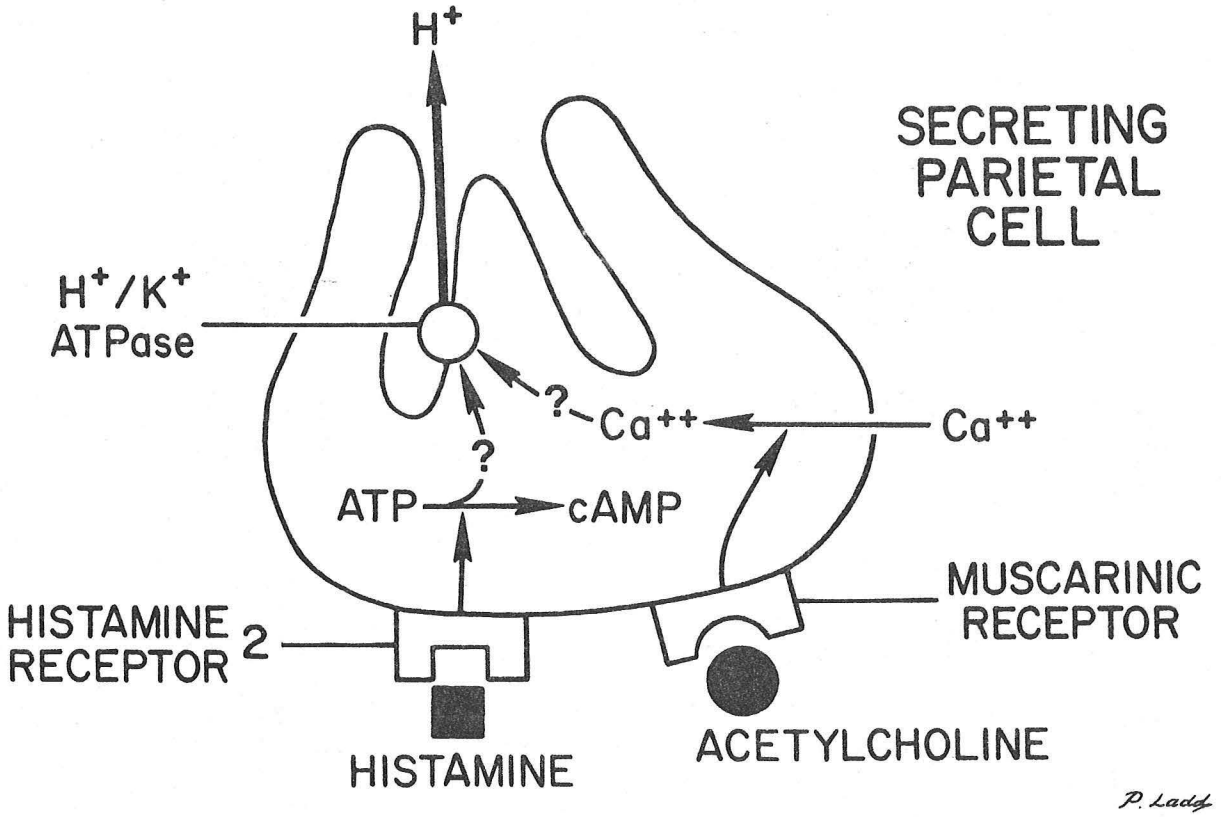
6I

NEW DEVELOPMENTS IN PEPTIC ULCER DISEASES



MEDICAL GRAND ROUNDS

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INTRODUCTION

Peptic ulcers occur in areas of the gastrointestinal tract exposed to acid and pepsin. The most common locations are the stomach and duodenal bulb, although they may also be found in the lower end of the esophagus. Rarely, peptic ulcers occur in other areas of the gastrointestinal tract. For example, they can develop in the jejunum of patients with acid-hypersecretory states such as Zollinger-Ellison syndrome or can occur in the ileum of patients with Meckel's diverticulum.

Peptic ulcers usually occur at or near mucosal junctions. For example, gastric ulcers are found near the junction of parietal cell (acid-secreting) and antral mucosa, whereas duodenal ulcers occur near the junction of antral and duodenal mucosa. Gastric ulcers usually are found on the antral side of the mucosal junction. Presumably, ulcers occur in junction or border zones because the mucosa in these areas is less resistant to acid, pepsin, or other damaging factors.

It is not known whether gastric and duodenal ulcers have a similar or different pathogenesis. Although there are differences with regard to age, sex, prevalence and incidence between patients with gastric and duodenal ulcers; in general, there is too much acid and pepsin for a given degree of mucosal defense. The relative importance of either increased acid and pepsin or decreased mucosal defense in the pathogenesis of peptic ulcers in individual patients is unknown. Some patients may get ulcers because of too much acid and pepsin while others may get ulcers because of too little mucosal defense. A combination of too much acid and pepsin and too little mucosal defense may be important in other patients. Other factors such as reflux of bile and pancreatic juice into the stomach, delayed gastric emptying, heredity, emotional stress, drugs (such as salicylates and other nonsteroidal antiinflammatory compounds), and cigarettes may play a role in the pathogenesis of peptic ulcers in some patients.

