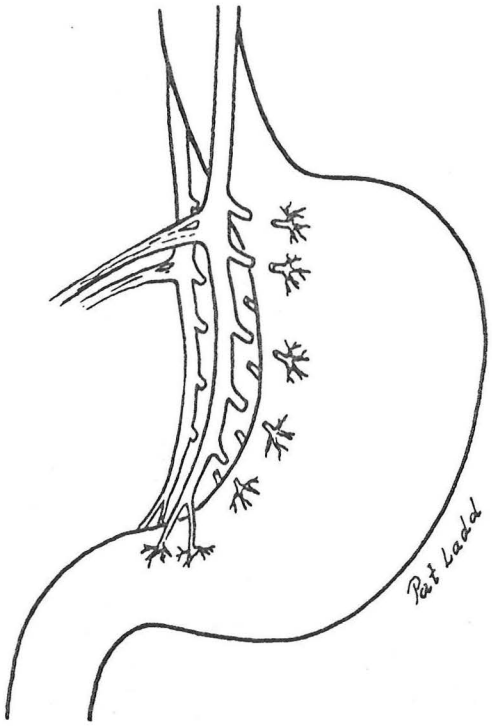
Gastro

SURGICAL THERAPY OF PEPTIC ULCER DISEASE



MEDICAL GRAND ROUNDS

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INCIDENCE OF PEPTIC ULCER DISEASE

According to some reports, deaths and hospitalizations resulting from peptic ulcer disease have decreased in the United States and United Kingdom during the past several years (1-6). The decrease in mortality is illustrated in Figure 1 while the decrease in hospitalizations are shown in Figure 2 (7).

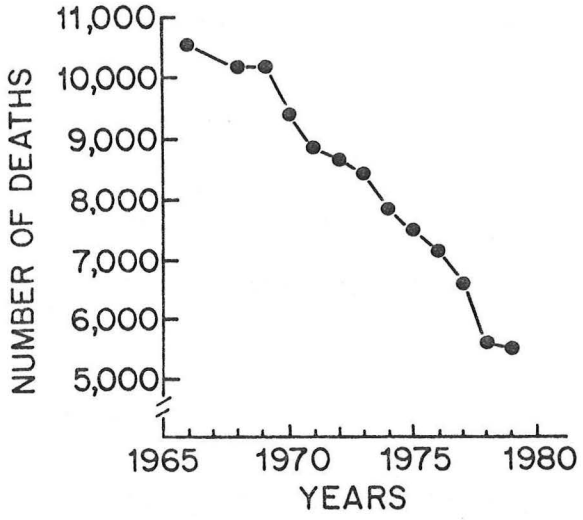

Figure 1. Number of deaths from ulcer disease in the United States from 1965-1980 (Adapted from Ref. 7).

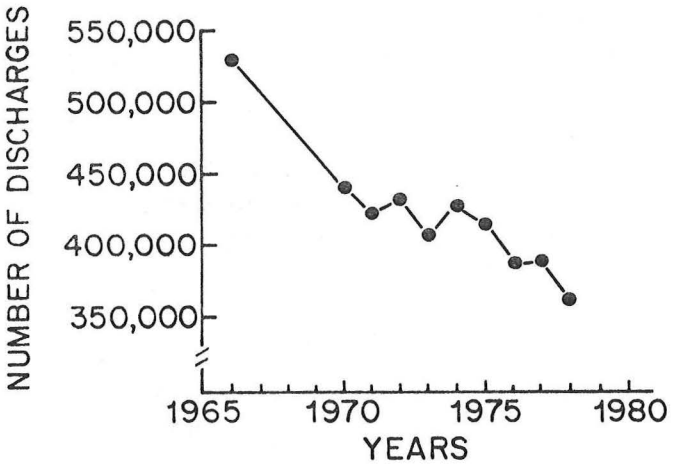

Figure 2. Hospitalizations for ulcer disease in the United States from 1965-1980. Data based on hospital discharges (Adapted from Ref. 7).

The reasons for these changes are unclear although several possible explanations have been given. These are listed in Table 1.

TABLE 1. POSSIBLE REASONS FOR DECREASE IN DEATHS AND HOSPITALIZATIONS FROM ULCER DISEASE (ADAPTED FROM REF. 1 AND 6)

1. True decrease in ulcer disease incidence.

   COMMENT: While there may be a slight reduction in incidence, it seems unlikely that this is a major factor. The incidence of ulcers actually has been increasing in women.

2. Fewer presumptive diagnoses of ulcer disease with the advent of endoscopy.

   COMMENT: Endoscopy clearly is better than barium x-ray at making a diagnosis of ulcer disease. Thus, some patients that once were diagnosed as having ulcer disease by x-ray, in reality may not have had ulcer disease at all. This would have led to over reporting of ulcers. This does not mean, however, that all patients with symptoms suggesting ulcer disease should have endoscopy to make a diagnosis. Some of the indications for endoscopy in patients with suspected ulcer disease are discussed in other parts of this protocol.

3. Changes in hospitalization criteria.

   COMMENT: This could account for some of the statistical changes relative to reduction in hospitalizations for ulcer disease. This especially is true with recent changes in health care delivery and the major emphasis on cost-effective medical care. Reductions in hospitalizations for ulcer disease began, however, before many of the recent changes in health care delivery. Thus, it is unclear whether these changes played a role in decreased hospitalizations. Changes in medical therapy of ulcer disease also may have played a role. For example, several years ago, hospitalization was recommended as a method of treating many patients with uncomplicated ulcer disease, especially those with gastric ulcers. This no longer is recommended except in patients with complications.

4. Changes in coding practices.

   COMMENT: There have been several changes during the past 20-30 years in the ICD-9 coding for ulcer disease. Evidence suggests that this may be a major factor in the decline in reported gastric ulcer mortality rates.

5. New medical therapies.

   COMMENT: The decrease in hospitalizations and deaths from peptic ulcer disease began prior to the widespread use of cimetidine and ranitidine. However, with the development of these drugs and with the advent of even more potent compounds, it is likely that hospitalizations and deaths from ulcer disease will decline even further.

While some reports (1-6) indicate that mortality from ulcer disease is decreasing, other statistics indicate that mortality in the United States may be on the increase. For example, data from the U.S. Office of Vital Statistics show that ulcer mortality increased from 2.5 to 2.7/100,000 people from 1978 to 1979 (8,9) and in 1982 increased to 3.0/100,000 inhabitants (10). Whether this trend will continue or level off remains to be determined.

Data also is available from other countries. Bonnevie reviewed data from the entire population of Copenhagen County, Denmark and found no appreciable change in peptic ulcer incidence between 1963 and 1978 (11,12). On the other hand, in Hong Kong there was a 21% increase in hospital admissions and a 14% decrease in deaths from peptic ulcer disease from 1970 to 1980 (13). In women in West Germany, there was an increase in mortality due to gastric and duodenal ulcers. Conversely, in men duodenal ulcer mortality has been relatively stable while gastric ulcer mortality has decreased (14).

SUMMARY: It is unlikely that the true incidence of peptic ulcer disease is diminishing in the United States. It is likely that hospitalizations for ulcer disease are decreasing. Whether mortality is decreasing slightly, remaining unchanged or even increasing slightly is unclear at the present time. It is likely that mortality will decrease in the future with the advent of better medical treatments.

INCIDENCE OF SURGERY FOR PEPTIC ULCER DISEASE

Data from the United States and United Kingdom suggests that the incidence of surgery for ulcer disease (especially duodenal ulcers) has decreased during the past 10-15 years. Prior to the development of H_2-receptor antagonists, surgical therapy for ulcer disease was diminishing. Thus, while these new drugs may have contributed to a recent decline in surgery (see below), they were not the inciting factor(s), especially for partial gastrectomy and vagotomy as a mode of surgical therapy (Figure 3). Parietal cell vagotomy, as a surgical technique, may have contributed to the decline in partial gastrectomy and vagotomy as a widely used form of ulcer surgery.

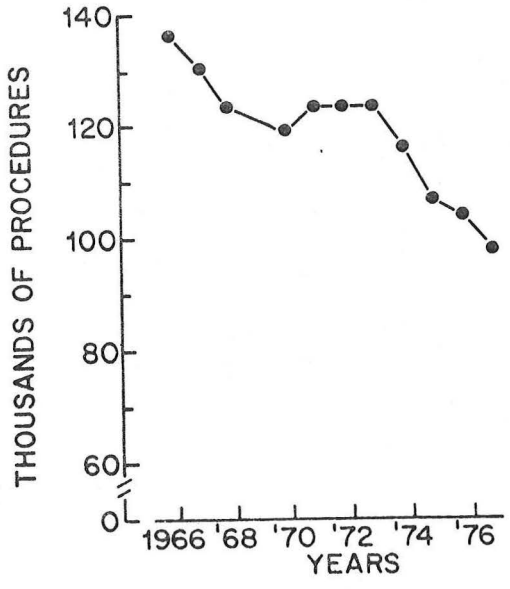

Figure 3. Decrease in the use of partial gastrectomy and vagotomy as a method of treating patients with ulcer disease from 1966-1976 (adapted from Ref. 7).

Data obtained from three Seattle-area hospitals suggests, however, that other forms of surgical therapy also declined during the 10-year period from 1966-1975 (15). Results of the Seattle survey are illustrated in Figure 4. Six hundred and twenty-five patients with duodenal ulcers were treated by vagotomy, gastrectomy, or vagotomy plus gastrectomy from 1966-1970, while only 395 were treated with one of these procedures from 1971-1975.

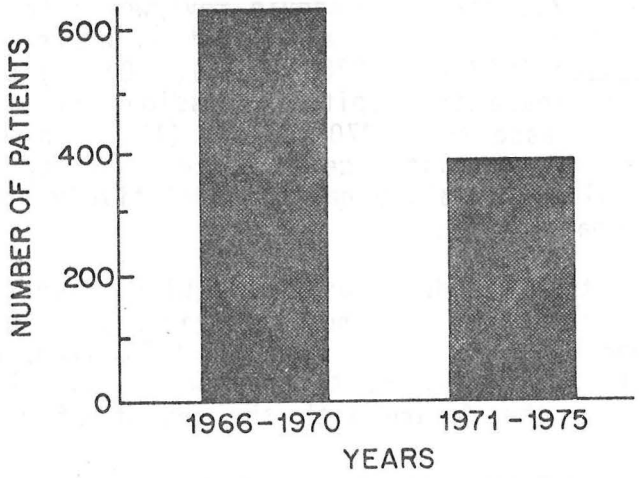

Figure 4. The number of patients with duodenal ulcer disease who had vagotomy, gastrectomy, or vagotomy plus gastrectomy in three Seattle-area hospitals (adapted from Ref. 15).

Further decline in surgical treatment of ulcer disease can be attributed to development of H_2-receptor antagonists. As illustrated in Figure 5, there was a sharp reduction in ulcer surgery from 1976 to 1977 in the United Kingdom (cimetidine was first marketed in the United Kingdom in 1976 and in the United States in 1977) (16). Recent data from the United States also suggests that the incidence of ulcer surgery has decreased as medical therapy of ulcer disease has improved.

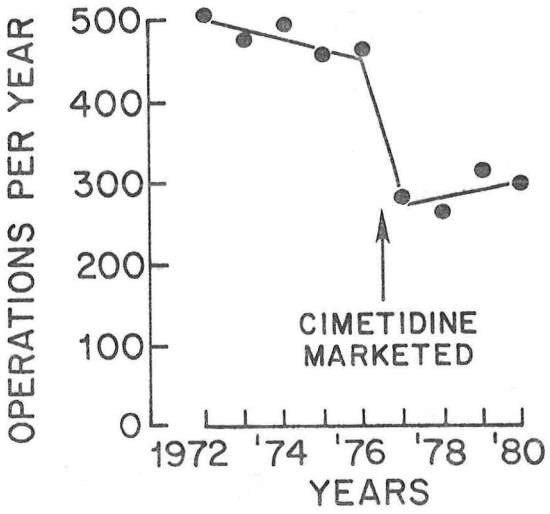

Figure 5. Incidence of surgery for ulcer disease in the United Kingdom from 1972 to 1980. The sharp decrease in operations for ulcer disease after 1976 has been attributed to the marketing of cimetidine (adapted from Ref. 16).

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PHYSIOLOGICAL BASIS FOR PEPTIC ULCER SURGERY

The causes of either duodenal or gastric ulcers are not known. It is believed that some patients develop ulcers because of too much acid and pepsin. Some patients acquire ulcers because of defective mucosal protective mechanisms, while others develop ulcers because of additional factors [genetics, emotional stress, non-steroidal anti-inflammatory drugs, infectious agents (? campylobacter), etc.]. Regardless of the cause of ulcers, most medical and surgical treatments are designed to reduce acid secretion, neutralize acid or prevent acid and pepsin from reaching the ulcer crater.

From a physiologic point of view, as far as acid secretion is concerned, the stomach is divided into two major parts (Figure 6).

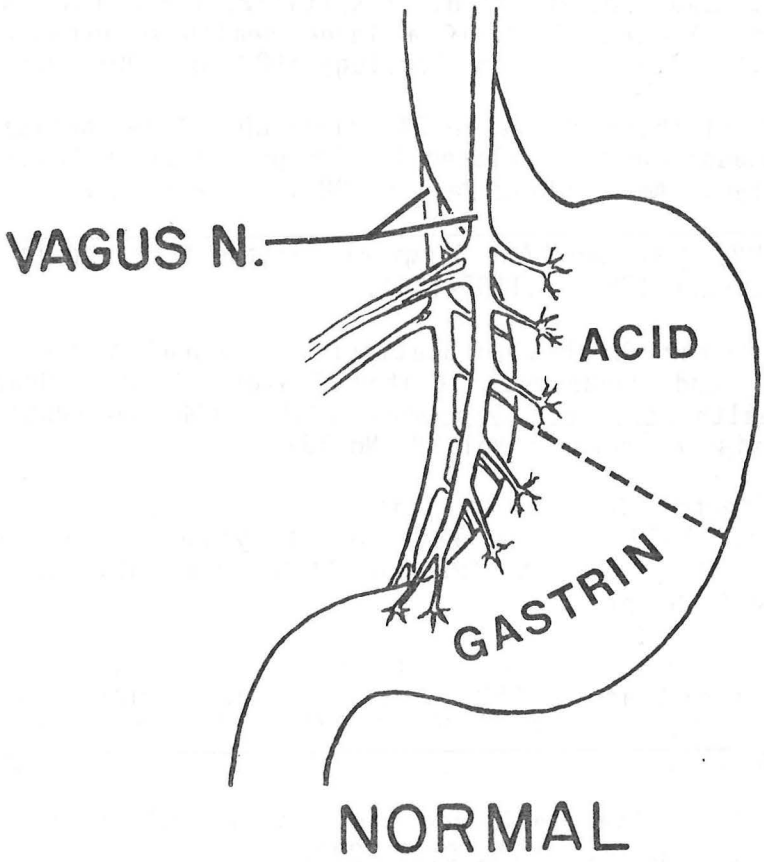

Figure 6. Physiologic anatomy of the stomach.

The upper part of the stomach (fundus and upper body) contains acid-secreting, parietal cells and pepsinogen-secreting, chief cells. The lower portion of the stomach contains the G-cells which produce the hormone, gastrin. Both the parietal and chief cell area and the G-cell area are innervated by the vagus nerves (Figure 6).

Physiology of Acid Secretion

There are two major types of acid secretion: basal or unstimulated secretion and acid secretion that is stimulated by exogenously administered histamine or pentagastrin or endogenously ingested food. Basal acid secretion is that which occurs in the absence of all intentional or avoidable stimulation. Acid secretion measured during sleep (nocturnal acid secretion) or acid secretion measured in the morning after an overnight fast are examples of basal acid secretion (1-3).

