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# Physiologic Responses to Gastric Acid Hypersecretion in Zollinger-Ellison Syndrome

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THE SYNDROME of gastric acid hypersecretion and intractable peptic ulcer associated with pancreatic islet-cell tumor was first clearly defined by Zollinger and Ellison.[1] Watery diarrhea as well as steatorrhea may also be present. Maynard and Point[2] suggested that low pH levels in the intestine result from inability of the upper small bowel to neutralize hydrogen ions produced by gastric hypersecretion. This low pH in the intestine is suboptimal for pancreatic enzyme activity. Summerskill[3] reported values as low as pH 1.50 in the jejunum in the fasting state and after meals. The continuous high rate of gastric secretion makes it difficult to assess pancreatic exocrine function by measurements of the bicarbonate or enzyme response to stimulation by secretin or pancreozymin.

This paper presents studies of 2 patients with gastric acid hypersecretion and intact stomachs. In Patient 1, pH levels at the duodenojejunal flexure following a test meal were normal and pancreatic exocrine function measured by bicarbonate secretion appeared normal. Tryptic activity of intestinal aspirates after a meal was almost normal. Diarrhea but not steatorrhea was controlled by anticholinergic therapy. Islet-cell hyperplasia without pancreatic tumor was demonstrated at total gastrectomy.

In Patient 2 intraduodenal pH levels and tryptic activity were extremely low after a test meal. Multiple pancreatic islet-cell adenomata showed histologic

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evidence of malignancy. Spontaneous gastric acid secretion could be completely suppressed in both patients by antisecretory drugs.

## CASE REPORTS

### *Case 1*

A 49-year-old male had jejunal peptic ulceration and repeated gastro-intestinal hemorrhages. Mild episodic abdominal discomfort had been present for 13 years, watery diarrhea for 10 years, and epigastric pain for 9 years. Five gastrointestinal hemorrhages occurred 1, 4, 6, 7, and 9 years after the onset of epigastric pain, with the most recent 2 months prior to the present investigation. Cholecystectomy performed shortly after diarrhea began did not reveal calculi and did not improve symptoms. Soon after the fourth bleed, when the hemoglobin was 8.8 gm./100 ml., laparotomy revealed a constricting jejunal lesion just beyond the duodenojejunal flexure, but no gastric, duodenal, or pancreatic lesions were found. A total of 10 cm. of jejunum was resected and end-to-end anastomosis was performed. A chronic jejunal ulcer extended almost completely through the muscularis with extensive scarring. Diarrhea persisted with an average of 5–6 watery stools daily, usually during the night and early in the morning. Epigastric pain returned about 6 months later.

Physical examination revealed that the patient was well nourished, with a slightly protuberant abdomen which was very tender when he was experiencing pain. Upper gastrointestinal series revealed slightly prominent gastric folds, dilation of the duodenal loop, persistent segmental narrowing just beyond the duodenojejunal flexure, and some segmentation and flocculation of barium in loops of small bowel.

The hemoglobin value was 13.9 gm./100 ml.; serum calcium, 8.0–9.7 mg./100 ml.; and fasting blood glucose, 68–84 mg./100 ml. Biopsy specimens from the proximal jejunum were histologically normal. Fecal fat losses averaged 13 and 31 gm. per day in two 2-day periods with nitrogen losses of 2.0 and 3.0 gm. per day. Gastric secretion and pancreatic function studies are detailed separately. Total gastrectomy was performed 3 months after the investigations reported here were begun. Careful exploration of the abdomen failed to reveal a tumor. The tail of the pancreas was resected and showed islet-cell hyperplasia. Although watery diarrhea ceased after surgery, steatorrhea persisted.