ACID SECRETION IN NORMAL HUMANS AND ULCER PATIENTS

NORMAL HUMAN SUBJECTS

Basal acid output (BAO) is the amount of acid secreted under unstimulated conditions. Peak acid output (PAO) is acid secreted in response to an injection of either 6 μg/kg pentagastrin or 40 μg/kg histamine. PAO is believed to be the most or maximum amount of acid that a normal subject or patient with ulcer disease can secrete. Studies have shown that PAO is also an estimate of parietal cell (acid secreting cell) mass (1). BAO/PAO represents the fraction of parietal cell mass that is functional under basal conditions. A higher than normal BAO/PAO means that a person has a basal hypersecretory state such as Zollinger-Ellison syndrome, increased vagal stimulation, or systemic mastocytosis.

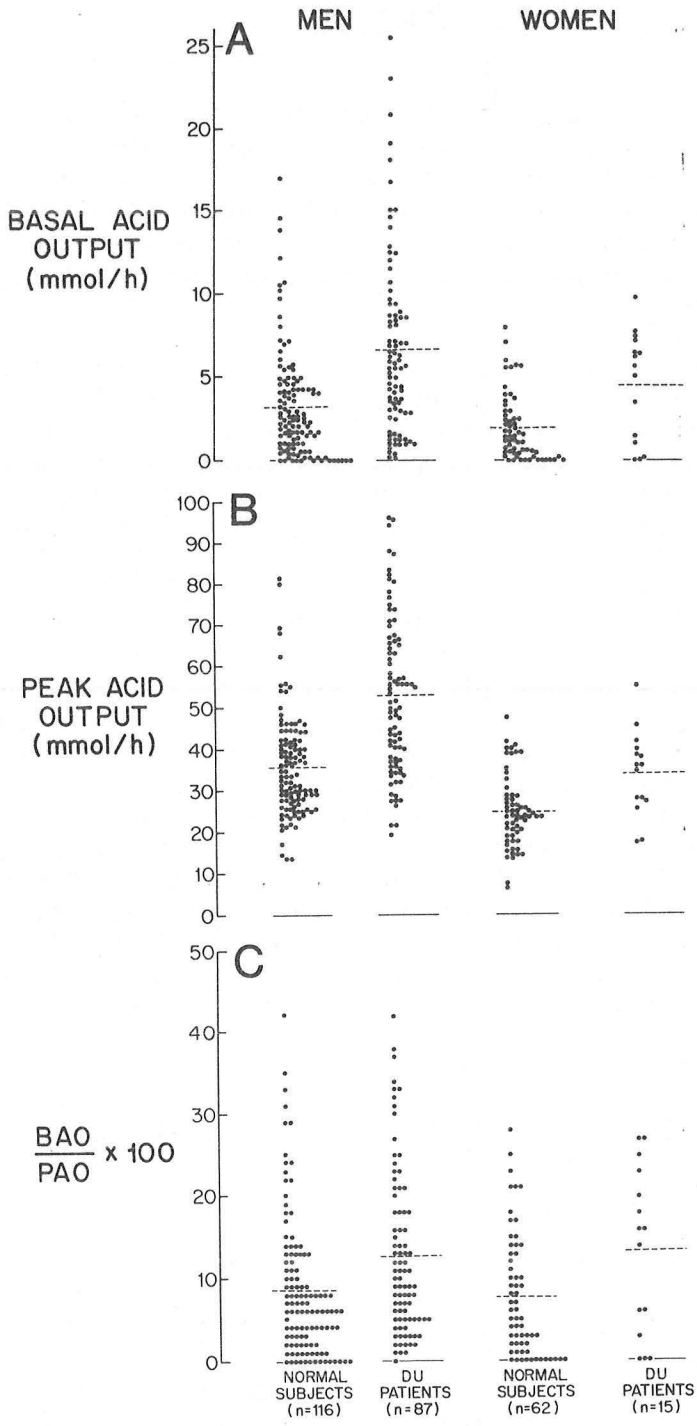

Figure 1. Basal acid output (BAO), peak acid output (PAO), and the ratio of BAO/PAO in normal men and women and in patients with duodenal ulcers. (Data from the Gastroenterology Research Laboratory, Dallas VA Medical Center).

The upper and lower limits of normal, based on data from Figure 1, are shown in Table 1.

TABLE 1. UPPER (ULN) AND LOWER (LLN) LIMITS OF NORMAL ACID SECRETION IN HEALTHY MEN AND WOMEN

	Acid Output (mmol/hr)		
	BAO*	PAO*	BAO/PAO
MEN (N=116)			
ULN	10.5	60.6	0.29
LLN	--	11.6	--
WOMEN (N=62)			
ULN	5.6	40.1	0.23
LLN	--	8.0	--

* The ULN for basal acid output (BAO) was determined by excluding the top 5% of values since values for BAO and BAO/PAO (Figure 1) were not normally distributed. There is no LLN for BAO or BAO/PAO since a large number of subjects had a BAO of zero. The ULN and LLN for PAO were determined by calculating the mean $\pm$ 1.96 S.D. since values for these parameters were normally distributed.

Men secrete more acid than women. This can be explained, in part, by differences in body size between the sexes. However, some studies have shown that men still secrete more acid than women even when acid secretion is calculated on a weight or lean body mass basis (2-4).