Food is the most important physiological stimulant of acid secretion. There are three mechanisms whereby food stimulates acid secretion: 1) cephalic-vagal stimulation, 2) distention-induced acid secretion, and 3) acid secretion stimulated by food interacting with gastrointestinal mucosa. Acid secretion in response to cephalic-vagal stimulation is called the cephalic phase of acid secretion while acid secretion in response to gastric distention and chemical reactions of food (especially protein) with gastric mucosa is called the gastric phase (Table 2). Once food leaves the stomach and enters the small intestine the intestinal phase is activated. Surgery for peptic ulcer diseases primarily alters the cephalic and gastric phases (vagotomy with or without antrectomy).

TABLE 2. PHASES AND MEDIATORS OF ACID SECRETION AS THEY RELATE TO SURGERY FOR PEPTIC ULCER DISEASE

PHASES OF ACID SECRETION	MEDIATORS
CEPHALIC	VAGUS N.
GASTRIC	VAGUS N. + GASTRIN

There are three important endogenous mediators of acid secretion. These are acetylcholine, gastrin and histamine. Acetylcholine is the vagal (neural) mediator of acid secretion while gastrin produced by G-cells in the antrum (Figure 6) is the hormonal mediator. Histamine is released by mast cells located in the lamina propria of the stomach near parietal cells and stimulates acid secretion by a paracrine mechanism. These three chemicals act on receptors believed to be located on the membrane of parietal cells and thus, stimulate acid secretion by this mechanism. Calcium ions also are important in stimulating acid secretion. Both calcium and magnesium ions stimulate release of gastrin.

Cephalic-Vagal Stimulation. The thought, sight, taste, smell and chewing of appetizing food activate centers within the hypothalamus of the brain that send messages to the dorsal motor nucleus of the vagus nerves. In turn, signals are transmitted to the stomach via these nerves (4). The preganglionic nerves terminate on the cell bodies of postganglionic nerves in the wall of the stomach. The postganglionic neurons are believed to terminate near receptors on parietal and gastrin cells. In turn, acid is secreted and gastrin is released (Figure 7).

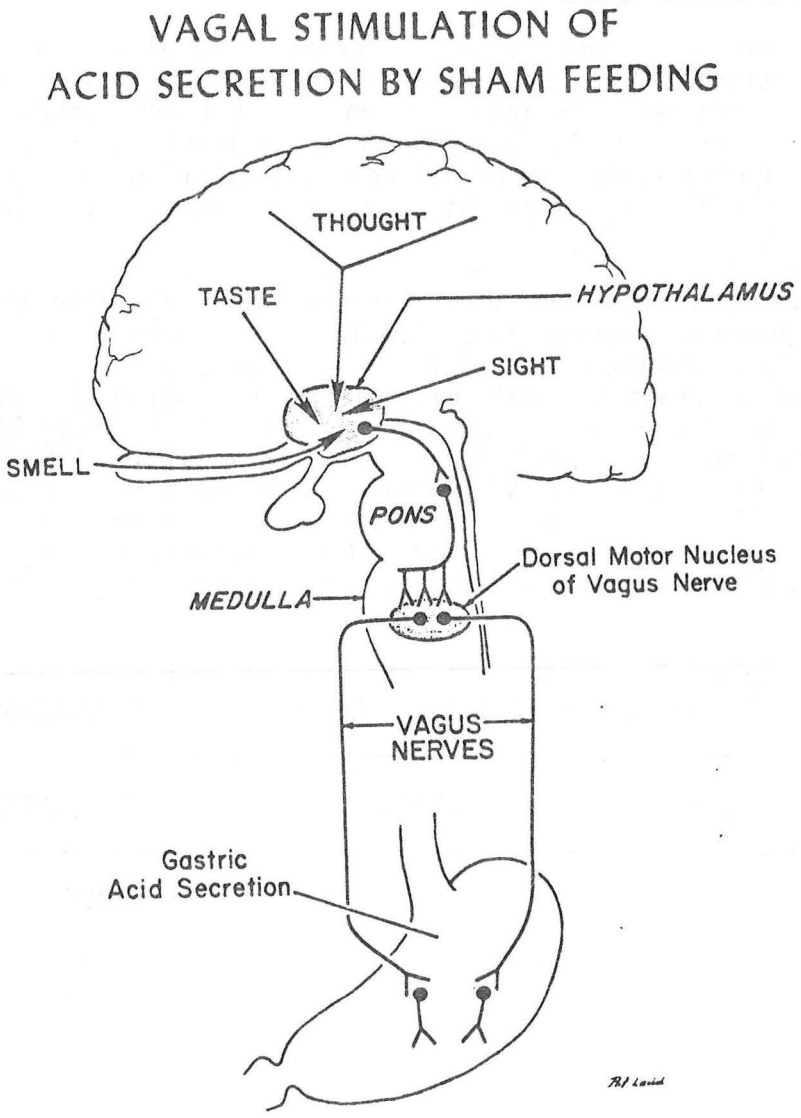

Figure 7. Model illustrating activating factors and neural pathways of the cephalic phase of acid secretion.

In humans and animals, cephalic-vagal stimulation of acid secretion can be evaluated by measuring acid secretion in response to sham feeding (5-11) (see section on Recurrent Ulcer Disease). In animals, sham feeding is carried out by surgically constructing an esophageal fistula. Animals eat food but the food exits through the fistula (12). In normal human subjects or patients with ulcer disease, sham feeding is carried out by having subjects or patients chew and spit out an appetizing steak and potato meal (modified sham feeding).

Acid secretion in response to sham feeding in normal subjects is illustrated in Figure 8.

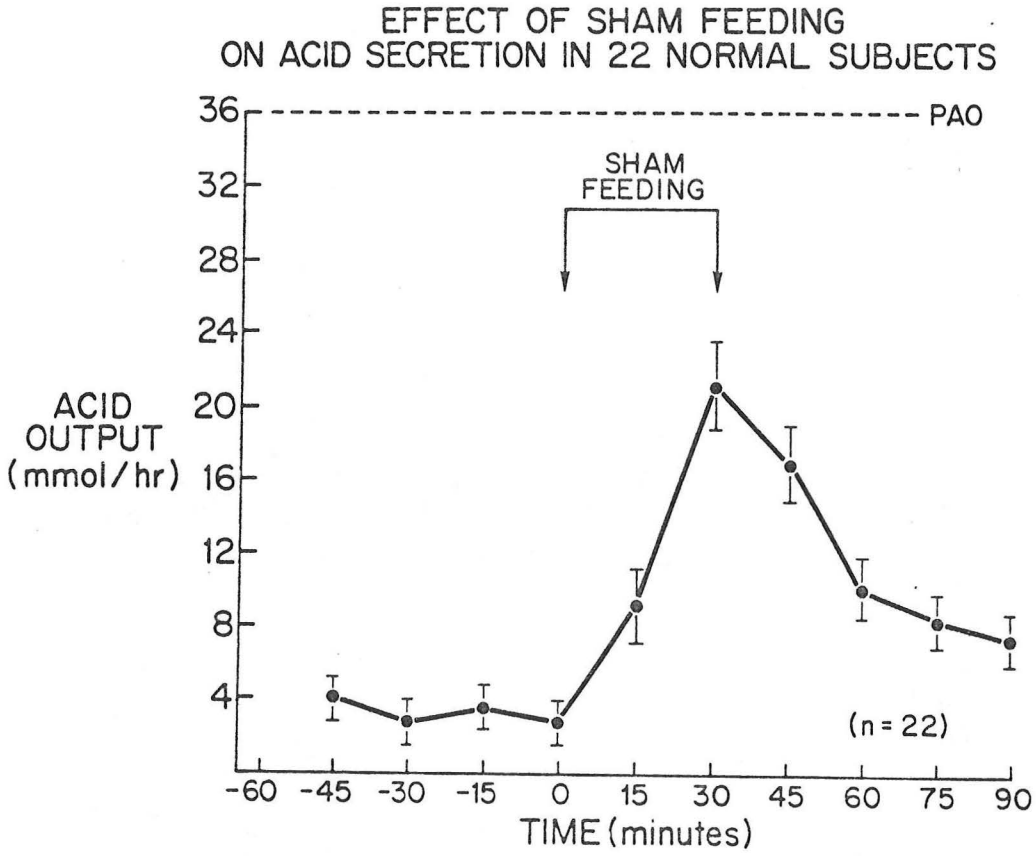

Figure 8. Effect of modified sham feeding on acid secretion in normal subjects. Basal acid secretion (measured from -60 to 0 minutes) and peak acid output in response to pentagastrin (PAO) are shown for comparison (from Ref. 1).

While sham feeding causes a relatively large increase in acid secretion in humans, the individual sensory stimuli that make up the sham feeding response, when evaluated independently, can also stimulate acid secretion (13). For example, acid secretion in response to the discussion of food is illustrated in Figure 9. In these experiments appetizing food was discussed with normal human subjects on one day while on another day (control), a topic such as sports or art was discussed. As shown in Figure 9, acid secretion increased in response to food discussion but did not increase during control discussion.

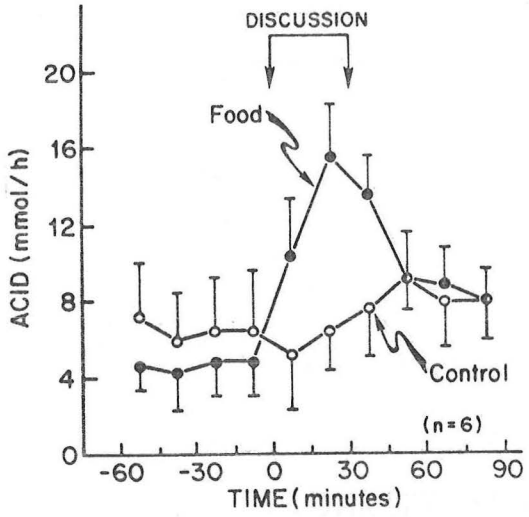

Figure 9. Effect of food discussion and control discussion in 6 normal subjects (from Ref. 13).

Acid secretion also increases with sight of food, smell of food and sight and smell of food as shown in Figure 10.

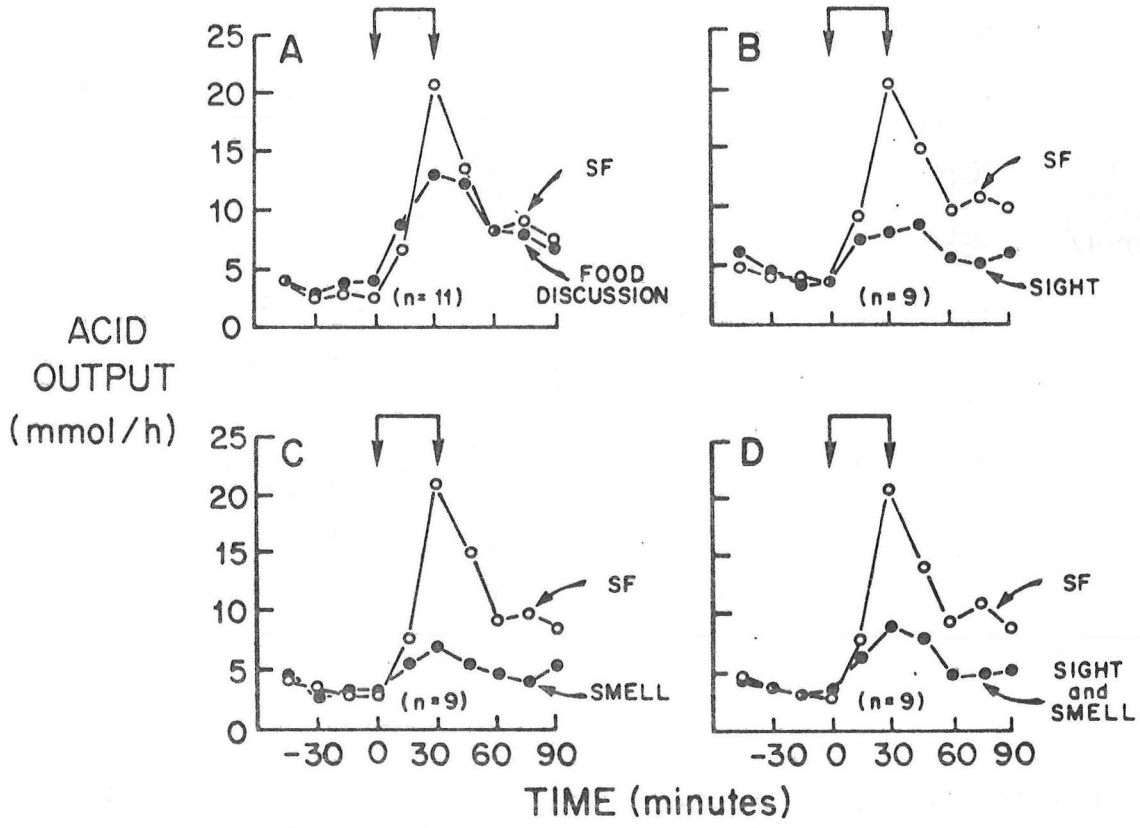

Figure 10. Comparison between gastric acid secretion in response to sham feeding (SF) and food discussion, sight of food, smell of food, and sight and smell of food (from Ref. 13).

Since the vagus nerves also innervate the antrum (Figure 6), serum gastrin concentrations also increase with sham feeding (1,2).

Effect of Food in the Stomach on Acid Secretion and Gastrin. As mentioned above, there are two mechanisms whereby food, once it reaches the stomach, causes acid secretion. Food distends the stomach. This causes secretion of acid and also causes release of gastrin (1,2,14,15). Distention stimulates acid secretion by activating both long vagovagal reflexes and short intragastric reflexes. It is likely also that gastrin, which is released by distention, plays some role in stimulating acid secretion via the distention mechanism.

Chemical reactions of food with the gastric mucosa are the most important factors in the gastric phase of acid secretion. Of the components of food, protein, especially amino acids, is the most important stimulant (16). While protein may interact directly with parietal cells to stimulate acid secretion to some degree, release of gastrin by amino acids is the most important mechanism whereby food stimulates acid secretion (17). Acid secretion in response to food is shown in Figure 11. For comparison, acid secretion in response to gastric distention by saline is shown also. Food or saline was infused directly into the stomach through a nasogastric tube to bypass the cephalic phase and acid secretion was measured by in vivo intragastric titration (18).

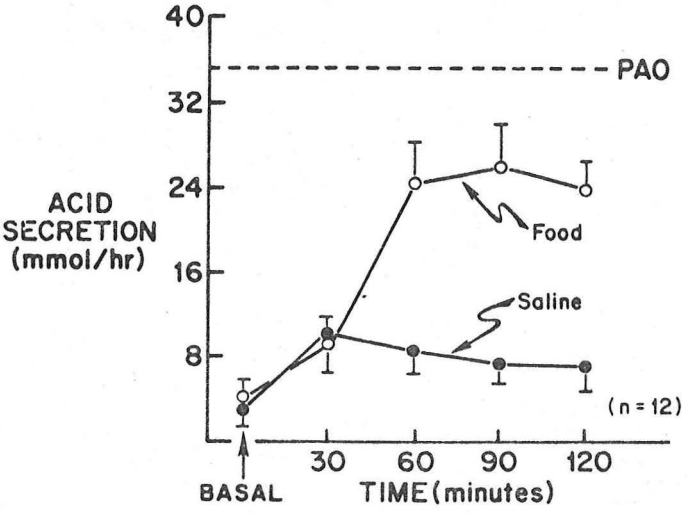

Figure 11. Acid secretion in response to food or saline infused into the stomach through a nasogastric tube. Basal acid secretion and peak acid output (PAO) are shown for comparison (From Ref. 2).