### *Case 2*

A 41-year-old man had malignant pancreatic tissue which secreted both a gastrin-like substance and insulin; he also had hyperparathyroidism. Episodes of mental confusion attributable to hypoglycemia began 3½ years before the studies reported in this paper. Nine months after the onset of symptoms, 3 histologically malignant pancreatic islet-cell adenomata were removed and the patient's symptoms disappeared. Eighteen months later, the patient developed diarrhea and began to lose weight. He passed a calculus in 1 of 3 episodes of ureteral colic. There was never epigastric pain. Physical examination was normal except for a small nodule in the suprasternal notch just right of the midline. Upper gastrointestinal tract X-rays revealed a coarse gastric rugal pattern, much fluid in the stomach and small intestine, and flocculation of barium in the small bowel. No ulcer crater was demonstrated. The hemoglobin value was 13.9 gm./100 ml. Fecal fat excretion was 12 and 26 gm. per day in two 3-day periods; during the second collection the patient received an anticholinergic drug, poldine, in a tolerance dose of 14 mg. q.i.d. Fasting blood glucose levels ranged from 28 to 65 mg./100 ml. A tolbutamide tolerance test and plasma insulin determinations confirmed hyperinsulinism. Serum calcium levels ranged from 10.1 to 11.7 mg./100 ml. and serum phosphorus from 2.8 to 2.0 mg./100 ml. Gastric secretion and pancreatic function studies are detailed separately. At laparotomy, multiple small histologically malignant islet-cell adenomata as large as 1.5 cm. in diameter were found to be scattered throughout the pancreas. There was a large node below the duodenojejunal flexure. Total pancreatectomy

with 45% gastrectomy was performed. There was no evidence of peptic ulceration. The duodenum was normal on histologic examination. Examination of the tumors demonstrated gastric-secretagogue activity in extracts of the large node. Hyperinsulinism has persisted since the operation but gastric acid secretion, despite the limited gastric resection, remains normal. Two years after the operation a parathyroid adenoma was removed from the patient's neck. This case has been previously reported in part.[4]

## METHODS

A tube was placed radiologically in the gastric antrum after an overnight fast and gastric juice was collected by intermittent suction of 40 mm. Hg with frequent syringe aspiration. Gastric juice was collected to measure spontaneous secretion until recoveries remained fairly constant in volume during a least 4 consecutive 15-min. periods. Maximal gastric secretion was estimated after an intramuscular injection of betazole hydrochloride (Histalog*), 1.5 mg./kg. body weight. Fluid from the small intestine was siphoned through a 12 Fr tube with a small mercury bag on the end and 6 holes in the terminal 10 cm.; the tube was placed radiologically in the duodenum or upper jejunum.

The effect of antisecretory drugs on gastric secretion and intestinal juice flow was examined after intramuscular injection of 50 mg. of hexamethonium bromide or chloride with 0.4 mg. of atropine sulphate, or by oral or intraduodenal administration of poldine (Nacton†) or tincture of belladonna. Tryptic activities were determined in intestinal aspirates collected before and after a test meal similar to the one used by Borgström.[5–7]

Hydrogen ion concentrations were determined by automatic titration to pH 7.4 with 0.1 N NaOH, chloride concentrations were determined on a Cotlove chloride titrator, and sodium and potassium concentrations by automated flame photometry. Tryptic activities were determined using N-alpha-benzoyl-arginine-ethyl-ester hydrochloride as the substrate and continuous automatic titration at pH 8.25.[8]

## RESULTS

### Gastric Secretion

The results of measurements of spontaneous and betazole-stimulated gastric secretion in the 2 patients are presented in Table 1. The electrolyte composition of the spontaneous secretion of Patient 1 is presented as the first line in Table 2. Although spontaneous secretion was excessive in each patient, stimulated secretion was much greater.

### Jejunal Juice Flow

In Patient 1 jejunal juice was siphoned from a short segment at and just beyond the duodenojejunal flexure (Table 3). During four 15-min. resting

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TABLE 1. SPONTANEOUS AND STIMULATED GASTRIC SECRETION

| Case No. | Spontaneous | | | Stimulated* | | |
|---|---|---|---|---|---|---|
| | Volume (ml./hr.) | Acid (mEq./L.) | Acid output (mEq./hr.) | Volume (ml./ 30 min.) | Acid (mEq./L.) | Acid output (mEq./ 30 min.) |
| 1 | 289 | 135 | 39 | 378† | 133 | 50 |
| 2 | 252 | 82 | 21 | 495 | 133 | 66 |

*Peak 30-min. secretion after betazole.
†Specimens were moderately bile stained.