PATIENTS WITH DUODENAL ULCERS

BAO, PAO, and BAO/PAO in patients with duodenal ulcers are also shown in Figure 1. Mean BAO, PAO, and BAO/PAO are higher in patients with duodenal ulcers than in normal subjects. However, when the upper limits for normal values for BAO, PAO, and BAO/PAO shown in Table 1 are applied to the data for patients with duodenal ulcer shown in Figure 1, it can be seen that most patients with duodenal ulcers have acid secretory rates that are in the normal range. Although not shown in Figure 1, mean acid secretion rates in patients with gastric ulcers are lower than normal. However, most patients with gastric ulcers also have acid secretion rates that are in the normal range. It is very unusual for a patient with a gastric ulcer to have higher than normal acid secretion.

Summary: Most patients with either duodenal or gastric ulcers secrete normal amounts of gastric acid. Since, in general, pepsin secretion parallels acid secretion, pepsin secretion is also normal in most ulcer patients.

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PATHOGENESIS OF ULCER DISEASE

PATIENTS WITH HIGHER THAN NORMAL ACID AND PEPSIN SECRETION

It is believed that patients with higher than normal rates of acid secretion probably get ulcers as a result of too much acid and pepsin. In other words, the aggressive effects of acid and pepsin overcome normal mucosal protective mechanisms (See page 6). There have been a number of different studies evaluating acid secretion and gastrin release in small groups of duodenal ulcer patients compared to normal subjects and several pathophysiologic defects have been described (Table 2). These abnormalities are thought to lead to higher than normal acid secretory rates in some ulcer patients.

TABLE 2. PATHOPHYSIOLOGIC ABNORMALITIES LEADING TO HIGH RATES OF ACID SECRETION IN SOME DUODENAL ULCER PATIENTS*

PATHOPHYSIOLOGIC ABNORMALITY	MANIFESTATION OR DISEASE
1. Increased parietal and chief cell mass (1-4).	Higher than normal PAO and serum pepsinogen I (serum pepsinogen I correlates with acid secretion rates).
2. Increased basal secretory drive (high BAO/PAO) (5-7).	Zollinger-Ellison syndrome (gastrinoma, increased gastrin); Systemic mastocytosis (increased histamine) Retained antrum (increased gastrin) Increased vagal tone (? increased acetylcholine) ? Antral G-cell hyperfunction ? Decreased inhibitors of acid secretion (? short bowel syndrome)
3. Increased food-stimulated acid secretion (8-14).	Decreased acid inhibition of gastrin release. Increased parietal cell sensitivity to gastrin and perhaps histamine

* Modified from Soll, A.H., and Isenberg J.I. Duodenal Ulcer Diseases. In: Gastrointestinal Disease: Pathophysiology, Diagnosis, Management. 3rd edition. Sleisenger, M.H., and Fordtran, J.S., eds., W.H. Saunders Co., Philadelphia, Pa, in press.

Studies have reported that some patients with duodenal ulcers also have increased gastric emptying (15,16). Thus, even in patients with normal rates of acid secretion, rapid gastric emptying might lead to increased acidification of the duodenal bulb.

Summary: In general, patients with higher than normal rates of acid secretion probably get ulcers because of too much acid and pepsin. However, other factors (see below) can not be excluded.

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PATIENTS WITH NORMAL RATES OF ACID AND PEPSIN SECRETION

Patient 1.

L. B. is a 45 year old man who has had intermittant epigastric pain for the past 5 years. He has been treated with cimetidine on at least 8 occasions during the past three years and with each course of cimetidine symptoms resolve. During a symptomatic episode, upper gastrointestinal x-ray revealed a deformed duodenal bulb with an active ulcer. Recently, he was admitted to the hospital because he developed hematemesis and melena. Upper gastrointestinal endoscopy showed an active duodenal ulcer. Because of the complication and the frequent recurrences of symptoms, acid secretion and serum gastrin concentration were measured to rule out Zollinger-Ellison syndrome.

BAO - 3.7 mmol/h
PAO - 39.8 mmol/h
Serum gastrin concentration - 80 pg/ml
(nl <200 pg/ml)

Why did ulcer disease develop in Patient 1? The answer to this question is not known, although ulceration in many patients with a normal BAO and PAO is believed to occur because of decreased mucosal defense. Under these circumstances, even normal amounts of acid and pepsin may lead to ulceration.

Prior to discussing possible reasons for altered mucosal defense, I will discuss normal mucosal protective mechanisms.

Normal Mucosal Protective Mechanisms

Factors thought to be important in mucosal protection are listed in Table 3.

TABLE 3. NORMAL MUCOSAL PROTECTIVE MECHANISMS

1. Mucus secretion
2. Bicarbonate secretion
3. Blood flow

In the stomach, mucus and bicarbonate are secreted by epithelial cells that line the pits and glands (Figure 2). Acid secreting (parietal) cells, pepsin secreting (chief) cells, and a few endocrine cells are also located in the pits (1).

The duodenum contains Brunner's glands. Brunner's glands are located in the submucosa, however they communicate with the mucosal surface through small ducts that open into the base of mucosal crypts. Brunner's glands, as well as the superficial epithelial cells of the duodenum, secrete bicarbonate and mucus (1). Mucus and bicarbonate are believed to protect the gastric and duodenal mucosa from acid, pepsin and other injurious agents.