The effect of the cephalic and gastric phases of food-stimulated acid secretion can be evaluated simultaneously by infusing a homogenized meal into the stomachs of normal human subjects and at the same time having the subjects carry out sham feeding. This simulates normal eating. The effect of sham feeding plus infused food on acid secretion is shown in Figure 12. The effect of an infused meal given alone is shown for comparison.

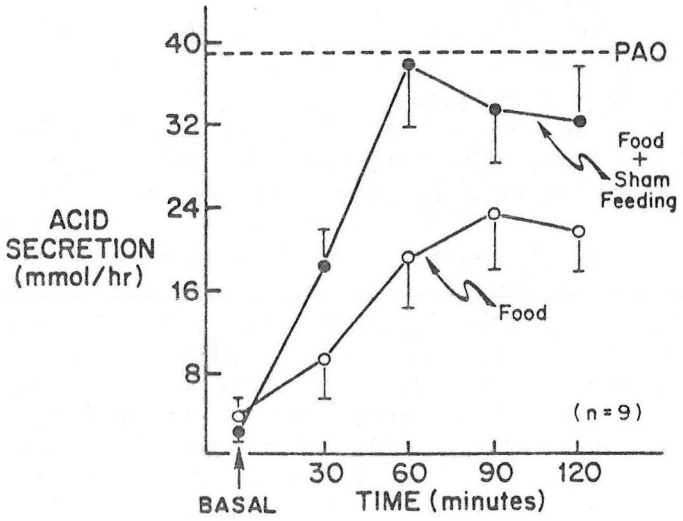

Figure 12. Effect of food infused into the stomach plus sham feeding on gastric acid secretion. The effect of food alone infused into the stomach is shown for comparison (From Ref. 1 and 2).

Acid Secretion in Ulcer Patients and Normal Subjects

Basal acid secretion, nocturnal acid secretion and acid secretion in response to pentagastrin or histamine (peak or maximum acid output) is higher in duodenal ulcer patients, as a group, than in normal subjects (2,19,20). Furthermore, as shown in Figure 13, acid secretion during the day and during the night is higher in duodenal ulcer patients than in normal subjects (21).

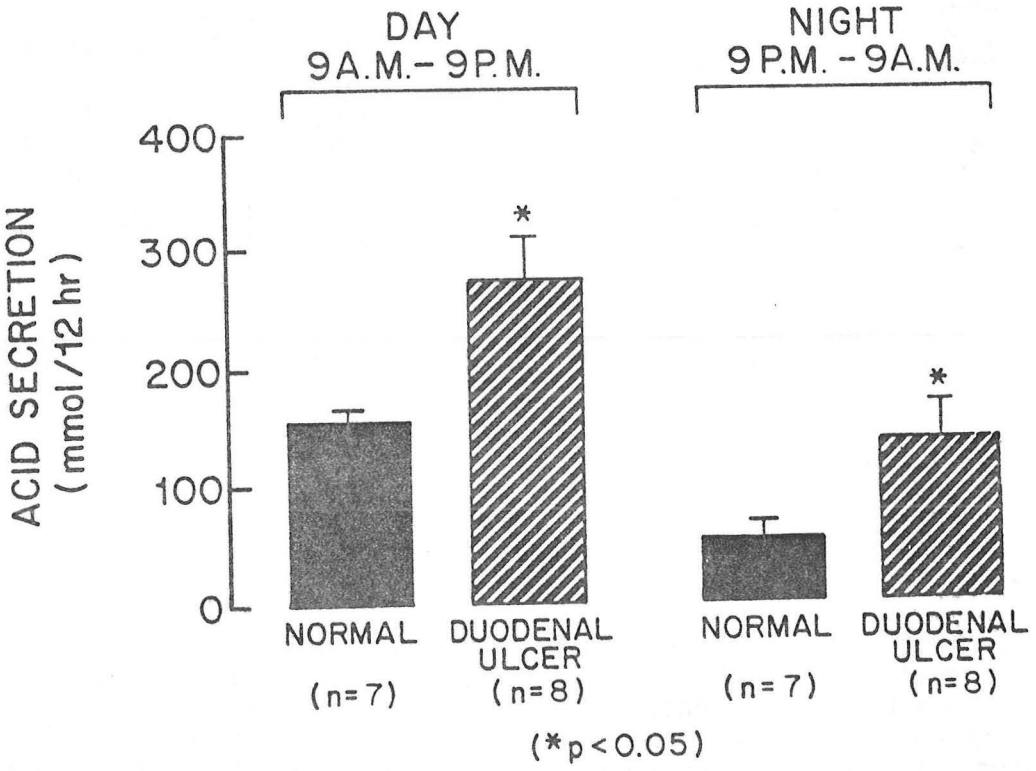

Figure 13. Mean (± SE) acid secretion during the day (defined arbitrarily as 9am-9pm) and during the night (defined arbitrarily as 9pm-9am) in 8 duodenal ulcer patients and 7 normal men (from Ref. 21).

In contrast to basal, nocturnal and peak acid output, food-stimulated acid secretion is similar in duodenal ulcer patients and normal subjects (??). Meals were infused into the stomachs of normal subjects and patients with duodenal ulcer disease. Food-stimulated acid secretion was similar in both groups. Furthermore, in another series of experiments, meals were infused into the stomach to activate the gastric phase of acid secretion and at the same time normal subjects and ulcer patients were sham fed meals to activate the cephalic phase. Acid secretion was nearly identical in patients with duodenal ulcer disease and normal subjects. Thus, the higher 24-hour acid secretory rates in duodenal ulcer patients is due primarily to increased basal, interprandial and nocturnal acid secretion.

The explanation for similar food-stimulated acid secretion rates in ulcer patients and normal subjects, despite a higher basal acid output and maximal capacity to secrete acid (higher PAO), is not known. These observations suggest that duodenal ulcer patients may release an inhibitor of acid secretion in response to food.

Patients with gastric ulcer have either normal rates of acid secretion or levels that are lower than normal (2,19,23). Acid secretion throughout a 24-hour period has not been measured in patients with gastric ulcer disease but presumably this too would be normal or lower than normal in gastric ulcer patients.

EFFECT OF SURGERY ON ACID SECRETION AND SERUM GASTRIN CONCENTRATIONS

Current surgical procedures are designed to either remove vagal stimulation of acid secretion (vagotomy), remove gastrin stimulation of acid secretion (antrectomy), or both. Truncal vagotomy and pyloroplasty reduces basal acid output by 80 to 90 percent and peak acid output by 50 to 60 percent. When antrectomy is combined with vagotomy, acid secretion is reduced more dramatically. Basal acid output is reduced by about 95% and peak acid output is reduced by 60-70%.

Effect of parietal cell vagotomy on basal, food-stimulated acid secretion and peak acid output to pentagastrin is shown in the top panels of Figure 14 (1,24). Before vagotomy (upper left) basal acid secretion (shown at 0 time) averaged 7 mmol/h and peak acid output (PAO) averaged 57 mmol/h. Basal acid output was reduced to near zero and peak acid output was reduced to 17 mmol/h after vagotomy (Figure 14, upper right). Food-stimulated acid secretion was also reduced markedly by parietal cell vagotomy. In contrast to acid secretion, both basal and food-stimulated serum gastrin concentrations were increased after vagotomy (Figure 14, bottom left and right). While the explanation for this is uncertain, there are at least two possibilities. First, antral pH is higher after than before vagotomy and this may contribute to a higher basal serum gastrin and may make the G-cells more responsive to food. Second, vagotomy may remove a vagal inhibitory mechanism that, under normal circumstances, suppresses gastrin release but when removed, allows higher serum gastrin levels.

The fact that basal and food-stimulated acid secretion is reduced after vagotomy even though basal and food-stimulated serum gastrin concentrations are increased suggests that parietal cells may become less responsive to circulating gastrin after vagotomy. This has been evaluated by infusing human gastrin-17 (G-17) into unoperated duodenal ulcer patients and also patients with duodenal

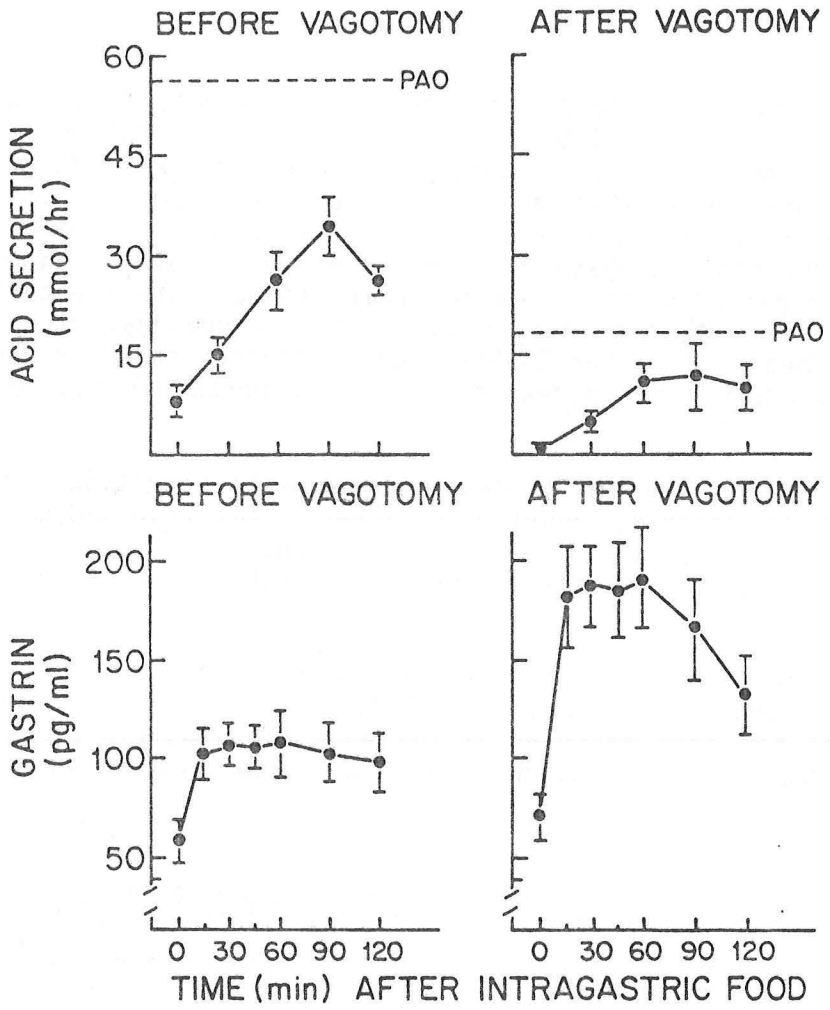

Figure 14. Basal acid output and peak acid output, food-stimulated gastric acid secretion and food-stimulated serum gastrin concentration before and after vagotomy in duodenal ulcer patients (From Ref. 1 and 24).

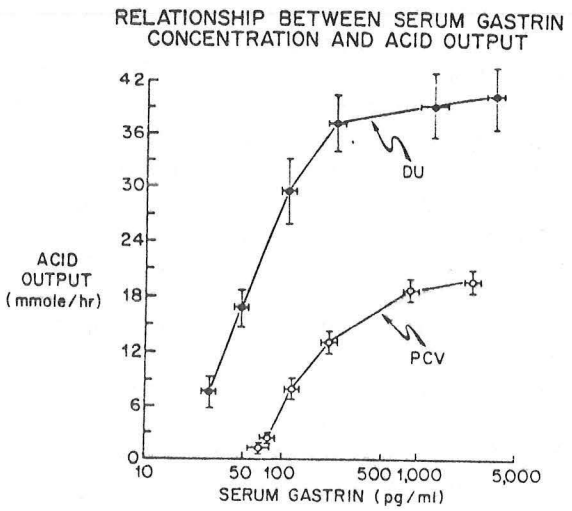

Figure 15. Relationship between mean (± SE) serum gastrin concentration and mean (± SE) acid output in 15 unoperated duodenal ulcer patients and 15 patients after parietal cell vagotomy From Ref. 25).

ulcer disease who have been treated by parietal cell vagotomy (25). As shown in Figure 15, patients who had had a parietal cell vagotomy, secreted less acid at a given serum gastrin concentration than unoperated patients with duodenal ulcer disease. Thus, patients are less responsive to gastrin after than before vagotomy.

Twenty-four hour acid secretion also has been measured in duodenal ulcer patients after parietal cell vagotomy and has been compared to results in normal subjects, duodenal ulcer patients and duodenal ulcer patients who have been treated with cimetidine (Figure 16) (21). Vagotomy reduced 24-hr acid secretion by more than 75% and to a greater extent than 400 mg cimetidine twice daily.

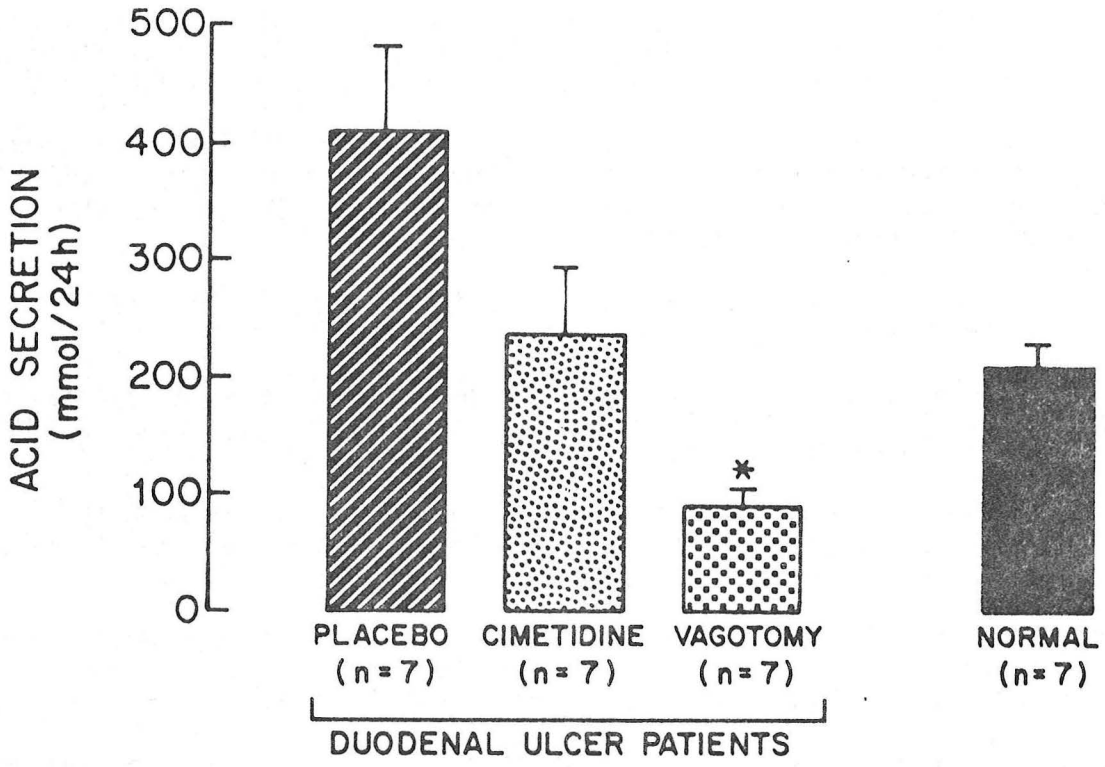

Figure 16. Mean (± SE) 24-h acid secretion 7 duodenal ulcer patients with and without 400 mg cimetidine twice daily, 7 duodenal ulcer patients after parietal cell vagotomy and 7 normal subjects. Acid secretion was significantly lower in vagotomy patients than in normal subjects or duodenal ulcer patients treated with placebo or cimetidine (asterisk, $P<0.05$) (From Ref. 12).