TABLE 2. FLOW RATES AND ELECTROLYTE COMPOSITIONS OF GASTRIC, JEJUNAL, AND ALKALINE JUICES IN CASE 1

| Juice | Mean flow rate (ml./ 15 min.) | $H^+$ (mEq./L.) | $Na^+$ (mEq./L.) | $K^+$ (mEq./L.) | $Cl^-$ (mEq./L.) | $HCO_3^-$ (mEq./L.) |
|---|---|---|---|---|---|---|
| Gastric (spontaneous) | 72 | 135 | 11 | 8.4 | 157 | 0 |
| Jejunal (resting) | 182 | 17 | 86 | 7.8 | — | 0 |
| Alkaline | ? | 0 | 135 | 7.0 | 88 | 54 |

collection periods, volumes varied only from 172 to 196 ml. (mean 182 ml.), and hydrogen ion concentrations varied from 10 to 32 mEq./L. (mean 17 mEq./L.). Mean electrolyte concentrations for these 4 periods are presented in the second line of Table 2. For 90 min. following a test meal, the pH levels of intestinal juice samples were similar to those found in normal patients.[5, 9] The mean tryptic activity of 8.8 μEq./min./ml. in the 90-min. period after the test meal is only slightly below the 9.6 μEq./min./ml. lower limit of normal patients.[7]

In Patient 2 juice was collected from the fourth part of the duodenum before and during 4 consecutive ½-hr. periods after the test meal (Table 3). Tryptic activities and pH levels in the duodenal aspirates were very low and showed only a temporary rise in the first ½ hr. after the test meal. The aspirates had the appearance of almost pure gastric juice except for the first ½ hr.

*Effect of Gastric Acid Secretion*

In Patient 1 the average volume of jejunal juice recovered prior to stimulation of gastric acid secretion, 182 ml./15 min. (Table 2), was similar to the maximal gastric acid output after stimulation by betazole and 2½ times the spontaneous gastric acid output of 72 ml./15 min. (Table 1). Similar volumes of jejunal juice and gastric juice were recovered on other occasions. A solution containing two dilution indicators, $^{51}Cr$ chromic chloride and phenol red, was infused slowly into the cardiac end of the stomach and small volumes of juice were aspirated at 10-min. intervals from the gastric antrum and from

TABLE 3. pH ACID CONCENTRATION, AND TRYPTIC ACTIVITY IN DUODENO-JEJUNAL OR DISTAL DUODENAL ASPIRATES COLLECTED BEFORE AND AFTER A TEST MEAL

| *Period (min.)* | *Volume (ml.)* | *pH* | *Acid (mEq./L.)* | *Tryptic activity (μEq./min./ml.)* |
|---|---|---|---|---|
| | | CASE 1 | | |
| Fasting | | | | |
| 0–15 | 196 | 4.6 | 12 | 1.4 |
| 15–30 | 172 | 6.45 | 10 | 3.6 |
| 30–45 | 186 | 2.55 | 32 | 0.1 |
| 45–60 | 174 | 5.3 | 13 | 2.5 |
| After test meal | | | | |
| 0–10 | 110 | 6.5 | — | 6.8 |
| 10–20 | 106 | 6.4 | — | 6.1 |
| 20–30 | 70 | 6.95 | — | 14.0 |
| 30–40 | 28 | 7.05 | — | 11.8 |
| 40–50 | 47 | 5.6 | — | 11.0 |
| 50–60 | 102 | 6.9 | — | 12.5 |
| 60–70 | 61 | 6.25 | — | 11.2 |
| 70–80 } 80–90 } | 265 | 4.65 | — | 6.3 |
| | | CASE 2 | | |
| Fasting | | | | |
| 0–10 | 134 | 1.45 | 43 | <2 |
| After test meal | | | | |
| 0– 30 | 166 | 5.7 | — | 5.0 |
| 30– 60 | 275 | 1.5 | — | <2 |
| 60– 90 | 420 | 1.2 | — | <2 |
| 90–120 | 106 | 1.5 | — | <2 |

the proximal jejunum. Results calculated from the chromic chloride marker indicated a jejunal flow rate 2–3 times the gastric secretory rate. Disparity between the 2 markers was consistent with absorption of 47 ± 14% of the phenol red from the stomach proximal to the collection site and 61 ± 11% before the jejunum was reached.