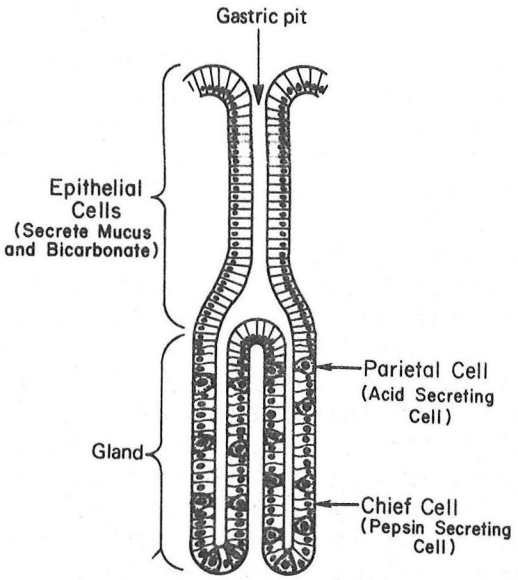

Figure 2. Model of gastric mucosa illustrating pits and glands. Parietal, chief and mucus cells lines the pits and glands.

Mucus Secretion

A thin coat of mucus covers the cells lining the gastric mucosa. Mucus is secreted as a glycoprotein gel that adheres to the cellular surface (Figure 3). It contrasts with other gastrointestinal secretions which are water soluble. Because of its gelatinous nature and because its structure contains complex glycoprotein molecules, mucus is difficult to study and its physiology and pathophysiology is poorly understood.

FUNCTION OF MUCUS GEL LAYER

1. **To protect underlying mucosal cells**
2. **To lubricate mucosa**
3. **To retain water and provide aqueous environment for cells**
4. **To form an unstirred layer impeding diffusion of hydrogen ions**

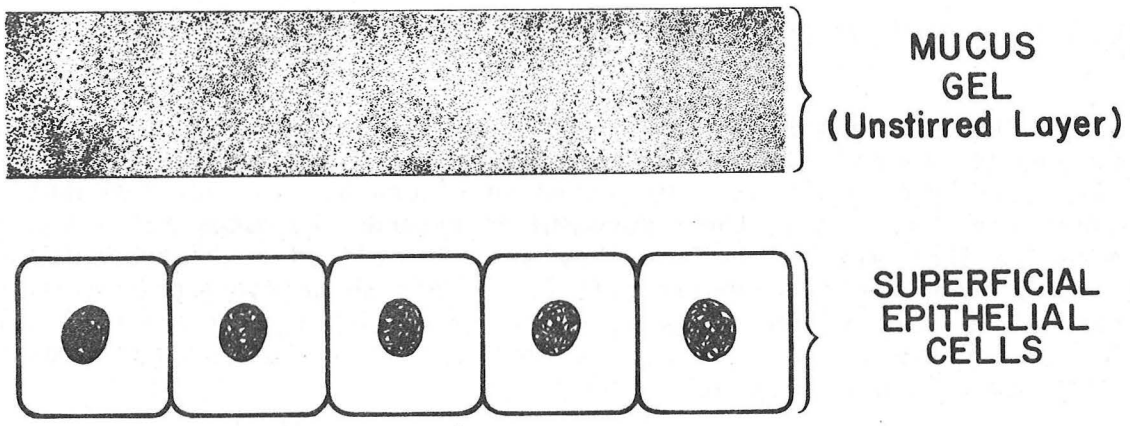

Figure 3. Model illustrating superficial epithelial cells, and mucus gel.

Mucus is secreted by three methods: 1) exocytosis, 2) apical expulsion and 3) exfoliation (Figure 4) (2).

Mucus is thought to have several functions. These are: 1) to protect underlying mucosal cells from mechanical forces of digestion; 2) to lubricate the mucosa assisting the movement of food over the surface; 3) to retain water within the mucus gel and provide a continuous aqueous environment for the mucosa; and 4) to form an unstirred layer impeding, but not blocking, diffusion of hydrogen ions from the gastric lumen to the apical membrane of epithelial cells. Mucus is constantly being produced but it also is being removed continuously from the epithelial surface by mechanical forces during the mixing and grinding of food and by pepsin, which degrades mucus into glycoprotein subunits (see Figure 8). The role (if any) that this process might play in causing the mucosa of ulcer patients to be more vulnerable to ulceration is discussed on pages 10 and 11.

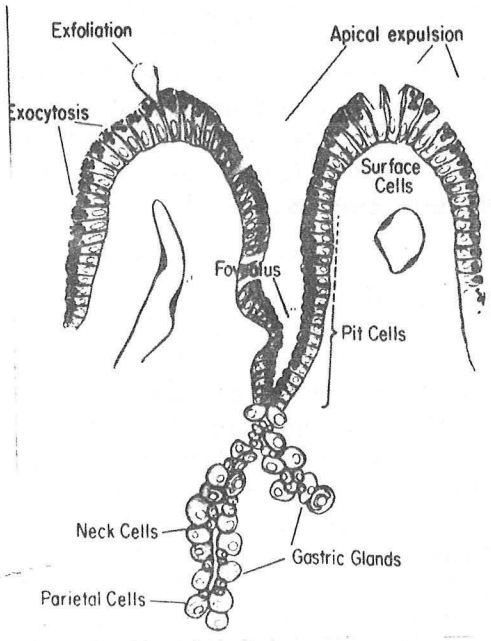

Figure 4. Diagram illustrating three mechanisms of mucus secretion.