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Figure 17. Theodor Billroth (1829-1894), the Father of Gastric Surgery (From Ref. 1).

Theodor Billroth (1829-1894) is the Father of Gastric Surgery (Figure 17) (1). The first gastric resection was performed by Jules Pean of Paris in April, 1879, but the patient died on the fifth postoperative day. In November 1880, Ludwig Rydigier of Culm, Poland attempted the second gastrectomy but his patient died 12 hours after surgery. In Vienna, Billroth, who had accepted a surgical chair in 1867 at the age of 38, was busy studying the technique of gastric resection in dogs. Working in animals, Billroth and his students proved that survival was possible after gastric surgery and resolved the question of whether gastric juice would dissolve scar tissue in the healing anastomosis between the gastric remnant and duodenum.

The first successful gastric resection was not performed to treat peptic ulcer disease but instead was carried out to treat gastric cancer. In January 1881, one of Billroth's assistants asked his chief to see a 43 year old woman, Therese Heller. Frau Heller had symptoms suggesting pyloric obstruction. In October, 1880, she developed nausea and vomiting and the symptoms progressed until she became bedridden, was extremely wasted and had continuous vomiting. When seen by Billroth, she was able to retain only small amounts of sour milk.

The surgical procedure was planned in great detail. Billroth and his assistants had already spent years in the research laboratory working out the techniques and prior to the procedure Billroth stated:

> "To reassure those who are of the opinion that my present operation is a foolhardy experiment on man is beside the question. Resection of the stomach has been as completely worked up anatomically, physiologically and technically by my students and myself as any other operation."

On January 29, 1881, the historic operation on Frau Heller was performed. Preoperative preparation consisted of washing the stomach with 14 liters of lukewarm water and administering peptone enemas. Chloroform was administered for anesthesia and antiseptic technique was used. Through a transverse incision, an infiltrating carcinoma of the pylorus was found. It involved more than one-third of the lower portion of the stomach. The tumor was resected. Billroth and his assistants were concerned whether the remaining stomach would reach the duodenum and whether the anastomosis would be successful. Fortunately, the two ends of cut tissue were approximated and sutured and the procedure now known as a Billroth I gastrectomy and anastomosis was completed successfully. The surgical procedure lasted for one and a half-hours.

Within a week the patient was doing well, the wound was healing and there was no evidence of infection. While the patient recovered from the operation, she died 4 months later because of diffuse metastasis to the liver and omentum. She was a pioneer in that she laid the foundation for all abdominal surgical procedures that followed. By 1890, Billroth and his associates had performed 41 gastric resections for cancer with 19 successes. In addition to being the Father of Gastric Surgery, Billroth also was the originator of the concept of reporting the total clinical experience of a department. His reports from Vienna contain operative mortality, complications and the 5-year follow-up of numerous surgical procedures including gastric resection.

Surgery for peptic ulcer disease had its beginning in the early 1900's. During this period operations were designed so that there was minimal disruption to normal anatomy and physiology (Figure 18).

Gastrojejunostomy (gastroenterostomy) was one of the earliest surgical procedures for treating patients with duodenal ulcer disease. The first gastrojejunostomy was performed by Codivilla in 1893 (2,3). The purpose of gastrojejunostomy was to improve gastric emptying, to put the duodenum at rest, and theoretically, to allow the ulcer to heal. Pyloroplasty and excision of ulcers were also used as surgical therapies. Although acid and pepsin had been proposed as factors in the pathogenesis of ulcer disease in 1852 by Guenzburg (2) and in 1879 by Lindau and Wolff (4), early operations for ulcer disease were not designed to reduce acid secretion (Figure 18).

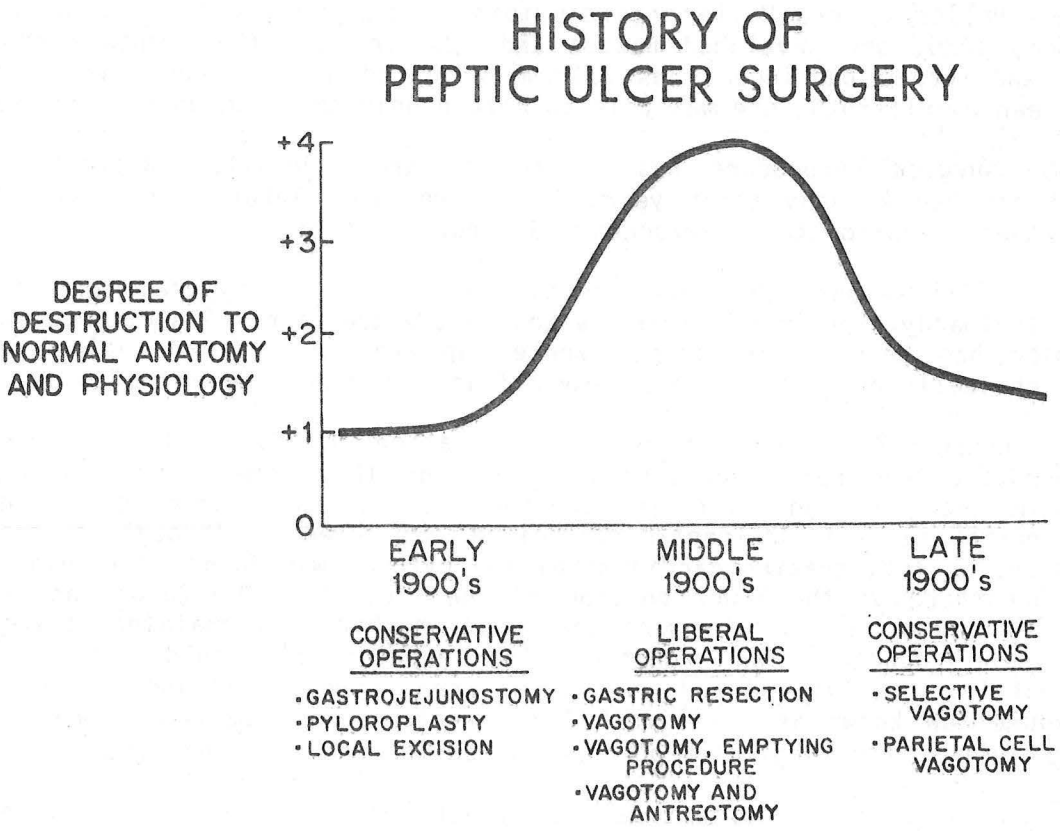

Figure 18. History of peptic ulcer surgery. Early operations were associated with minimal disruption to normal anatomy and physiology. During the mid-1900's surgical procedures were associated with marked disruption to anatomy and physiology. Presently, parietal cell vagotomy is becoming more accepted as surgical therapy of duodenal ulcer disease. This operation is associated with less disruption to normal anatomy and physiology.

Surgery for duodenal ulcer disease was supported strongly by Moynihan (Moin'yanz), a British surgeon (5). He stated -

> "Cases are within the experience of all in which prolonged medical treatment... is powerless to ward off the recurrence of dyspepsia... I do not know any operation in surgery which gives better results, which gives more complete satisfaction both to the patient and to his surgeon than gastroenterostomy for chronic ulcer of the stomach."

In 1910, Moynihan reported a series of 186 patients in which there was a 2% mortality rate, no failures and no mention of recurrence after gastrojejunostomy (6). Mayo also reported excellent results in patients followed for 2 years after gastroenterostomy (7). Although many of the complications of gastric surgery such as diarrhea, malabsorption, weight loss and "dumping" were not associated with gastroenterostomy, by 1913, stomal (anastomotic) ulcers were a recognized complications of the operation (8). It is surprising that stomal ulcers were not recognized by Moynihan and Mayo in their patients but the short-term nature of their follow-ups probably explain their enthusiasm for gastrojejunostomy. By 1920, stomal ulcers were reported in as many as 59 percent of patients having a gastroenterostomy for ulcer disease (9-12).

Interest in gastrojejunostomy, as a method of treating patients with ulcer disease, began to decrease in Europe before it did in the United States and in Europe gastric resection became the preferred therapy. In 1918, Finsterer suggested resection of two-thirds of the stomach (13). He believed that this operation would lead to a permanent reduction in acid secretion. It was believed that, for resection to be successful, it had to be extensive and gastric emptying rapid enough to reduce acid secretion. Some surgeons believed that only by removing a large amount of stomach (three quarter subtotal gastrectomy) could one be confident that gastric contents would be alkaline (14).

Gastric resection was not accepted uniformly by all, and in fact, stimulated great controversy. Even though gastroenterostomy clearly led to stomal ulcers in many patients, gastric resection was viewed as causing post-operative complications of other types. In fact, Rodman stated that "the cure is worse than the disease" (15) and gastroenterostomy (rather than gastric resection) continued to be the treatment of choice by some as recently as 1944 (16).

By 1940, however, subtotal gastric resection was accepted widely in the United States. Because lesser gastric resections were perceived as giving poorer results (in terms of recurrent ulcers), more surgeons began to adopt high gastric resection. It was soon recognized that low ulcer recurrence rates occurred with gastric resection but these operations were associated with a 20 to 50 percent incidence of post-gastrectomy side effects (see Long-term Consequences of Ulcer Surgery). The side effects varied with the individual patient, the amount of stomach removed and the size of the anastomosis between what remained of the stomach and the duodenum (Billroth I anastomosis) or jejunum (Billroth II anastomosis) (Figure 19).

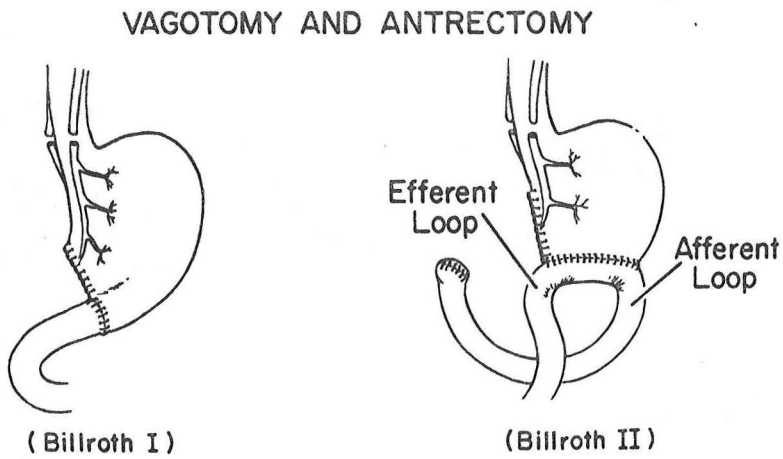

Figure 19. Model illustrating a vagotomy and antrectomy with a Billroth I (left) or Billroth II (right) anastomosis (From Ref. 17).

It was recognized that it was essential that all of the antrum be removed in performing a gastric resection because it contained a hormone that stimulated acid secretion (see Physiological Basis for Ulcer Surgery). The importance of removing the antrum was underscored by the high rate of recurrent ulcers associated with antral exclusion operations that had been performed by some (18). It later was recognized that antral exclusion led to increased levels of gastrin and increased acid secretion because the excluded antrum was exposed continuously to alkaline juice (acid inhibits gastrin release). A form of antral exclusion was later recognized as the cause of Retained Antrum Syndrome after gastric resection and Billroth II anastomosis (see Long-term Consequences of Ulcer Surgery).

Although gastric resection was used widely as surgical therapy for peptic ulcer disease, surgeons continued to look for better treatments. This was due in part to the dissatisfaction with the large number of patients who had "post-gastrectomy" problems and also to the relatively high mortality associated with gastric resection. Interest turned to vagotomy as a surgical option. In 1846, Rokitansky had stated that the "proximate cause of duodenal ulcer may be looked for in diseased innervation of the stomach owing to a morbid condition of the vagus and to extreme acidification of gastric juice" (19). Laterjet was the first to use vagotomy to treat 5 patients with gastric or pyloric ulcers (2). He knew that a drainage procedure was essential after vagotomy yet when vagotomy was first performed in this country (see below) an emptying procedure was not performed and the lesson taught by Laterjet had to be relearned.

Latejet's six patients did well but he thought that the good results might have been because of the gastrojejunostomy and not necessarily the result of vagotomy. Laterjet suggested that vagotomy might be performed as adjunctive therapy in combination with gastroenterostomy.

A number of investigators evaluated vagotomy in humans and animals during the 1920's and 1930's (20-22). However, the modern era of vagotomy began in 1943 when Dragstedt and Owens performed a transthoracic vagotomy without a drainage procedure (23). Their major goal was to develop an effective yet safe surgical procedure for patients with duodenal ulcer. They were disappointed in the morbidity and mortality associated with gastric resection and believed that there should be virtually no mortality associated with surgery for a benign disease. Dragstedt believed that vagotomy had failed during the 1920's and 1930's because the stomach had not been totally denervated.

There was much opposition to vagotomy as a form of ulcer therapy (24,25). An evaluation of vagotomy was carried out by the American Gastroenterological Association in 1952 and results of this study showed that results of vagotomy and gastroenterostomy were similar to that of gastric resection as far as patient satisfaction was concerned (26).

With time, the transthoracic, bilateral truncal vagotomy performed by Dragstedt and Owens was followed by subdiaphragmatic truncal vagotomy and gastroenterostomy and then vagotomy and pyloroplasty (Figure 20) to provide adequate gastric emptying (27,28). Vagotomy was then combined with antrectomy or hemigastrectomy to eliminate both the cephalic and gastric phases of acid secretion (29-31). It was hoped that this procedure also would reduce the possibility of producing a gastric cripple caused by radical resection of the stomach or the high recurrence rate that was being reported with vagotomy and drainage.

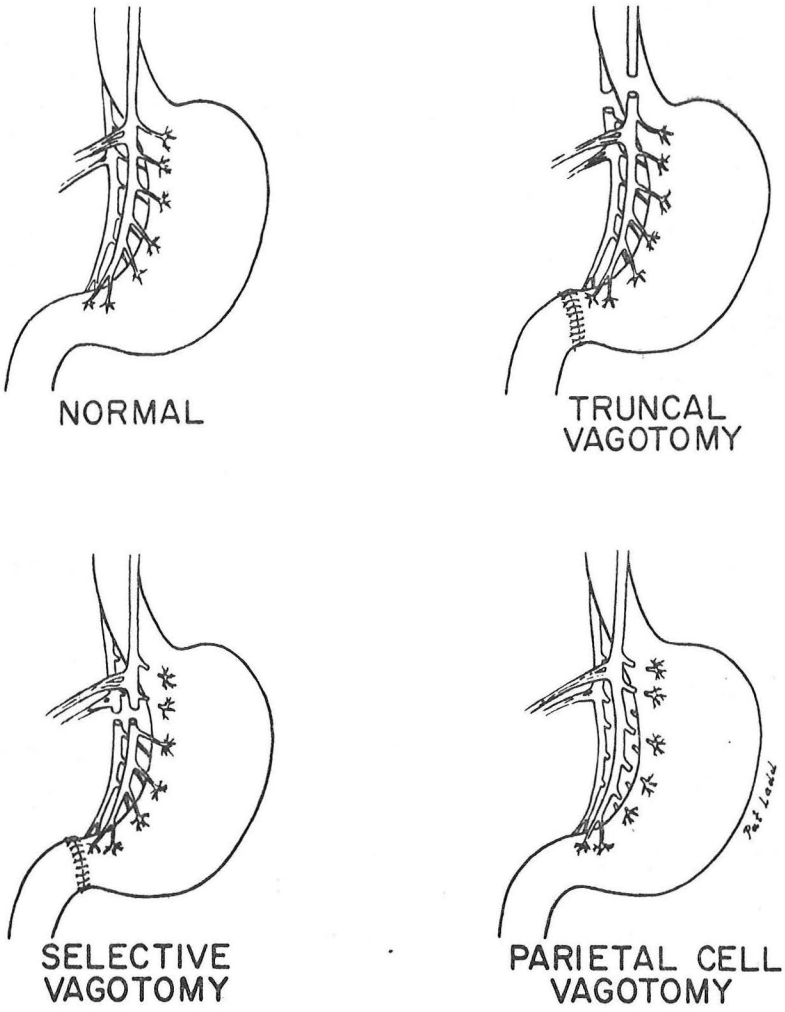

Figure 20. Model illustrating normal vagal anatomy, truncal vagotomy and pyloroplasty, selective vagotomy and parietal cell vagotomy.