*Effect of Gastric Juice Aspiration*

Jejunal and gastric juices were recovered from Patient 1 through 2 separate tubes placed radiologically in the proximal jejunum and in the gastric antrum (Table 4). Jejunal aspiration was begun first and large volumes of juice were obtained with pH levels as low as 1.95 and acid concentrations as high as 24 mEq./L. Jejunal flow rate decreased rapidly after gastric aspiration began and the pH of the jejunal aspirates rose to 8.5.

## Composition of the Alkaline Juice

Although acid juice was recovered most of the time from the sampling tube when it was placed in the second part of the duodenum, quite large volumes

TABLE 4. JEJUNAL JUICE FLOW AND GASTRIC ACID OUTPUT IN CASE 1

| | *Consecutive 15-min. periods (No.)* | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Juice* | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* |
| Gastric | | | | | | | | | | | | | | | | | | | |
| Volume | — | — | — | 226 | 113 | 108 | 97 | 65 | 7 | 3 | 0 | 1 | 0 | 0.5 | 1 | 3 | 7 | 19 | 21 |
| pH | — | — | — | 1.2 | 1.15 | 1.15 | 1.2 | 1.25 | 1.2 | 1.35 | — | 1.7 | — | 2.0 | 2.75 | 3.0 | 4.85 | 2.6 | 1.9 |
| Acid (mEq./L.) | — | — | — | 112 | 119 | 122 | 115 | 100 | 116 | 74 | — | 46 | — | 46 | 28 | 18 | 9 | 18 | 23 |
| Jejunal | | | | | | | | | | | | | | | | | | | |
| Volume | 116 | 94 | 166 | 165 | 48 | 3 | <1 | 0 | 0 | 0 | 9 | 7 | 10 | 6 | 4 | 7 | 15 | 4 | 5 |
| pH | 4.15 | 1.95 | 2.15 | 3.05 | 7.25 | 8.5 | — | — | — | — | 8.15 | 8.4 | 7.65 | 8.0 | — | 8.25 | 7.1 | 8.4 | 8.15 |
| Acid (mEq./L.) | 8 | 24 | 16 | 9 | 1 | 0 | — | — | — | — | 0 | 0 | 0 | 0 | — | 0 | — | 0 | 0 |

Gastric juice aspiration began at the end of Period 3. The 50 mg. hexamethonium chloride and 0.4 mg. of atropine was given by intramuscular injection at the end of Period 7.

of alkaline, lightly bile-stained opalescent juice were obtained at intervals. The electrolyte composition of the most alkaline sample is given as the third line in Table 2. The bicarbonate concentration was calculated as the difference between the sum of the sodium and potassium concentrations and the chloride concentration in mEq./L.

### Effect of Antisecretory Drugs

Intramuscular injection of 50 mg. of hexamethonium bromide or chloride with 0.4 mg. of atropine sulphate caused a temporary cessation of gastric acid secretion in both patients (Table 4). The results in Case 2 have been reported elsewhere.[4] Anticholinergic drugs were given orally to tolerance in both patients. Patient 2 received poldine in a maximum tolerance dose of 14 mg. q.i.d. In the third hour after the day's first dose, gastric acid output was reduced to 2.9 mEq. or to 14% of the spontaneous gastric acid output of 21 mEq./hr. Patient 1 received tincture of belladonna. There were mild side effects after a dose of 18 drops given q.i.d. In a 1-hr. period which began 3½ hr. after the day's first dose, gastric acid output was reduced to 10.5 mEq. or to only 27% of the spontaneous gastric acid output of 39 mEq./hr. When belladonna was increased to 20 drops 5 times a day, which included a 2 A.M. dose, stool output decreased from 5–6 watery stools to 1–2 well-formed stools a day. The fecal fat excretion was 13 and 31 gm. per day in two 2-day periods before belladonna was given, and 12.5, 23, and 24 gm. per day during three 3-day periods with belladonna given in a maximum tolerance dose. Abdominal pain and bloating decreased, although steatorrhea did not.