Bicarbonate Secretion

Non-parietal (non-acid) secretion which is believed to consist primarily of a bicarbonate-rich fluid is secreted from surface epithelial cells (Figure 5). Although some bicarbonate reaches the lumen much of the secreted bicarbonate remains below or within the mucus layer (3). Thus, in most patients, the mucosal surface is in contact with neutral fluid, regardless of the amount of acid within the lumen. Mucus and bicarbonate together serve to protect the mucosa from damaging effects of hydrochloric acid and pepsin.

Hydrogen Ion Gradient from Lumen to Surface Epithelial Cells

In 1959, Heatley hypothesized that a pH gradient existed through the mucus layer so that if luminal pH was low, the pH next to mucosal cells would be 7 or above (4). This hypothesis is illustrated in Figure 5. As hydrogen ions diffuse through the mucus layer, their movement is retarded by mucus gel and as they come closer to the cellular surface they are neutralized by bicarbonate ions. The pH near the surface is approximately 7.4. This pH gradient presumably will be maintained as long as the mucus layer is normal in quanity and quality, as long as the secretion of bicarbonate is normal, and as long as the amount of acid in the lumen is not inordinately high.

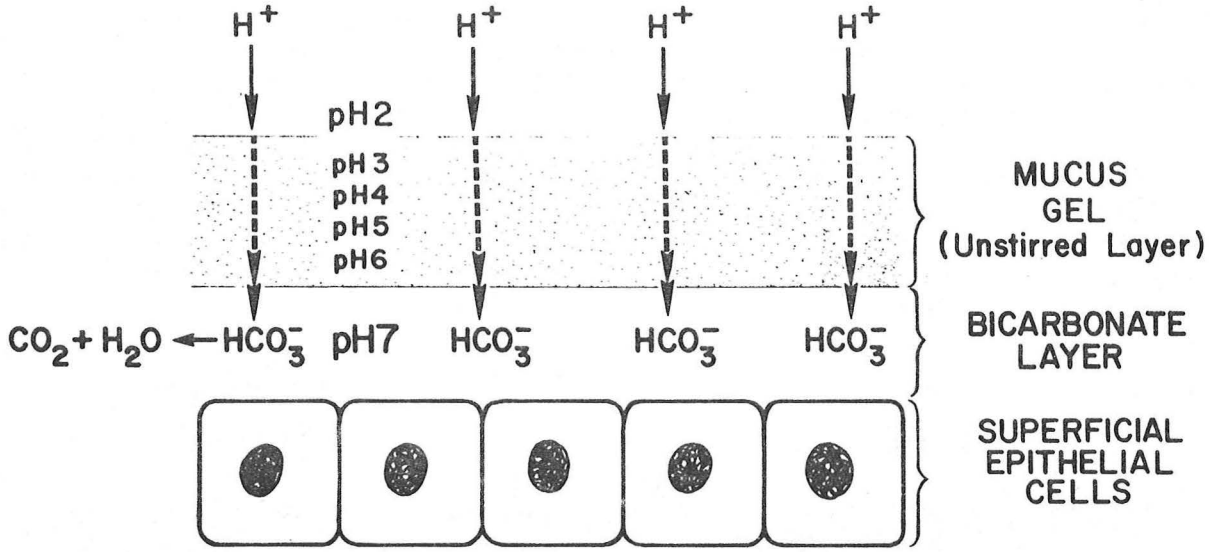

Figure 5. Model illustrating pH gradient in mucus layer and neutralization of hydrogen ions by bicarbonate as they reach surface epithelial cells.

Recently, Heatley's hypothesis has been confirmed in vivo in rats and rabbits (5,6). A pH probe was used to measure luminal pH and then the pH probe was passed through the mucus layer of rat gastric mucosa and pH was measured at various steps. As the probe passed through the mucus layer and approached cell membranes, pH increased (Figure 6). pH decreased as the probe entered epithelial cells.

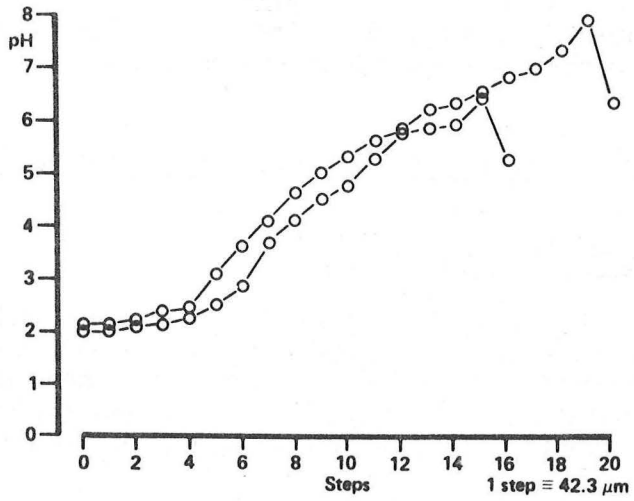

Figure 6. Demonstration of pH gradient across layer of mucus gel in the stomach of rats (from ref. 5).