The clinical results that occurred with truncal vagotomy and drainage and truncal vagotomy and antrectomy were great improvements over earlier operations such as gastroenterostomy, pyloroplasty without vagotomy, local excision or limited gastric resection. The major benefit, however, of these newer operations was reduction in ulcer recurrence. Unfortunately, "post-gastrectomy" problems occurred with greater frequency (see below). As experience with newer surgical techniques evolved, surgeons began to subject their results to critical evaluation by prospective, randomized trials. Goligher was one of the first to report his results (32). He compared results of subtotal gastric resection, truncal vagotomy and gastroenterostomy and truncal vagotomy and hemigastrectomy. As far as morbidity was concerned, results with these operations was similar, however there was a higher incidence of recurrent ulcers with vagotomy and gastroenterostomy.

Selective vagotomy was developed to allow gastric denervation but prevent denervation of other intra-abdominal organs (32,33). With this procedure the antrum is denervated so a pyloroplasty is necessary (Figure 20). This operation has never been used widely because there is no major advantage of it over truncal vagotomy and pyloroplasty and it is more difficult to perform. Parietal cell vagotomy (proximal gastric vagotomy, selective proximal vagotomy) was first proposed in 1957 based on experiments in dogs (34). In this operation, the nerves to the antrum are spared (Figure 20), motor function and gastric emptying remain virtually intact and a pyloroplasty is not required. The use of this procedure in humans was reported in 1970 in separate publications by Andrup and Jensen (35) and Johnston and Wilkinson (36). Morbidity and mortality are low with this operation. Mortality is less than 0.5 percent and disabling side effects are extremely rare primarily because vagal innervation to the antrum remains intact and a pyloroplasty is not performed. Recurrence rate is higher than with vagotomy and antrectomy and has ranged as high as 30%. Nevertheless, parietal cell vagotomy is the surgical procedure of choice in many centers for treating patients with duodenal ulcers. Parietal cell vagotomy is discussed in greater detail later in this protocol.

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INDICATIONS FOR ULCER SURGERY

There are several reasonably clear-cut indications for ulcer surgery (1-8). Others require more thought and in some instances are more controversial. "Intractability" or persistent ulcers with symptoms as an indication for ulcer surgery requires the most thought.

Most indications for surgery are guidelines. The potential problem with any guideline is that it will be used as a "hard and fast" rule. Good clinical judgement plays a major role in all medical and surgical decisions.

1) Upper gastrointestinal tract bleeding (from an ulcer) that does not cease with medical therapy within a reasonable period of time.

While the amount of bleeding allowed in an individual patient prior to referring the patient for surgery varies, in most instances bleeding requiring 6 to 8 units of blood during a 24- to 48-h period is an indication for ulcer surgery. Another rule of thumb that has been used is the requirement for blood transfusions at a continuing rate of more than 500 ml every 6 hours to maintain stable vital signs. Clinical judgement plays an important role, however, in this decision. For example, if a patient is elderly or has other medical problems such as pulmonary, cardiac or renal disease then surgery might be delayed. Unfortunately, there are no good data to help make the decision of when to take this type of patient to surgery. Perhaps, some of the newer endoscopic techniques for controlling active bleeding from ulcers will be proven effective and useful especially in elderly patients or those with severe medical or surgical illnesses other than ulcer disease.

2) Recurrent hemorrhage while hospitalized for a bleeding ulcer.

If a patient rebleeds from an ulcer while undergoing therapy in the hospital, he/she should be considered a surgical candidate. This is a general rule, but, as above, clinical judgement must play a role in the decision process. If the rebleeding episode is relatively minor (i.e. does not require additional transfusion or requires only one additional unit of blood) or if the patient has multiple medical problems in addition to ulcer disease then surgery should not be performed unless absolutely necessary (i.e., unless the patient continues to bleed). As above, there are no good data to support or refute taking a patient to surgery for rebleeding.

Type of Surgery for Indications 1 and 2. If the patient has bled from a duodenal ulcer or has recurrent bleeding during hospitalization from a bleeding duodenal ulcer, a truncal vagotomy and pyloroplasty is usually the operation of choice. Sufficient data are not available to evaluate parietal cell vagotomy as a surgical procedure in patients with these indications. Also, parietal cell vagotomy usually requires more time to perform and operating time during emergency surgery should be kept at a minimum. Vagotomy and antrectomy also is used sometimes in patients with bleeding duodenal ulcers. The bleeding duodenal ulcer is oversewn at the time of surgery.

In patients with bleeding gastric ulcers, partial gastric resection (including the ulcer crater) is usually performed. If the ulcer crater can not be removed because it is in the upper part of the stomach, the ulcer should be oversewn. Occassionally, a vagotomy is added in patients with bleeding gastric ulcers. Again, operative time should be kept to a minimum.

3) Several episodes of upper gastrointestinal hemorrhage.

There are no good data to indicate how many separate bleeding episodes should be allowed in an individual patient prior to referring the patient for surgery. Most physicians recommend surgery after 2 documented episodes of bleeding from a duodenal ulcer. Clinical judgement must play a role in the decision process. For example, if a bleeding episode is minor and does not require a blood transfusion then this might not count in the total number of bleeding episodes. Also, time between bleeding episodes should be taken into consideration. For example, if a patient bled from an ulcer in 1963 and 1973 but was well until 1986 at which time he/she had another bleeding episode, then surgery for ulcer disease might not be indicated. The above example is relevant especially since between 1973 and 1986 H_2-receptor antagonists were developed for treating patients with ulcer disease. In some patients chronic therapy with H_2-receptor antagonists may prevent recurrent hemorrhage from ulcers. This is illustrated by the case history below.

- M.C. is a 43 year old man with chronic duodenal ulcer disease
- 1969 - Hospitalized at DVAMC for bleeding from a duodenal ulcer.
- 1970 - Hospitalized for upper gastrointestinal hemorrhage.

  Basal acid output - 30 mmol/h
  Peak acid output - 50 mmol/h
  Serum gastrin - 60 pg/ml

- 1971 - Hospitalized for bleeding duodenal ulcer. Surgery recommended but patient refused an operation.
- 1973 and 1974 - Guaiac positive stools; presumed to be bleeding from duodenal ulcer. Surgery recommended but patient refused surgery.
- 1975 - Treated with cimetidine on experimental protocol
- 1977-Present - Treated with cimetidine. No evidence of bleeding since 1974.

Admittedly, the above case history is only an example. There are no randomized studies to compare surgery versus medical therapy in preventing recurrent bleeding in ulcer patients who have bled previously from an ulcer. Results of such a study would not only be interesting but also would be clinically relevant now that better medical treatment (H_2-receptor antagonists) and surgical treatment (parietal cell vagotomy) are available. In general, patients who have bled from a duodenal ulcer should be given a trial of maintenance therapy with cimetidine or ranitidine. If a patient rebleeds on therapy with a H_2-receptor antagonist, surgery is indicated in most of these patients. In my opinion, parietal cell vagotomy is the surgical treatment of choice. Some would argue that vagotomy and antrectomy is the procedure of choice in a patient who has bled from a duodenal ulcer because acid secretion is reduced to a greater extent with vagotomy and antrectomy and ulcer recurrence are lower than with parietal cell vagotomy. It should be remembered, however, that there is no data to support either operation over the other in patients who have bled from a duodenal ulcer and the long-term consequences of ulcer surgery are less with parietal cell vagotomy.

If a patient has bled once or twice from a gastric ulcer, many clinicians would be more inclined to recommend surgery than in patients with duodenal ulcer disease. Again, the data are soft at best to support this. Also, the role of aspirin and other non-steroidal anti-inflammatory drugs in the pathogenesis of gastric ulcer and bleeding in an individual patient should be considered. In my opinion, a patient, who has bled once from a gastric ulcer but in whom bleeding has stopped, should be treated with maintenance cimetidine or ranitidine. If rebleeding occurs while on maintenance therapy, the patient should be referred for surgery unless there is a contraindication to surgery. The type of surgery is controversial but probably a gastric resection with or without a vagotomy is indicated in patients with gastric ulcers.

4) Perforated ulcers.

With rare exceptions, all patients with a perforated ulcer should have surgery to close the perforation (Graham closure). Most patients with perforated ulcers are seen within 6 hours of perforation. In a review by Sawyers et al (6), 95% of 360 patients were seen within 6 hours while 5% were first seen by a surgeon 1 to 3 days after perforation. In patients who are not seen within the first few hours after perforation, surgery should consist only of simply closure of the perforation since peritonitis likely has developed. In patients who are seen acutely, an important issue in management relates to whether a definitive ulcer operation should be performed at the time of closure of the perforation. Whether or not there is a past history of ulcer disease usually plays a role in helping to decide whether a definitive ulcer operation should be performed at the time of Graham closure. The numbers of patients who have had a history of ulcer disease prior to the perforation varies although in the series by Sawyers and co-workers, 63% had a past history of ulcer disease (6). In these patients it is easier to consider performing a definitive operation at the time of Graham closure than in patients who have not had known ulcer disease previously. Mortality and morbidity with procedures which include a gastric resection are relatively high in the setting of perforation. Therefore, parietal cell vagotomy has been evaluated as a definitive ulcer operation to be performed at the time of Graham closure (7,8). Data indicate that parietal cell vagotomy should be considered as a definitive form of ulcer therapy at the time of Graham closure in most patients with a perforated ulcer assuming that the patients are seen soon after ulcer perforation.

5) Gastric outlet obstruction.

Some patients with gastric outlet obstruction secondary to pyloric channel ulcers, prepyloric ulcers or proximal duodenal ulcers will respond to medical therapy with nasogastric suction and intravenously administrated H_2-receptor antagonists. Many patients will not respond and will require surgery. The type of surgical procedure is controversial. Many surgeons are hesitant to perform a vagotomy even with a gastric resection or pyloroplasty because of fear of gastric atony after vagotomy in obstructed patients but there are no good data to support this.

Parietal cell vagotomy and dilatation of the obstructed pylorus at the time of surgery has been suggested and used by some in treating patients with obstruction (9). Also, a few patients have been treated successfully with H_2-receptor antagonists plus balloon dilatation of an obstructed pylorus (10). More data must be obtained with each of these latter procedures before they can be recommended for general use in patients who have obstruction secondary to benign peptic ulcer disease.

6) Patients with "intractable" or persistent duodenal or gastric ulcers.

Most patients who undergo surgery for ulcer disease do not have one of the indications list in 1 through 6 above. For these patients it is much more difficult to decide if surgery is needed since these patients are those who are referred for surgery for what is called intractability. Decisions to operate in these patients have always been difficult but they are even more difficult today since long-term medical therapy is a viable option in many of these patients.

With current medical therapy with cimetidine, ranitidine or sucralfate for 4-6 weeks, ulcers will heal in 75-80% of patients with acute duodenal ulcers (11). In patients with gastric ulcers, the ulcers will heal in 85-90% of patients if medical treatment is continued for 8-12 weeks (12). Pain will be relieved in most patients treated with one of the drugs within one to two weeks of beginning therapy.

There are two types of patients with intractable ulcers: a) those patients in whom pain continues and the ulcer does not heal on medical therapy within the period of time outlined above and b) those patients in whom a symptomatic ulcer recurs frequently or, more importantly, recurs while on chronic therapy with cimetidine or ranitidine. In patients with peptic ulcer disease, it is likely that asymptomatic ulcers develop and heal spontaneously without causing symptoms (11). Thus, in the strictest sense only those patients with pain and documented duodenal ulcers should be considered to have intractable duodenal ulcer disease. In patients with gastric ulcers the situation is different. Even in the absence of pain, most patients with persistent (non-healing) gastric ulcers should be considered for surgery if the ulcer does not heal within 12-15 weeks. This is true since the ulcer may be malignant despite biopsy evidence that it is benign. If the patient is taking a non-steroidal anti-inflammatory drug, this should be discontinued and attempts made to heal the ulcer with medical therapy prior to surgery (see Long-term Consequences of Ulcer Surgery, the "Albatross" Syndrome).

Causes of Intractable (Non-Healing) Ulcers

a) The medical regimen may be inadequate. Some patients have increased acid secretion and thus require more than the usually recommended doses of medication or may need the combination of a H_2-receptor antagonist and antimuscarinic drug. This is true especially in patients with Zollinger-Ellison syndrome. All patients with persistent ulcers or frequently recurrent ulcers should have serum obtained for gastrin measurement to rule out Zollinger-Ellison syndrome. Other patients may also require the combination of a H_2-receptor antagonist and sucralfate antacid or antimuscarinic drug.

b) Patients may not be taking medication as prescribed either because they are non-compliant and would not take medication under any circumstances or because they do not understand the physician's directions.

c) Some patients may have a penetrating ulcer. Frequently, these patients will have an ulcer penetrating into the pancreas. Such patients likely will have an elevated amylase and lipase.

d) Patients may be taking aspirin or other non-steroidal anti-inflammatory drugs. While it is unclear whether these drugs contribute to duodenal ulcers,

there is reasonably good evidence that the drugs are associated with development of gastric ulcers in some patients. Patients should be advised to stop taking these drugs and great care should be exercised in referring patients for surgery who take large amounts of non-steroidal anti-inflammatory drugs (See Long-term Consequences of Ulcer Surgery).

e) Cigarette smoking is associated with recurrent ulcers (13) and delays healing of duodenal ulcers (14-16). It is likely that smoking contributes to intractability in some patients and patients should be advised to stop smoking prior to considering surgery as a treatment for intractability.

f) Patients may be experiencing undue psychological stress. Emotional stress has been associated with ulcer disease in some patients (16) and may contribute to the persistence of ulcer disease in a few patients. Prior to surgery it is extremely important to ask about stressful life events since the same events that are present prior to surgery will also be present after surgery (see Long-term Consequences of Ulcer Surgery).

P.T. (below), represents an example of a patient who was under severe emotional stress, was being treated with maintenance H_2-receptor antagonist, and was scheduled for surgery. A few modifications in his life-style as well as therapy with cimetidine led to relief of persistent ulcer symptoms and to healing of the ulcer. While he has continued to have symptoms periodically (18), he works every day and carries on a normal life.

- P.T., 37 y.o. man

- 1975 - Duodenal ulcer with symptoms

- 1976-1980 - Several episodes of pain associated with duodenal ulcer.

- 1980 - Severe pain which persisted for several months as well as a duodenal ulcer documented by endoscopy.