## DISCUSSION

Knowledge of dilution of acid gastric juice in the duodenum[10] is almost as old as recognition of the presence of hydrochloric acid in gastric juice.[11] Pavlov found that pancreatic secretion is proportional to the amount of acid entering the duodenum.[12] Bayliss and Starling showed that this effect was mediated by a hormone which they named secretin.[13] In dogs with chronic pancreatic fistulas, pancreatic response was related to the total amount of acid which entered the duodenum, rather than to the volume or concentration.[14] When acid, secreted by the stomach in response to maximal histamine stimulation, entered the duodenum, bicarbonate output from the pancreas equalled the maximal pancreatic response to secretin infusions. Lagerlöf *et al.*[15] used continuous acid infusions into human stomachs to show a linear relationship between the amount of acid which entered the intestine and the rate of bicarbonate secretion. Since an alkaline fluid with bicarbonate concentration of about 40 mEq./L. was secreted in response to acid infusion in patients with gross pancreatic insufficiency, organs other than the pancreas must contribute to the diluting fluid. Neutralizing capacity as high as 30 mEq./hr. has been found when acid was infused directly into the human duodenum.[16, 17] Neu-

tralization does actually occur high in the duodenum, since when gastric secretion is maximally stimulated by betazole in normal man, most of the excess acid delivered through the pylorus has disappeared by the time the postbulbar duodenum is reached.[18, 19] The maximal stimulated secretory capacities of the stomach for hydrogen ions[20–22] and of the glands which secrete bicarbonate in response to secretin[22–25] are similar. Thus the quantity of alkaline fluid secreted into the duodenum in man has the neutralizing capacity required for normal gastric output.

This alkaline fluid is composed of the secretions of the pancreas, liver, and Brunner's glands. The bicarbonate contents of canine pancreatic juice and hepatic bile are flow-dependent and rise to maximal concentrations of 130–160 mEq./L. for pancreatic juice[26, 27] and 60 mEq./L. for bile.[28] The bicarbonate concentration of secretions of Brunner's glands may reach 90 mEq./L. in some animals.[29] Infusion of acid into the jejunum stimulates all of these secretions; secretin is the mediator for pancreatic juice and bile, but another hormone may stimulate Brunner's glands.[30, 31] In normal man gastric acid is also buffered by food and saliva, which may have a bicarbonate concentration as high as 60 mEq./L.[32]

In the patient in Case 1 there was a continuous outpouring into the duodenum of alkaline juice with a bicarbonate concentration of about 54 mEq./L. The osmolality of the jejunal aspirates, as indicated by the sum of the sodium, potassium, and hydrogen ion concentrations (Table 2) is considerably lower than that of plasma or any gastrointestinal secretion obtained during fasting.[33] This low osmolality can be explained; mixing acid gastric juice with alkaline duodenal juice leads to the formation of carbon dioxide and its loss by diffusion through the epithelium. If this juice is a mixture of acid gastric juice and alkaline duodenal juice and if the net movement of water and ions across the mucosa is small, volume flow of alkaline duodenal juice and the bicarbonate output can be calculated from data in Table 2. If $G$, $J$, and $A$ represent gastric juice, jejunal juice, and alkaline duodenal secretions, respectively, and $V$ is the volume flow in milliliters per 15 min., and $(H^+)$, $(HCO_3^-)$, and $(Na^+)$ are the hydrogen, bicarbonate, and sodium ion concentrations in mEq./L, then:

$$(H^+)_G \times V_G - (H^+)_J \times V_J = (HCO_3^-)_A \times V_A \qquad (1)$$

or: $135 \times 72 - 17 \times 182 = 54 \times V_A$; $V_A = 123$ ml./15 min. by this calculation.