So far, methods have not been developed to measure pH through mucus layers in humans in vivo.

Blood Flow

The gastric mucosa has a rich blood supply, consisting of arborizing mucosal capillaries which traverse the glandular layer of the stomach (Figure 7). In addition, beneath the muscularis mucosa, there is an extensive system of arteriovenous anastomoses which are thought to play an important role in regulating blood supply to the surface cells (7). This arrangement of vessels in the mucosa and submucosa is the same in all parts of the stomach. However, the blood supply to these mucosal and submucosal vessels is different on the lesser curvature of the stomach than on the greater curvature and in other areas of the stomach. For example, on the lesser curvature, mucosal capillaries and submucosal arteries arise directly from the left gastric artery whereas in other parts of the stomach, mucosal capillaries arise from a submucous plexus of larger vessels (Figure 7).

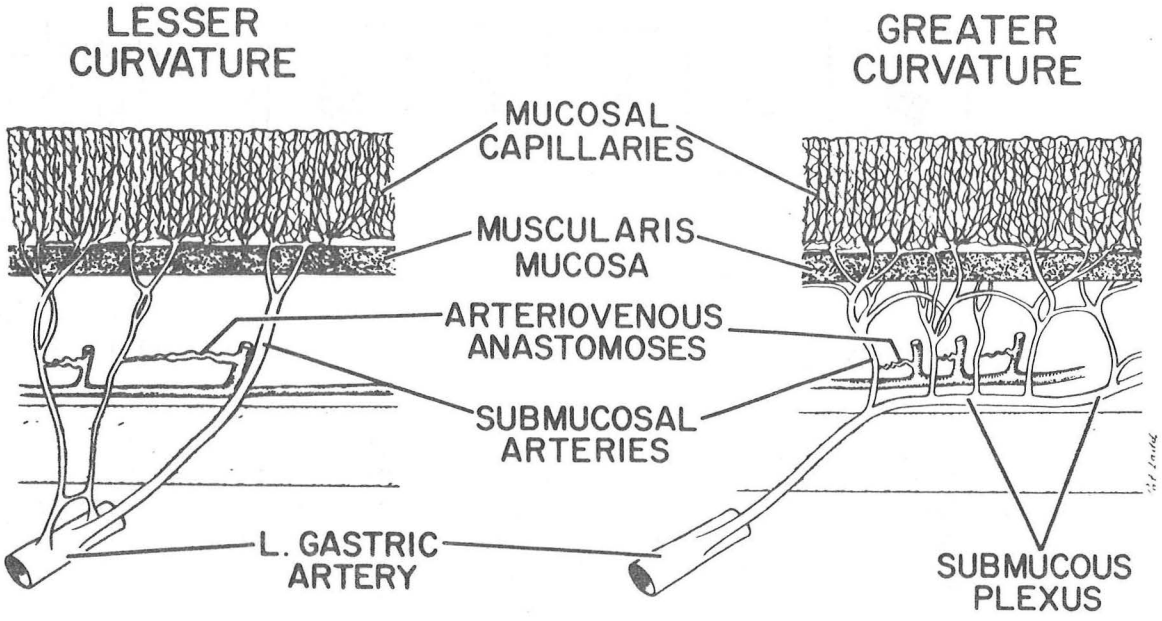

Figure 7. Diagram illustrating blood flow to the gastric mucosa. Note differences in blood flow between lesser and greater curvatures.

Mechanisms Whereby Alterations in Mucosal Defense May Lead to Ulcer Disease

Mucus Secretion

The quantity and quality of mucus gel is believed important in maintaining mucosal defense. There are at least three methods whereby mucus gel may be altered. These are 1) increased degradation of mucus by pepsin, mechanical forces, and perhaps, bile salts and pancreatic enzymes; 2) decreased secretion of normal mucus; or 3) secretion of structurally abnormal mucus.

1. Increased degradation of mucus by pepsin, mechanical forces, or ? bile salts and pancreatic enzymes. Mucus is continuously secreted onto the surface of gastric and duodenal mucosa but is also continuously being degraded by pepsin (Figure 8). Bile salts, pancreatic enzymes, and mechanical forces may damage the gastric mucosa by a similar mechanism (8).