- Psychological History - Patient worked 12 hours daily at the post office and worked for 12 days prior to being given a day off. The work cycle was then repeated. Patient also had an extremely unhappy home life.

- Resolution - His employer was contacted by the physician and his work schedule was altered. The patient resolved his home situation by getting a divorce. Pain diminished and the ulcer healed.

- Follow-up - The patient has had occasional episodes of ulcer pain during the past 6 years and is treated with maintenance H_2-receptor antagonists. He has not had severe or persistent pain and leads a normal life.

g) Altered natural history of ulcer disease (19). This has been postulated by Bardhan in the United Kingdom. He has observed that in some patients ulcers respond to H_2-receptor antagonists for a period of time but then something changes and some patients develop ulcers that are refractory to medical therapy. He admits that he does not know the cause for this change but he has ruled out a) through f) above as a cause. He postulates that there is a change in the natural history of the disease process to explain development of non-healing ulcers in patients who previously had ulcers responsive to medical therapy.

One of the most difficult decisions a physician faces in treating patients with ulcer disease is when to refer patients with "intractable ulcer disease"

for surgery. While there are no data to assist in making this decision, several guidelines should be followed:

a) The physician should be certain that the patient is receiving an appropriate medical regimen. It may be necessary to increase the amount of medication (for example increase the amount of H_2-receptor antagonist) or add another drug in combination with cimetidine or ranitidine. Using an experimental drug such as omeprazole (20,21) or prostaglandin analogue also should be considered. The physician should be as certain as possible that the patient is taking the prescribed medication (some physicians consider non-compliance with medical therapy as an indication for surgery but there are no data to support or refute this).

b) Attempts should be made to alleviate stress by talking with patients and perhaps, treating patients with a mild sedative.

c) The physician must be certain that the diagnosis is correct. Endoscopy should be performed to confirm the presence of an ulcer before surgery is performed. Surgery should not be carried out for pain without evidence that the patient has an active ulcer. If pain is present but an ulcer is not, gallbladder disease, non-ulcer dyspepsia, pancreatic disease, irritable bowel syndrome or some other intra-abdominal event should be considered as a possible cause of pain.

Once an ulcer is deemed refractory, the patient should be referred for surgery. In most patients with intractable duodenal ulcer disease, a parietal cell vagotomy is the procedure of choice although some would disagree (22). In patients with gastric ulcers there is greater controversy. Many physicians recommend a gastric resection to include the ulcer crater. A vagotomy may or may not be performed as well. Recent data indicates that parietal cell vagotomy combined with excision of the ulcer crater can be used to treat successfully some patients with non-healing, benign gastric ulcer (23).

Surgery in Patients with Refractory Duodenal Ulcers

The management of patients with duodenal ulcers that do not heal with medical therapy or that recur with maintenance treatment with H_2-receptor antagonists has been evaluated in several open clinical trials and has been reviewed by several investigators (22,24-29). The available data is difficult to evaluate because various investigators have different definitions for refractory ulcer disease. Results suggest that most patients with non-healing duodenal ulcers or ulcers that recur on maintenance medical therapy should have surgery. Parietal cell vagotomy is recommended because of fewer late post-operative complications. As mentioned above, results of one study suggest, however, that patients who do not respond to medical treatment with H_2-receptor antagonists may not respond to therapy with parietal cell vagotomy (22) and another type of surgical procedure (vagotomy and antrectomy) may be necessary in some of these patients.

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LONG-TERM CONSEQUENCES OF ULCER SURGERY ("POST-GASTRECTOMY SYNDROMES, POST-VAGOTOMY SYNDROME, POST-GASTRECTOMY DYSFUNCTION").

A large number of patients (up to 50% in some reports) who have had partial gastric resection, vagotomy and antrectomy, or vagotomy and pyloroplasty have some type of morbidity after ulcer surgery. Frequently, symptoms are minimized and are considered the price that must be paid for surgical cure of ulcer disease. Approximately 10% of patients who have had one of the conventional surgical procedures for ulcer disease will be impaired to the point that they lose time from work at least temporarily (1). Many of these patients seek help from a variety of physicians including internists, surgeons and gastroenterologists and often a number of tests are performed searching for a cause of debility other than abnormal function secondary to the surgical procedure. Frequently, these patients will also have additional operations in an attempt to correct what was done at the first procedure. For example, if a patient had a vagotomy, antrectomy and gastroduodenostomy or jejunostomy, the second operation may be performed to interpose a jejunal loop with reversed peristalsis in an attempt to correct diarrhea. If a patient has gastritis, a second operation may be performed to create a Roux-en-Y anastomosis to prevent "bile reflux" (see Figure 22). Often these second or even third or fourth operations are not successful and the search for perfect gastrointestinal function continues, frequently to no avail. Since about 50,000 people in the United States have ulcer surgery each year, even a 10% incidence of severe postoperative morbidity creates a major social and economic burden. It is extremely important, therefore, to carefully consider the indications (see Indications for Ulcer Surgery) and type of surgical procedure (see Parietal Cell Vagotomy) before patients are referred to surgery for ulcer disease. Fortunately, chronic morbidity from ulcer surgery occurs infrequently when a parietal cell vagotomy is performed.

Abnormal Physiology After Ulcer Surgery

Acid Secretion. As discussed previously, reduction in acid secretion is the goal, not only of current surgery for ulcer disease but also medical therapy. Most post-operative morbidity from ulcer surgery is not related to reduction in acid secretion. Occasionally, gastric atrophy may occur after ulcer surgery and pernicious anemia may develop. This is extremely rare, however. Gastric cancer has been reported in some patients 15-20 years after ulcer surgery (partial gastrectomy; antrectomy) (2-5). Reports have primarily been from countries other than the United States although a few patients with gastric cancer following gastric resection have been reported in this country.

Motor and Reservoir Function. The stomach normally functions as a reservoir for liquids and solids and allows food to pass at a controlled rate into the small intestine (6). The proximal stomach is the main reservoir for food. Food which is retained initially in the proximal stomach subsequently passes into the distal stomach where mixing and grinding of the meal takes place. Mixing and grinding increases the surface area of solid food particles which allows more efficient chemical digestion in the stomach and intestine.

Vagal innervation of the proximal stomach is extremely important for normal reservoir function. As food reaches the proximal stomach, stretch receptors in the stomach wall initiate reflexes. Vagal fibers are important both in completing the afferent portion of the reflex and in mediating the efferent limb of these reflexes (6). Receptive relaxation, a vagally-mediated reflex, was described first by Cannon and Lieb in 1911 (7). They observed that as food entered the stomach, gastric relaxation occurred and this could be eliminated by

vagotomy. Gastric accommodation is the other vagally-mediated reflex. Studies have shown that inflation of a balloon in the proximal stomach is followed by gastric relaxation and intragastric pressure remains nearly constant over a wide range of volumes (8,9). If accommodation does not occur, increasing intragastric volume causes increased intragastric pressure which, in turn, alters gastric emptying (10). Vagotomy alters gastric accommodation which likely causes rapid gastric emptying especially of liquids (6).

Pyloroplasty, gastrojejunostomy and antrectomy also alter markedly the manner in which food is handled and emptied by the stomach. As mentioned above, mixing and grinding takes place in the distal stomach and if the antrum has been removed then obviously this function will be altered.

From this brief description of gastric motor function, it can be seen that vagotomy, antrectomy and/or emptying procedures can markedly alter the reservoir, mixing, grinding and emptying mechanisms of the stomach (For a more detailed discussion of gastric motor function see references 1 and 6).

Diarrhea

Although diarrhea can occur after any of the traditional surgical procedures for peptic ulcer, the incidence seems to be higher when a vagotomy is performed. For example, in the Leeds/York Trials, the incidence of diarrhea with subtotal gastrectomy (alone) was approximately 7% whereas if a vagotomy was performed (vagotomy and antrectomy, vagotomy and pyloroplasty or vagotomy and gastroenterostomy) the incidence was 20 to 25% (11,12). Additional studies, on the other hand, have found that diarrhea occurs with the same frequency regardless of the type of surgical procedure (13,14).

Pathophysiology. The cause of diarrhea following ulcer surgery is not known. Several mechanisms have been postulated. These are listed in Table 3.

Table 3. Postulated Mechanisms Contributing to Diarrhea After Gastric Surgery

1. Disordered and rapid gastric emptying (15) - This may be a contributory factor. However, many patients have rapid emptying following vagotomy (with or without antrectomy) but only a few patients have diarrhea.

2. Small bowel mucosal changes (16) - Jejunal histology is normal in most patients after vagotomy.

3. Denervation of small bowel by truncal vagotomy - This may be a factor although studies have revealed no consistent motility disturbances (17). Diarrhea still occurs with selective vagotomy (nerves to parietal cell area and antrum are cut and a pyloroplasty is performed, Figure 20) although the incidence seems reduced. However, when parietal cell vagotomy is performed, diarrhea infrequently occurs.

4. Increased fecal output of bile acids (18) - This has been postulated as a mechanism, and there is some evidence that diarrhea improves with cholestyramine. This, however, is controversial.

5. Changes in bacterial population - Except in the bacterial overgrowth syndromes (See Malabsorption), there is no evidence of alterations in the bacterial population of the small bowel of patients with diarrhea without malabsorption (19).

The treatment of diarrhea initially should be limited to dietary manipulations. The physician and dietician should talk with the patient and the patient should be advised to eat small meals, frequently, as opposed to large meals. If the patient has had a vagotomy, the reservoir function of the stomach will be altered because of abnormal receptive relaxation and accommodation. Patients should be told to eat a high protein, high fat, low carbohydrate diet. Fat and protein may delay gastric emptying even after antrectomy whereas carbohydrate will add to the osmotic load in the small bowel and may contribute to diarrhea. Avoidance of lactose and/or caffeine containing foods is occasionally helpful. Sometimes, lactose intolerance is unmasked by gastric surgery. Symptoms resolve spontaneously in some patients.

A variety of antidiarrheal agents have been tried but results are variable. Although cholestyramine has been prescribed with some success, it is unclear whether the reduction in diarrhea is the result of decreased bile salts or a non-specific effect of the drug. The incidence of diarrhea after ulcer surgery can be markedly reduced by performing a parietal cell vagotomy rather than truncal or selective vagotomy.

Malabsorption

The incidence of malabsorption after ulcer surgery varies with the degree to which normal anatomy is altered (see Figure 18). For example, the incidence is higher after subtotal gastrectomy or vagotomy and antrectomy than after vagotomy and pyloroplasty. The incidence of clinically significant malabsorption (> 8 percent fecal fat excretion daily) is extremely low when a parietal cell vagotomy is performed. The likelihood of developing chemical evidence of steatorrhea or clinically important malabsorption with various surgical procedures is shown in Table 4.

Table 4. Percent of Patients Developing Chemical Evidence of Steatorrhea or Clinically Important Malabsorption with Various Surgical Procedures

OPERATION	CHEMICAL EVIDENCE OF STEATORRHEA	CLINICALLY SIGNIFICANT MALABSORPTION
Vagotomy and Pyloroplasty	<10%	<5%
Gastric Resection with Billroth I Anastomosis	About 25%	<10%
Gastric Resection with Billroth II Anastomosis	About 50%	<20%

The most common cause of postoperative malabsorption is poor timing and poor mixing of food with gastrointestinal juices (bile acids, pancreatic enzymes, etc.). Poor timing and mixing are also the most difficult causes to treat. Medical therapy usually includes prescription of antidiarrheal agents and antimuscarinic drugs (anticholinergics) (theoretically, to slow gastric emptying and allow more contact time among food, bile acids, enzymes, and the small bowel mucosa). Sometimes supplemental pancreatic enzymes will help.

Other, less common causes of malabsorption include bacterial overgrowth (20, 21), unmasking of latent celiac sprue (22), gastroenterocolic fistula, and inadvertent gastroileostomy (rather than gastroduodenostomy or gastrojejunostomy) (23). Bacterial overgrowth occurs because of decreased acid secretion and/or stasis, either in the efferent loop in a patient who has had a Billroth II anastomosis (Figure 19) or stasis in the small intestine due to postoperative adhesions. Bacteria deconjugate bile salts, making them less effective in aiding fat absorption. Bacterial overgrowth is usually treated with broad-spectrum antibiotics. Celiac sprue is treated with a gluten-free diet, whereas gastroenterocolic fistula and inadvertent gastroileostomy must be treated surgically.

Vitamin and mineral malabsorption can occur also and lead to clinically important problems. For example, in some patients calcium and vitamin D malabsorption can cause severe metabolic bone disease. Iron, folic acid, and/or vitamin B_{12} malabsorption can lead to anemia. Specific therapy is available for each of these vitamin and mineral deficiencies. Unfortunately, in the case of calcium and vitamin D malabsorption, the condition is often not recognized until severe bone disease is already present. For this reason, some physicians recommend prophylactic therapy with calcium and vitamin D in patients with subtotal or total gastrectomy or vagotomy and antrectomy.

Dumping Syndrome

The term "dumping" was coined in 1922 by a physician, Dr. Charles Mix, who observed that barium emptied rapidly from the stomach of a patient following gastrojejunostomy (24). The patient's major symptoms were pain, vomiting and weight loss. Today, the term, "dumping syndrome", is used to describe a variety of postprandial symptoms, including epigastric fullness, a sensation of abdominal distention, nausea, borborygmi, drowsiness, fatique, palpitations, and sweating. Patients usually have one or several but not all of these symptoms. In some patients, symptoms occur in the immediate postoperative period and then subside with time.

The incidence of dumping is difficult to evaluate because the diagnosis is not always based on objective criteria. For example, in some series, patients are included who have mild postprandial symptoms. Therefore, in these reports the incidence of dumping is quite high, whereas in others it is near zero (25,26). The incidence of severe dumping is less than 10 percent.

The cause of dumping is thought to be related to rapid emptying of hypertonic food products into the upper small bowel. This causes movement of plasma water into the gut lumen, which, in turn, leads to hypovolemia. Although a number of studies have shown that this sequence of events occurs after eating, it has not been established that it causes symptoms. The term "early" dumping has been given to the symptoms that occur in some patients during the immediate postprandial period. Other postulated mechanisms include presence of hypoglycemia and release of vasoactive substances such as serotonin or bradykinin. Hyperglycemia commonly occurs during the immediate postprandial period in many patients who have undergone gastric resection, and in some patients hypoglycemia occurs 3 to 4 h after a meal. Thus, abnormal glucose tolerance test results are found in many post-gastrectomy patients. Whether these blood sugar alterations are related to symptoms of dumping syndrome is controversial, since they can occur in patients with or without symptoms.

There are several theories as to the mechanisms of post-gastrectomy hypoglycemia. Perhaps, the most popular explanation is that "early" postprandial hyperglycemia (Figure 21) causes an excess level of insulin in the

circulation. This, in turn, produces "late" hypoglycemia. Other theories for the development of "late" hypoglycemia include (1) increased sensitivity to insulin; (2) enteroglucagon release which blocks the hyperglycemic affect of glucagon; (3) release of gastric inhibitory peptide (GIP) which in turn stimulates insulin release and (4) interruption by vagotomy of vagally-mediated pancreatic glucagon release.