$$(Na^+)_G \times V_G + (Na^+)_A \times V_A = (Na^+)_J \times V_J \qquad (2)$$

or: $11 \times 72 + 135 \times V_A = 86 \times 182$; $V_A = 110$ ml./15 min. by this alternate calculation. These calculated values of 123 and 110 ml./15 min. differ little from 110 ml./15 min., the observed difference between recovered volumes of jejunal juice and gastric juice. Thus the net movement of water and ions across the duodenal mucosa contributed little to neutralization of gastric acid during its passage through the duodenum. An alkaline juice flow rate of

110 ml./15 min. with a bicarbonate concentration of 54 mEq./L. gave the bicarbonate output of 24 mEq./hr., similar to the mean maximal output of about 30 mEq./hr. in normals.[22–25] This effective bicarbonate secretion together with the buffering capacity of food resulted in normal or nearly normal pH levels in the upper small bowel of the first patient for at least 90 min. after a meal.

In contrast, in the patient in Case 2 low pH levels in the distal duodenum both before and after the test meal showed that acid was neutralized much less effectively. This may have been due to organic pancreatic insufficiency or to pancreatic exhaustion. A dissociated pancreatic exhaustion was shown in dogs with chronic pancreatic fistulas by prolonged stimulation with continuous secretin infusions. Bicarbonate concentration in the fistula juice declined over several hours to about 40 mEq./L. below the initial peak bicarbonate concentration, while the volume did not change.[27, 34] This phenomenon may be partially responsible for the apparently grossly abnormal pancreatic function before operation in Patient 2. It may also account for the observation of Vogel *et al.* that abnormal pancreatic function in a patient with Zollinger-Ellison syndrome was followed by normal function when spontaneous gastric hypersecretion was controlled by atropine.[35] It is also possible, but not demonstrated, that large quantities of acid continuously entering the duodenum may cause chronic depletion of secretin with secondary functional pancreatic insufficiency. The very low tryptic activities in the intestinal aspirates of Patient 2 do not necessarily indicate subnormal trypsin secretion since trypsin, although most stable at pH 3 and stable even below that pH in the absence of pepsin, is inactivated by peptic digestion at these levels.

Excessive spontaneous gastric acid secretion can be effectively reduced by antisecretory drugs in some patients with Zollinger-Ellison syndrome.[4] Administration of 50 mg. hexamethonium bromide or chloride with 0.4 mg. of atropine sulphate by intramuscular injection caused temporary anacidity in both patients described in this paper. One patient (Case 2) was proven to have a "gastrin"-secreting tumor. Belladonna (Case 1) or poldine (Case 2) in maximal tolerance doses taken orally effectively reduced spontaneous gastric acid secretion without reducing fecal fat losses. The bowel habit of the first patient changed from 5–6 watery stools to 1–2 well-formed stools daily. The relationship demonstrated between the scheduling of anticholinergic drugs and diarrhea suggested that excessive spontaneous gastric secretion was as much responsible for watery diarrhea as any effect on pancreatic enzymes secreted after food. In contrast to our results, steatorrhea has been effectively reduced by anticholinergic drugs in 2 patients.[35, 36] However, the maximal gastric acid output in these patients was much less than in ours and control of spontaneous gastric secretion in one[35] resulted in a normal acid secretory pattern.

The pathophysiology of the diarrhea which occurs in 36% of patients with

the Zollinger-Ellison syndrome is complex.[37] Watery diarrhea, steatorrhea, or both occur. The pancreatic tumors may cause an exocrine insufficiency of bicarbonate and enzymes. Even with normal pancreatic function, gastric hypersecretion can overwhelm the maximal neutralizing capacity of the proximal small bowel. A low intraluminal pH results. The possible causes of diarrhea include:

1. The low pH in the intestine irritates the mucosa and could increase the motor responsiveness of the bowel and reduce transit time.[38] The persistence of irritation well into the upper intestine is evidenced by the 25% of ulcers which lie beyond the first part of the duodenum in patients with this syndrome.[37] Thus acid peptic digestion in the Zollinger-Ellison syndrome extends well beyond the sites of ordinary peptic ulcer. In addition to peptic ulceration, histologic abnormalities include blunting of villi and atypism of cells,[35, 39] but these were absent in Patient 1 except near the jejunal peptic ulcer, and were entirely lacking in Patient 2. Such an irritant effect would not subside as soon as introduction of acid gastric juice into the duodenum is decreased by gastric aspiration or by an anticholinergic drug. The persistent steatorrhea may be due to this mechanism but it is unlikely that it caused the watery diarrhea of Patient 1. In Patient 2, whose intestinal pH was lower and in whom neutralization was less effective, watery diarrhea was not present.