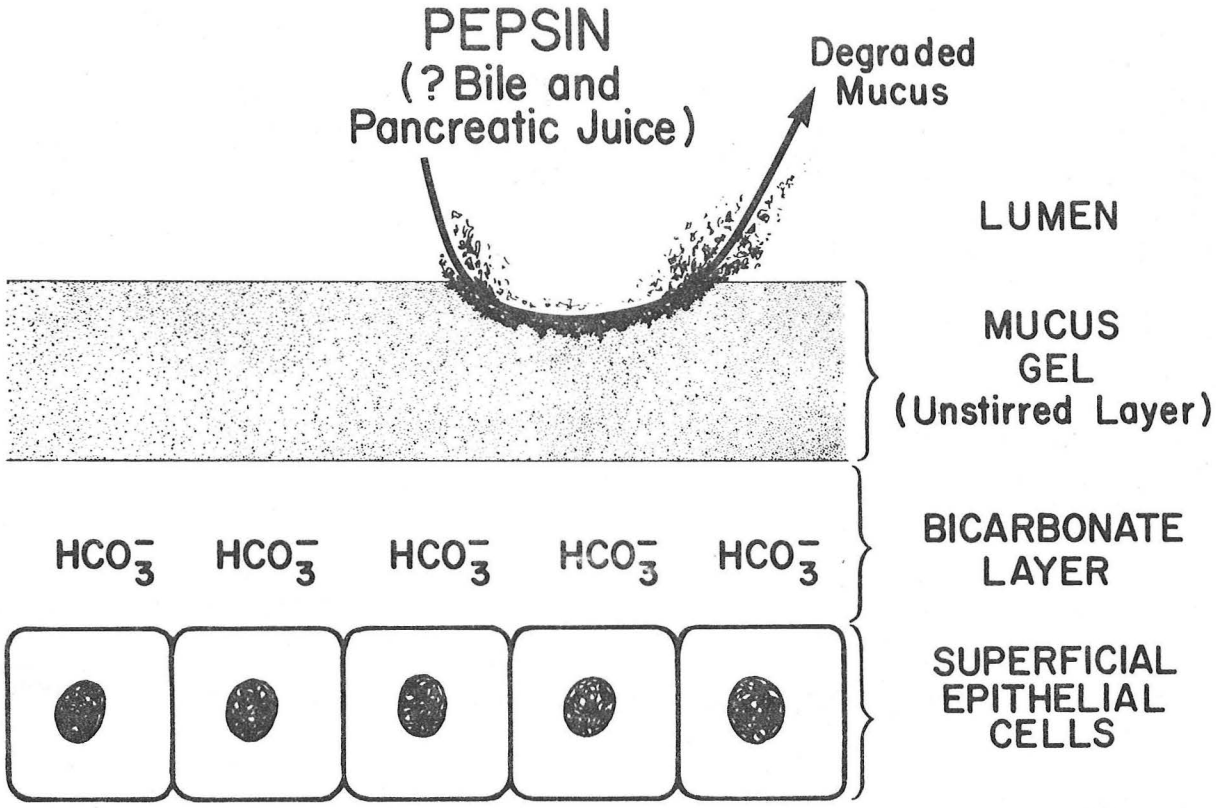

Figure 8. Model illustrating degradation of mucus by pepsin.

If patients make large amounts of acid and pepsin (see Figure 1), then, theoretically, more of the mucus layer will be degraded by pepsin; the flow of hydrogen ions through the mucus layer will be impeded less well; and the pH near the cell surface will be lower since more hydrogen ions will be present for the amount of bicarbonate secreted. Hydrogen ions and perhaps pepsin may lead to cellular damage. Although this hypothesis seems plausible there is no way at the moment, to prove it in humans. First, there is no method of measuring pH gradients in humans; and second, there is no way to measure accurately the thickness of mucus gel in humans. Mucus gel thickness has recently been measured in dogs, using a slit lamp technique (9). Hopefully, this method can eventually be applied to measurement of mucus gel thickness in normal humans and in patients with ulcer disease.

2. Reduced secretion of mucus. Some patients may secrete an inadequate amount of mucus. Under these circumstances the mucus gel layer would be abnormally thin. This would theoretically allow greater back-diffusion of hydrogen ions and pepsin through the mucus layer to cell surfaces.

3. Abnormal Quality of Mucus. Patients may secrete normal amounts of mucus, but the structure may be abnormal. Under these circumstances the density and strength of the mucus gel would be abnormal. A recent study has shown that mucus gel in gastric ulcer patients as a group (compared to normal subjects), contained a larger quanity of lower molecular weight mucus glycoproteins, a type of glycoprotein that is associated with weaker mucus (10). This abnormality was also found to a lesser extent in duodenal ulcer patients.

Bicarbonate Secretion

There are no studies in humans comparing bicarbonate secretion in ulcer patients with that in normal subjects. Theoretically, some ulcer patients may have decreased bicarbonate secretion from mucosal cells in the stomach and duodenum or Brunner's glands in the duodenum. Reduced bicarbonate secretion would conceivably lead to decreased neutralization of hydrogen ions at the cell surface. Lower pH at the cell surface could, in turn, lead to cell damage.

Blood Flow

Gastric mucosal ischemia is believed to be an important factor in the pathogenesis of acute mucosal injury, as occurs in patients with severe medical or surgical illnesses (stress ulceration). Whether similar alterations in blood flow contribute to the development of chronic gastric or duodenal ulcers is not known. It is theoretically possible that the anatomic differences in blood supply to the lesser curvature compared to the remainder of the stomach (Figure 7), may somehow contribute to chronic ulceration on the lesser curvature.

Unfortunately, most methods to evaluate mucosal blood flow are inadequate to detect differences in regional blood flow in normal subjects or differences in blood flow between patients with ulcer disease and normal people. Therefore, the potential role of blood flow abnormalities in the pathogenesis of chronic gastric or duodenal ulcers has not been adequately studied.

Prostaglandins and Mucosal Defense

Prostaglandins are saturated, oxygenated fatty acids. Most natural prostaglandins contain 20 carbon atoms and differ from one another by changes in the five-carbon ring and by the number of double bonds in the molecule (Figure 9) (11).