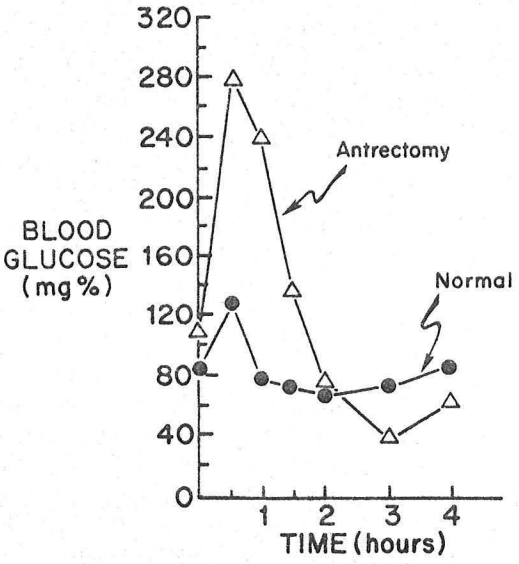

Figure 21. Post-prandial blood glucose curves in a normal subject and patient after antrectomy.

In evaluating patients with "dumping" several points should be remembered:

1. The diagnosis of "dumping" can usually be made by taking a careful history.

2. Only a few patients have symptoms severe enough to require treatment.

3. In many patients symptoms occur in the immediate post-operative period and then subside with time.

4. A Glucose Tolerance Test is not helpful because most (if not all) post-gastrectomy patients will have an abnormal glucose tolerance test.

5. Diagnostic tests (such as small bowel biopsy, stool fat, etc.) should be reserved for those few patients who fail non-surgical therapeutic measures discussed below.

"Dumping" symptoms can usually be controlled by advising dietary manipulations. The same dietary changes described in the section on diarrhea apply to the dietary treatment of "dumping". It is extremely important and helpful for the physician to explain to patients why they have symptoms and why alterations in diet should alleviate some if not all symptoms. For example, the physician should explain that many of the symptoms result from rapid emptying of food and liquid from the stomach (or whats left of it) into the small intestine. Protein and fat in the diet may help slow gastric emptying whereas carbohydrates may make "dumping" symptoms and diarrhea worse because of osmotically active particles. Liquids also empty rapidly from the vagotomized stomach and therefore, liquids should be ingested slowly and primarily between meals. A dietician should also talk with the patient.

In patients who fail dietary manipulations, drug therapy with antimuscarinic

drugs has been tried with minimal success. Various surgical procedures (narrowing of gastric outlet, interposition of intestinal loops, etc.) have been tried, but again, the success rate is low in patients who fail medical therapy.

Anemia

Anemia develops after gastric surgery as a result of iron, vitamin B_{12} and/or folic acid deficiency. There are several reasons why these deficiencies might occur. First, food ingestion is often diminished after ulcer surgery. Thus, there may be inadequate intake of vitamins and minerals. Second, a few patients have chronic blood loss (for example, from a recurrent ulcer) and lose excessive amounts of iron. Third, malabsorption of food-bound iron can occur after ulcer surgery and can lead to iron deficiency. The small intestine may fail to absorb vitamin B_{12} as a result of intrinsic factor deficiency. Intrinsic factor deficiency may occur following total gastrectomy or as a result of atrophic gastritis, which can develop (although rarely) after antrectomy or subtotal gastrectomy. All of these factors can contribute to the development of anemia in postoperative patients.

Metabolic Bone Disease

The association between gastric surgery and bone disease has been recognized for a number of years (28-31) and it almost certainly results from both malabsorption of calcium and vitamin D. It occurs more often in patients who have had a subtotal gastric resection or antrectomy and vagotomy than in those who have had a vagotomy and pyloroplasty. In one study 36 patients who had undergone gastric resection 3 to 9 years before the study were subjected to an ileac crest biopsy (32). Abnormal findings were discovered in 16 patients. Fifteen patients had osteoid indexes greater than 2 standard deviations from the normal mean, 6 had total bone indexes 2 standard deviations from the normal mean and 5 patients had both abnormalities.

Although bone abnormalities are frequent in patients who have had gastric resection and some patients have suffered fractures resulting from bone disease, it is unclear whether all patients should be treated with calcium and vitamin D following gastrectomy. Clearly, patients with evidence of metabolic bone disease should be treated with calcium and vitamin D.

Post-Gastrectomy Problems in Patients with Personality Defects: The "Albatross" Syndrome (33)

This syndrome was described initially in 7 patients out of a series of 130 patients undergoing operations for peptic ulcer disease at Vancouver General Hospital (33). The major features of this post-gastrectomy syndrome are -

1) Persistent abdominal pain without demonstrable cause,

2) Nausea and vomiting of an intermittent and inexplicable nature,

3) Continued analgesic drug dependence and

4) Marked nutritional deficiencies.

The case histories of the 7 patients are summarized in Table 5. The decision to operate in each case was based on the assumption (and in some cases proof) that the patient had peptic ulcer disease. In each patient, it was assumed that symptoms were secondary to ulcer disease. Two of the 7 patients probably did have peptic ulcer disease independent of analgesic abuse although

the others either had ulcers associated with aspirin ingestion or did not have ulcer disease as the source of their pain.

As the authors (33) stated, "looking back, it is easy to say that more careful selection would have eliminated an operation on such patients." In each of the patients, the multiplicity of their complaints, seemingly associated with ulcer disease, literally "drove" the surgeon into performing an operation to treat ulcer disease. The procedure became known to these surgeons as an "albatross" procedure, because in these 7 patients, the results of the physicians' deeds remained with them and their colleagues seemingly forever as did the deed of the Ancient Mariner (34). These surgeons were so impressed with the patients and the outcome of their surgery that they described these patients in detail in hopes of preventing similar events in others.

Table 5. Age, Sex, Type of Surgery, Surgical Findings and Clinical Outcome in 7 Patients with the "Albatross" Syndrome (33)

AGE	SEX	TYPE OF SURGERY	SURGICAL FINDINGS	CLINICAL OUTCOME
47	M	1) V and P	No active ulcer	Pain, nausea, vomiting, weight loss, multiple hospital admissions, drug addiction before and after surgery
		2) Subtotal Gastrectomy	No active ulcer	
42	F	Vagotomy, 2/3 Gastrectomy, Billroth II	Severe, perforated DU	Pain persisted after surgery, diarrhea, nausea, vomiting, severe malnutrition, salicylate addiction before and after surgery
35	F	2/3 Gastrectomy Billroth I	? cm chronic benign GU	Severe chronic constipation, abdominal pain, bloating, malnutrition, salicylate addiction before and after surgery
56	M	60% Gastrectomy, Billroth I	Small benign GU	Pain,diarrhea,weakness,addiction to codeine and salicylate abuse
37	F	1) Partial Gastrectomy, Billroth I 2) Converted to Billroth II	2 benign prepyloric ulcers	Abdominal pain, depression; after second operation she developed toothaches and backaches; consumed large amounts of salicylates and phenacetin; several episodes of coma and metabolic acidosis; renal failure - death
46	F	Partial Gastrectomy	Thought to have gastric outlet obstruction; instead had mesenteric artery compression of duodenum; no ulcer found	Abdominal pain, vomiting, anemia, nutritional deficiency, psychoneurosis; developed more severe symptoms after gastrectomy; 15 psychiatric admissions, 6 admissions for overdose of sedative drugs and finally she was committed to a mental hospital
58	F	Vagotomy; Gastroenterostomy	No ulcer disease found	Vomiting, postprandial distress, bile reflux,barbiturate addiction

The surgery in these patients was performed by experienced surgeons. All but one of the patients had an operation for presumed intractability of their ulcer disease. However, it appears that except for one patient (#2) the ulcer disease was not intractable but instead the symptoms were due to multiple factors related primarily to the personality of the patient or their underlying psychiatric disease. The benign gastric ulcers were believed to be secondary to massive ingestion of salicylates. Patients with personality defects undergoing ulcer operations appear to be in three groups:

1) those with true chronic peptic ulcer disease but in whom the indications for surgery were not carefully considered (see Indications for Surgery; Intractability).

2) those with ulcer disease in whom the primary factor was salicylate addiction.

3) those who underwent ulcer operations in the absence of signs of chronic ulceration.

In the first group with true peptic ulcer disease, the problem is determining the best method of treating the ulcer. It is extremely important to document the presence of an ulcer by endoscopy. Also, with current medical therapy, it is now easier to treat ulcers medically than when the "Albatross" syndrome was first described. If a patient has a history of psychiatric disease, medical therapy should be pursued vigorously and except in rare circumstances, surgery should be reserved for complications of ulcer disease in these patients. Every effort should be made to treat their psychiatric disease.

The second group of patients are those with a history of ingestion of large amounts of salicylates or other non-steroidal anti-inflammatory drugs. It is likely that in these patients aspirin or other similar drugs leads to gastric ulceration. If salicylate addiction is diagnosed, it should be remembered that the underlying personality defect led to the addiction which requires therapy and not the ulceration. The only effective treatment in many of these patients is to try to get them to discontinue salicylates and begin psychiatric therapy. Surgery, without addressing the addiction, simply results in recurrence of ulceration without any relief of the underlying problem. In addition, after ulcer surgery, the patients usually have other post-gastrectomy complaints plus recurrent ulceration.

The third group of patients are those who have no evidence of ulcer disease. Surgery clearly has no place in these patients but frequently these patients have multiple tests searching for the source of pain. Eventually they have a upper gastrointestinal barium x-ray which is interpreted as showing some abnormality. With this and with the insistence of the patient, an ulcer operation is eventually performed. Almost invariably these patients are worse off after surgery and many of them eventually have multiple surgical procedures looking for the source of their pain and in an attempt to solve their post-gastrectomy problems. The key to treating this type of patient is not to allow such a patient to have surgery without documenting the presence of a non-healing ulcer by endoscopy. Even with this, there is no absolute way to prove that the non-healing ulcer is the cause of pain or that the operation will solve the patient's problems.

The major lessons to be learned from review of patients with the "Albatross" syndrome is to be wary of referring patients to surgery for ulcer disease if 1) they have a history of drug addiction (especially salicylate or

other non-steroidal anti-inflammatory drugs), 2) they have a known personality disorder or history of psychiatric disease, or 3) they do not have an ulcer documented by endoscopy.

Gastritis Following Gastric Surgery

Gastritis is a common histologic and endoscopic finding after either a subtotal gastrectomy or antrectomy has been performed for peptic ulcer disease. This form of gastritis is often referred to as bile reflux or alkaline gastritis, reflecting the theory that it is caused by the reflux of bile or pancreatic juice or both into the gastric remnant (35). Features believed to be compatible with the diagnosis include 1) epigastric pain, heartburn, nausea, and vomiting (often vomiting of bile-containing material) and/or weight loss; 2) presence of bile in the gastric remnant; 3) endoscopic evidence of gastritis; and 4) histologic evidence of gastritis. None of these features, however, are specific for the diagnosis. For example, such symptoms frequently occur following ulcer surgery with or without histologic or endoscopic evidence of gastritis. Furthermore, histologic or endoscopic changes can occur in postoperative patients who are asymptomatic. The presence of bile in the gastric remnant also does not mean necessarily that patients have bile-induced gastritis, because it is very easy for bile and other duodenal contents to reflux into the gastric remnant. Thus, caution should be exercised in making the diagnosis of bile reflux gastritis.

Cholestyramine or aluminum hydroxide antacids, as bile acid-binding agents, have been given to patients with postgastrectomy gastritis, but they usually do not alleviate symptoms or reverse the histologic appearance of gastritis. As noted, bile acids alone may not be responsible for symptoms associated with "bile reflux gastritis;" other substances such as pancreatic secretions may be needed to produce gastritis. Corrective surgery has consisted of procedures designed to divert duodenal contents away from the gastric remnant. The most commonly used operation is called a Roux-en-Y diversion (Figure 22). Some but not all studies have shown this procedure to be successful in relieving symptoms. Surgery should be reserved for patients with incapacitating symptoms.

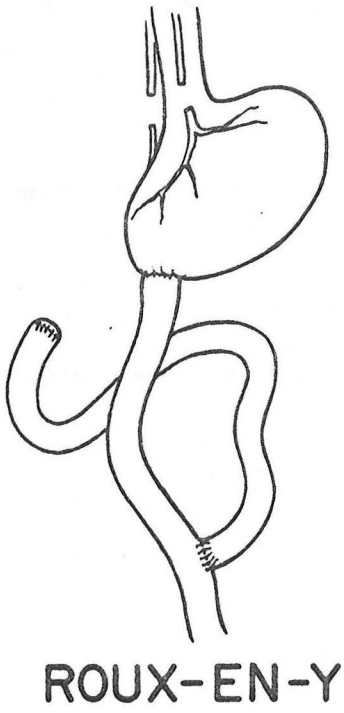

Figure 22. Model illustrating a Roux-en-Y diversion.

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Recurrent Ulcer After Ulcer Surgery

While diarrhea, malabsorption, weight loss, "dumping," and other postoperative side effects are troublesome clinical problems, recurrent ulcer after ulcer surgery is one of the most important sequelae since the original operation was performed to hopefully cure the disease (1,2). As much as any other single postoperative problem, recurrent ulcer has been a major impetus for developing new surgical approaches to ulcer therapy. For example, it was recognized that sub-total gastrectomy was not an adequate treatment, especially in patients with duodenal ulcer disease. This led to the popularization of vagotomy and pyloroplasty and vagotomy plus antrectomy (see section on History of Peptic Ulcer Surgery).

Incidence. Recurrent ulcers after ulcer surgery occur more commonly in males than females (1,3-5). The majority of recurrent ulcers (about 95%) occur following surgery for duodenal ulcer disease while 2 to 4% occur following gastric ulcer surgery and 2% develop after surgery for combined gastric and duodenal ulcers (3,7).

Most recurrent ulcers occur distal to an anastomosis. For example, if a patient has had a gastroduodenostomy (Billroth I), the recurrent ulcer will be in the duodenum. On the other hand, if the patient has had a gastrojejunostomy alone or with an antrectomy (Billroth II), the recurrent ulcer will usually be in the jejunum.

The incidence of recurrent ulcer differs with the various operations used to treat patients with ulcer disease. For example, simple gastroenterostomy for uncomplicated ulcer disease has a very high recurrence rate (34% in some series) (8). The explanation for this high recurrence rate is uncertain but likely is due to the fact an acid reducing (i.e., vagotomy) operation was not done initially. History has demonstrated that the lowest incidence of recurrence occurs with vagotomy and gastric resection which is associated with recurrences of 0 to 3.3% (9,10). Other less destructive surgical procedures (relative to anatomy and physiology, see Figure 18) such as gastric resection alone or vagotomy and emptying procedure are associated with recurrences of 1 to 15% (11,12) and 2 to 27% (13,14) with the two procedures, respectively. The mortality and 5-year cumulative incidence of recurrent ulcer in the Veterans Administration Cooperative Study are shown in Table 5 (15).

Table 5. Mortality and 5-Year Cumulative Incidence of Recurrent Ulcer in 1357 Patients Randomized to Various Forms of Ulcer Surgery: Veterans Administration Cooperative Study (from Ref. 15)

TYPE OF SURGERY	MORTALITY	RECURRENT ULCER (%)
Subtotal Gastrectomy		3.7
Vagotomy and Hemigastrectomy	0.6	0.9
Vagotomy and Antrectomy	0.9	0.7
Vagotomy and Drainage	0.6	6.2

Signs and Symptoms. As with ulcer disease prior to the initial operation, pain is the most common manifestation of recurrent ulcer, occurring in about 45% of patients (16). Bleeding as a presenting sign of recurrent ulcer is more common in patients with ulcer after surgery than in those with pre-operative ulcer disease. For example, hemorrhage occurs in about 41% of patients with recurrent ulcer. Other signs and symptoms of recurrent ulcer disease include obstruction (12%) and perforation (1%).

Diagnosis. Endoscopy is the best method of diagnosing a recurrent ulcer. After most operations for ulcer disease the anatomy of the stomach and small bowel is distorted and frequently it is difficult to diagnose postoperative recurrent ulcers on a barium x-ray.