2. Large volumes of acid and diluent in the small bowel could cause an osmotic watery diarrhea. This type of diarrhea will respond quickly to measures which control spontaneous gastric hypersecretion, such as anticholinergic drugs (Case 1),[36] or which limit entry of acid into the duodenum, such as continuous gastric aspiration.[38, 40] Such diarrhea would be similar to that of lactase deficiency or that which occurs after oral mannitol administration.

3. Failure to absorb nutrients may be caused by mucosal malabsorption or pancreatic insufficiency. The former is suggested by the histologic[35, 39] and functional[41] abnormalities found in some patients. Pancreatic insufficiency can be primary (organic) or secondary to chronic depletion of duodenal secretin, pancreatic exhaustion,[27, 34] or a low intraluminal pH. The low pH is suboptimal for the action of pancreatic enzymes and probably also suboptimal for the hydrolytic enzymes of the brush border. It is optimal for the peptic degradation of these enzymes. Although these changes may well account for steatorrhea, it is not clear how they relate to watery diarrhea.

4. Occasionally patients with pancreatic islet-cell tumors and watery diarrhea have normal gastric secretion or even anacidity.[42] Because diarrhea has ceased following removal of such a tumor and tumor extracts have failed to show gastrin-like activity, a humoral factor other than gastrin has been postulated..[42, 43] Such a hormone has not yet been clearly identified. The results for the patient in Case 1 implied that the large volume of juice flowing through the upper small bowel and the watery diarrhea were directly related to the excessive acid secretion. This was shown by the cessation of jejunal flow

following gastric aspiration and the decrease in watery diarrhea with belladonna. There is no need to postulate a second humoral factor for this patient.

The use of markers in gastrointestinal research has come under critical review in recent years.[44–46] Chromic chloride is poorly absorbed at low pH levels, but phenol red, although poorly absorbed at ordinary intestinal pH, is absorbed from an acid medium. In Patient 1, in whom the intraluminal pH was acid in the fasting state at least as far as the proximal jejunum, very significant amounts of phenol red were absorbed from both the stomach and the duodenum.

## SUMMARY

Two patients with gastric acid hypersecretion and intact stomachs had diarrhea with steatorrhea. In 1 patient continuous outpouring of large volumes of alkaline juice into the duodenum, combined with the buffering capacity of food, resulted in normal or near normal pH levels in the upper small intestine for at least 90 min. after a meal. The tryptic activities in intestinal aspirates after the meal were essentially normal. Watery diarrhea was controlled when an anticholinergic drug was given both night and day, but steatorrhea was not reduced. In the other patient the alkaline secretions of the upper intestine were inadequate to neutralize the gastric acid output. The mechanisms by which acid secreted by the stomach is neutralized in the upper small bowel and the mechanisms of diarrhea are discussed.

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## Bockus International Society of Gastroenterology

### *Tenth Anniversary*

The tenth anniversary of the Bockus International Society of Gastroenterology will be celebrated in conjunction with the forthcoming gastroenterology sessions at Philadelphia during the week of May 12, 1968. The Bockus Society represents alumni of the Graduate School of Medicine, University of Pennsylvania, from the United States, Canada, and 29 foreign nations.

Members and guests of the Society will pay special tribute to Dr. H. L. Bockus at a banquet to be held at the Overbrook Country Club, Friday, May 17. The regularly held business meeting of the Society will be at luncheon, Saturday, May 18, at the Bellevue-Stratford Hotel.

Further information may be obtained from DR. W. S. HAUBRICH, Secretary, The Henry Ford Hospital, Detroit, Mich. 48202.