arthur M. and P. K. Knoefel: The Measurement of Human Gastric Secretion. J. Lab. Clin. Med., **32**:345, 1947.
12. West, Philip M., F. W. Ellis and B. L. Scott: A Simplified Method for Determining the Excretion Rate of Uropepsin. J. Lab. and Clin. Med., **35**:159, 1952.
13. Woldman, E. E.: Acute Ulcers of the Upper Gastrointestinal Tract, Their Relation to Systemic Stress and Adrenal Damage. J. A. M. A., **149**:984, 1952.

Discussion

Dr. Benjamin F. Byrd, Jr.: I rise principally to discuss the papers of Dr. Gilchrist and Dr. Drye. The effect of stress on the stomach is probably the most momentous problem which attracts the gastro-intestinal physiologist at present. The factors of stress that affect peptic ulcer aggravation are still largely unknown, and I simply want to report on an individual who was on the surgical service of Vanderbilt University Hospital some few weeks ago with an example of this variable picture. This woman was 82 years old when she came in with abdominal pain of about four hours duration. She was taken to the operating room and explored and found to have an anterior wall perforated duodenal ulcer. This was closed and Levine tube suction was instituted; she got along very nicely. There were one or two things that worried us. She maintained a packed cell volume of about 61, and she was given serum albumin and intravenous fluids. She went along for two days and still maintained the high packed cell volume. She had had a routine physical examination one week prior to admission and no particular abnormality was found, but she had a hemoglobin of 15 grams. We still were unable to reduce the apparent hemoconcentration after 48 hours. She continued to do fairly well, and on the afternoon of the third day she expired suddenly. The postmortem examination was remarkable for two reasons.

(Slide) Suffice it to say that the anterior wall lesion was closed but she had a posterior wall ulcer that was not closed. She had had *simultaneous* perforation of non-connecting duodenal ulcers, and the posterior wall ulcer had perforated into the peritoneal cavity.

(Slide) This shows the tip of the ulcer perforation in the posterior wall.

(Slide) Here are the two ulcers; the posterior wall ulcer quite separate and distinct from the other.

Then we got to wondering what was going on in the adrenal glands. It just so happened that our assistant resident, Dr. Kenneth Classen, had become curious about her adrenal function 24 hours prior to her demise. This shows the increased 17-ketosteroids and dihydrocorticosteroids. She had an adenoma in her adrenal cortex which again fits in with the picture of functioning benign adrenal tumor.

Thus, we have an 82-year-old woman with two perforated ulcers and with a functioning adrenocortical adenoma, and we can only conclude that the continuity of events between the adrenocortical function and the peptic ulcer must have been the specific factor in the case.

Dr. Curtis Artz: Dr. Gilchrist has presented an important entity, the so-called "stress ulcer." A similar type ulcer, called Curling's ulcer, is seen in burned patients. During the period of 6½ years from December 1949, through May 1956, one thousand burned patients were hospitalized at the Brooke Army Medical Center. The total number of deaths among these patients was 80 during this period. Gastro-intestinal ulceration was found in 17 of the 80 patients. Three patients survived who were thought to have Curling's ulcer. Seven patients were entirely asymptomatic. Hemorrhage occurred in 10 instances, and 3 patients experienced abdominal pain. The majority of the ulcers occurred in the duodenum. In only seven instances were the ulcerations multiple. Three patients treated medically after severe hemorrhage survived. Two patients with continuing hemorrhage had subtotal gastrectomy and both died. There was complete failure of all incisions to heal. Both