Causes of Recurrent Ulcer Disease. There are several possible explanations for recurrent ulcer after ulcer surgery. The most frequent cause is inadequate surgery, usually in the form of incomplete vagotomy. When gastric resection alone (without vagotomy) has been performed in patients with ulcer disease (especially duodenal ulcer), recurrent ulcers have occurred as a result of inadequate gastric resection. For example, in patients with duodenal ulcer disease, resections of 30 to 50% of the stomach were associated with recurrences of 36% whereas resections of 50 to 70% had an incidence of recurrence of only 12% (17).

The causes of recurrent ulcers after surgery are summarized in Table 6.

Table 6. Causes of Recurrent Ulcer After Ulcer Surgery

1. Incomplete Vagotomy
2. Drugs (aspirin, other non-steroidal anti-inflammatory drugs)
3. Zollinger-Ellison syndrome
4. Obstruction (usually obstruction at the anastomosis or in the proximal efferent loop)
5. Ulcer in an area of non-absorbable suture
6. Cancer (in gastric mucosa)
7. Retained antrum syndrome

Incomplete Vagotomy. As stated previously, this is the most common cause of recurrent ulcer after ulcer surgery. Incomplete vagotomy can occur after truncal vagotomy and pyloroplasty, truncal vagotomy and antrectomy or parietal cell vagotomy. Stimulation of acid secretion by the intact or partially intact vagal nerves almost certainly is the cause of ulcer disease in these patients. In fact, these patients serve as one of the models adding credence to the hypothesis that acid, at least in some patients, causes ulcers.

Non-Steroidal Anti-inflammatory Drugs. These agents cause ulcers in patients both before and after surgery primarily by decreasing mucosal defense. Inhibition of prostaglandin synthesis is believed to be the major mechanism whereby this occurs (18).

Zollinger-Ellison Syndrome. This syndrome was described first in patients who developed recurrent ulcers after ulcer surgery. Today, the diagnosis is made usually preoperatively because of the ready availability of serum gastrin assays. Occasionally, however, patients have surgery for what is believed to be ordinary peptic ulcer disease but later are found to have Zollinger-Ellison sydnrome when they reappear with recurrent ulcers.

Obstruction. This is a rare cause of recurrent ulcers. Patients occasionally have a narrowed anastomosis either because of improper surgical technique or because of scarring. Recurrent ulcers presumably occur because of delayed gastric emptying. Sometimes the obstruction may develop in the efferent loop of a Billroth II anastomosis.

Ulcer in Area of Suture. This, too, is a rare cause of recurrent ulcers. The suture can usually be visualized by endoscopy and can also be removed by passing small clippers through the biopsy channel of an endoscope. The suture is clipped and removed via the endoscope.

Cancer. When an ulcer recurs in the stomach rather than the duodenum or jejunum, cancer should be considered. Biopsies should be obtained from the ulcer margins and the patient should be followed until the ulcer heals completely (see section on Long-Term Consequences of Ulcer Surgery).

Retained Antrum Syndrome. This is an extremely rare cause of recurrent ulcers. The retained antrum is located at the distal end of the afferent loop of a Billroth II anastomosis (Figure 23). The antral tissue in the "blind loop" is continually bathed with alkaline juice. The fact that acid does not reach the gastrin-containing tissue to inhibit gastrin production means that gastrin is released continually into the circulation and serum gastrin concentration increases dramatically.

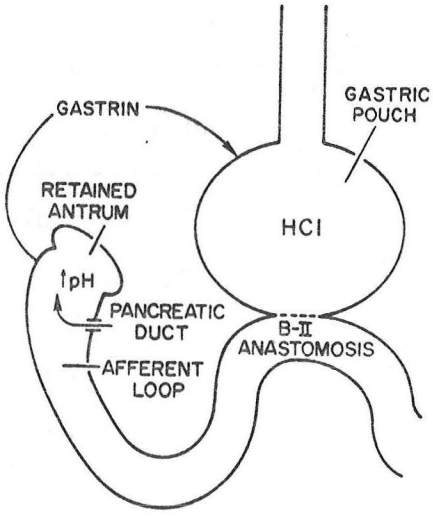

Figure 23. Model illustrating retained antrum.

Evaluation. Patients with suspected recurrent duodenal or gastric ulcer after ulcer surgery should have an endoscopy to confirm the diagnosis and also to look for a retained suture. If a gastric ulcer is present, biopsies (at least 8 to 10) should be obtained. Assuming that the patient has a benign gastric ulcer or duodenal ulcer, serum gastrin concentration should be measured to rule out Zollinger-Ellison syndrome. In addition, a careful history should be obtained to rule out excessive ingestion of aspirin or other non-steroidal anti-inflammatory drugs. If serum gastrin concentration is normal, a test of vagal function should be performed. Historically, insulin was used to induce hypoglycemia. Hypoglycemia stimulates acid secretion via central-vagal mechanisms. Therefore, an increase in acid secretion with insulin hypoglycemia suggests an incomplete vagotomy (Hollander Test) (19-21). The Hollander Test, however, is dangerous and several patients have developed myocardial infarctions,

cerebrovascular accidents and even death as a result of insulin hypoglycemia (21). Sham feeding can be used as a method of testing vagal function (22-26). The test is carried out by feeding an appetizing meal consisting of sirloin steak, french fried potatoes and water (22,23). The meal is chewed and expectorated by the patient. The design of the test is illustrated in Figure 24.

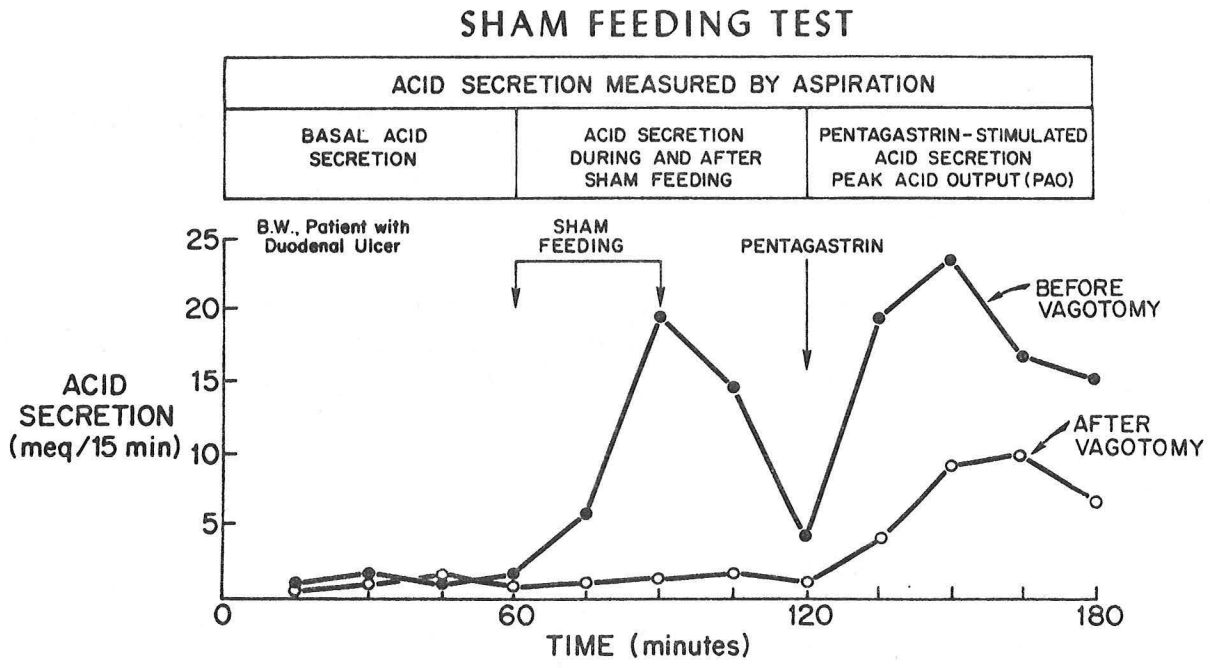

FIGURE 24. Design of the sham feeding test of vagal function. Results in a patient before (closed circles) and after (open circles) vagotomy are shown.

Basal acid output (BAO) is measured for one hour, sham-feeding stimulated output (SAO) is measured the second hour, and pentagastrin-stimulated peak acid output (PAO) is measured for the third hour. As can be seen in Figure 23, BAO, before vagotomy, averaged about 1-3 meq/15 min. With a 30 minute period of sham feeding, acid secretion increased to 19 meq/15 min and then returned to near basal levels during the next 30 minute period. With pentagastrin, acid secretion increased again and reached a level of 23 meq/15 min at 30 minutes after pentagastrin injection. After vagotomy, the response to sham feeding was markedly reduced as was the response to pentagastrin (PAO).

Interpretation of the Sham Feeding Test. Sham acid output (SAO) is calculated by adding together acid output during each 15 minute period of the 30 minutes of sham feeding and the 30 minutes immediately after sham feeding. Using the example in Figure 24, SAO would be 43 meq/60 minutes before vagotomy and 3 meq/60 minutes after vagotomy. Pentagastrin-stimulated, peak acid output (PAO) is calculated by adding the acid secretion rate during the two highest consecutive

15 min periods and multiplying the results by 2 to express acid output in meq/60 min. In the example above, PAO would be 76 meq/60 minutes before vagotomy and 33 meq/60 minutes after vagotomy.

Results of the Sham Feeding Test are calculated by the following equation:

$$\frac{SAO}{PAO} \times 100 = \_\_\%$$

Using the numbers shown above after vagotomy, the results would be:

$$\frac{3}{33} \times 100 = 9\%$$

Based on results of sham feeding tests in a number of normal subjects and duodenal ulcer patients, it has been determined that a SAO/PAO of greater than 10% indicates an incomplete vagotomy while a SAO/PAO less than 10% suggests a complete vagotomy (Figure 25) (23).

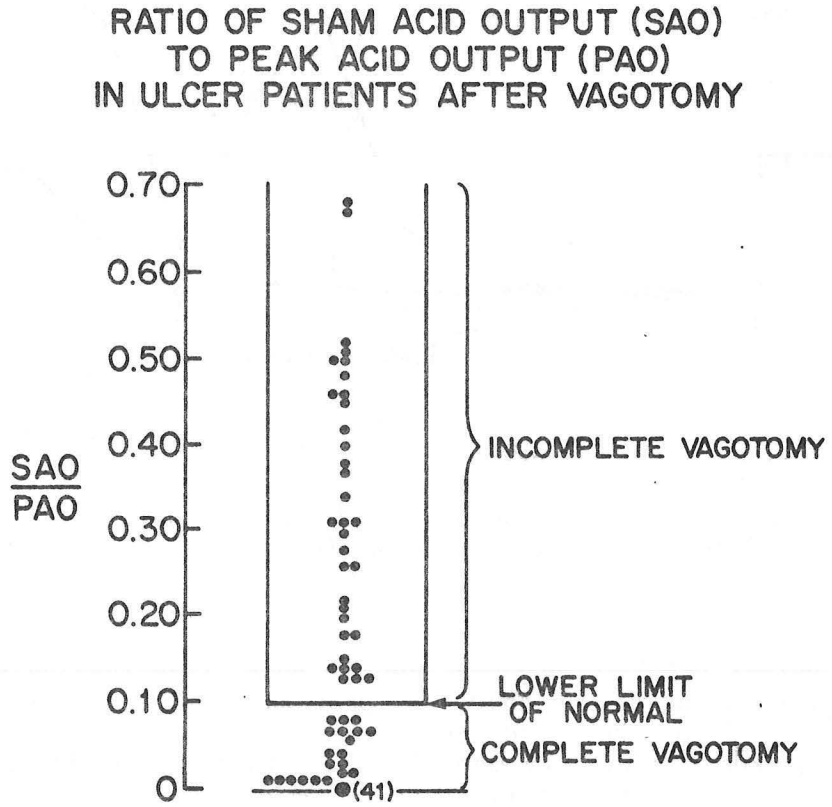

Figure 25. Results in patients with recurrent ulcers who have had a sham feeding test. The limits of normal were determined by performing sham feeding tests in groups of normal subjects and duodenal ulcer patients who had not had a vagotomy. Patients represented by dots within the rectangle have an incomplete vagotomy while dots below the rectangle (ratio less than 0.10) represent results in patients who have had a complete vagotomy.

Treatment of Recurrent Ulcers After Ulcer Surgery. Prior to the advent of cimetidine and ranitidine, almost all patients with recurrent ulcers (especially those with incomplete vagotomy or Zollinger-Ellison syndrome) were treated surgically. Now it is possible to treat many of these patients medically.

Medical Therapy. Results of several studies indicate that patients with recurrent ulcers after ulcer surgery can be treated medically (26-30). For example, 80-90% of postoperative recurrent ulcers will heal within 6-8 weeks when patients have been treated with cimetidine, 200 mg with meals and 400 mg at bedtime or with ranitidine, 150 mg twice daily. Even though healing of active postoperative recurrent ulcers with H_2-receptor antagonists is as good as healing of active ulcers in patients who have had surgery, the incidence of relapse once medication is stopped is quite high in patients with recurrent ulcers. Since most patients with postoperative recurrent ulcers have incomplete vagotomy, it is likely that continued acid secretion in an individual patient bathing susceptable duodenal or jejunal mucosa explains the high incidence of recurrence. Because the likelihood of another ulcer is so high, maintenance therapy with cimetidine or ranitidine is recommended in patients with postoperative recurrent ulcers. The doses usually prescribed for maintenance treatment are 400-800 mg cimetidine or 150 mg ranitidine at bedtime. Even with maintenance therapy, 10-16% of patients will develop another recurrent ulcer while taking maintenance cimetidine or ranitidine (26). Also, once long-term therapy is stopped, 75% of patients develop another ulcer recurrence within 18 months of cessation of maintenance treatment. Thus, if a patient with postoperative recurrent ulcer is treated medically, he should be treated for life.

It seems reasonable to treat most patients medically who have their first post-operative recurrent ulcer. These patients should be treated initially for their active ulcer and then placed on maintenance therapy. If a recurrence develops while on medication, surgery should be recommended in most of these patients.

Surgical Therapy. Indications for surgery in patients with postoperative recurrent ulcers are similar to those in patients with ordinary peptic ulcer disease. Surgery should be performed in most patients with postoperative recurrent ulcers that fail to heal on medical therapy or that develop a recurrent ulcer while on maintenance medical therapy. Most patients with perforation or obstruction should have surgery. In general, patients who bleed from a postoperative recurrent ulcer should have surgery. However, the age and medical condition of the patient should play a role in deciding when to operate on someone for a bleeding postoperative ulcer. Also, if a patient has a recurrent ulcer with bleeding and the patient has been taking large amounts of non-steroidal anti-inflammatory drugs, consideration should be given to stopping non-steroidal therapy and treating the patient with cimetidine or ranitidine.

If the decision is made to operate, the type of repeat surgery is controversial (31-35). If a sham feeding test indicates incomplete vagotomy (see Figure 24), the patient should have a repeat vagotomy. If a patient has had a previous vagotomy and antrectomy, a transthoracic vagotomy is the surgical therapy of choice (31). On the other hand, there is controversy as to the type of surgery in patients who have had vagotomy and pyloroplasty as the initial operation. Some recommend transthoracic vagotomy as the repeat procedure while others suggest repeat abdominal vagotomy and antrectomy. If a patient has had a parietal cell vagotomy as the initial operation, a transthoracic vagotomy is contraindicated since the patient has not had an emptying procedure. An abdominal vagotomy and antrectomy is probably the treatment of choice in a patient who has had an inadequate parietal cell vagotomy as the initial procedure.

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