Every mammalian cell is believed to synthesize prostaglandins. Prostaglandins are synthesized from arachnidonic acid, an essential fatty acid. Arachnidonic acid is transformed into endoperoxidases, which then form prostaglandins by an enzyme called prostaglandin cyclooxygenase. Most nonsteroidal antiinflammatory compounds, such as aspirin and indomethacin, block the activity of this enzyme, which leads to inhibition of biosynthesis of prostaglandins. Presumably, this is the mechanism whereby nonsteroidal antiinflammatory compounds cause gastric mucosal damage.

It was believed originally that the beneficial effect of prostaglandins in healing peptic ulcers in humans and the

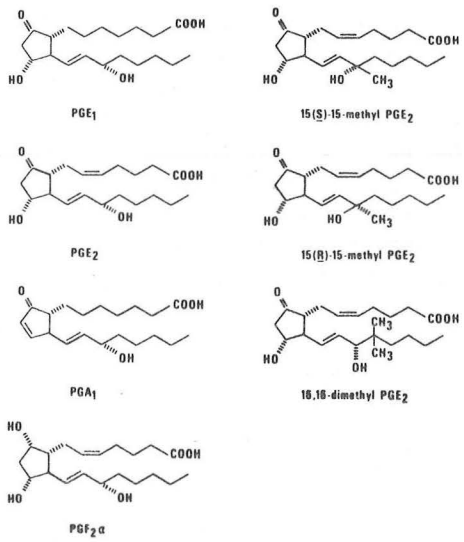

Figure 9. Structures of several prostaglandins (from Ref. 11).

prevention of mucosal lesions in animals was due to their antisecretory effect (see page 47). However, it was soon realized that prostaglandins, given in doses that did not reduce acid secretion, also had a protective effect on gastric mucosa. Furthermore, several prostaglandins that did not inhibit acid secretion provided mucosal protection. The mucosal protective ability of prostaglandins has been labled "cytoprotection" (12).

Mechanisms of Cytoprotection

Most prostaglandins are better cytoprotective agents when given orally than parenterally. Thus, local effect on the gastric mucosa appears to be important. In addition, the onset of action of cytoprotection is rapid, occurring as early as 1 min after oral administration. Postulated methods whereby prostaglandins protect mucosa are listed in Table 4.

TABLE 4. METHODS WHEREBY PROSTAGLANDINS ARE BELIEVED TO PROTECT GASTRIC MUCOSA

1) Stimulation of mucus secretion.
2) Stimulation of bicarbonate secretion.
3) Increased mucosal blood flow.
4) Stimulation of protein synthesis.

Prostaglandin Inhibitors and Ulcer Disease

If prostaglandin synthesis is inhibited (e.g., by nonsteroidal antiinflammatory drugs) mucus and bicarbonate secretion and mucosal blood flow presumably will be reduced. With this in mind, it is relatively easy to understand how mucosal damage might occur via mechanisms previously discussed.

Aspirin and other nonsteroidal antiinflammatory drugs cause superficial gastric mucosal lesions. It is unclear, however, whether these agents cause chronic ulcers. Several epidemiological studies suggest that chronic gastric ulcers occur more frequently in patients taking large doses of aspirin than in control populations (13-15). However, a definite relationship between aspirin intake and the development of chronic ulcers has never been established. The same is true of other nonsteroidal antiinflammatory drugs. It is also not known whether any of these compounds cause duodenal ulcers. If these agents do cause ulcers, it seems likely that they do so by blocking prostaglandin synthesis with subsequent reduction in mucus and bicarbonate secretion and decrease in mucosal blood flow.

ENVIRONMENTAL FACTORS AND ULCER DISEASE

Environmental factors postulated to play a role in the pathogenesis of ulcer disease include taking of nonsteroidal antiinflammatory drugs, smoking cigarettes, drinking alcohol or caffeine containing beverages and emotional stress. The roles that these factors may play in the pathogenesis of ulcer disease are discussed below.

Nonsteroidal Antiinflammatory Agents

These drugs are discussed on page 13 under Prostaglandins.

Smoking

Smoking cigarettes has not been demonstrated to cause gastric or duodenal ulcers. However, there is epidemiologic evidence suggesting an association between the two (16-18). Several studies have shown that ulcer patients smoke more commonly than control subjects. In addition, there is a positive correlation between the quantity of cigarettes smoked and the prevalence of gastric ulcer disease. Duodenal ulcers are less likely to heal in cigarette smokers than in non-smokers, however, it is not known whether this also applies to the healing of gastric ulcers (19-21). The decreased ability of duodenal ulcers to heal has been demonstrated in patients treated with either placebo, antacid, cimetidine or ranitidine (Table 5). Epidemiologic studies also have shown that death rates from peptic ulcers are higher among patients who smoke cigarettes than among those who do not.

TABLE 5. PERCENT OF DUODENAL ULCERS HEALED AT 4 WEEKS IN SMOKERS AND NON-SMOKERS

MEDICATION	% INCIDENCE OF HEALING		P	REF.
	SMOKERS	NON-SMOKERS		
PLACEBO	32(25)*	69(13)	=0.03	19
MYLANTA II	39(13)	67(12)	<0.03	20
CIMETIDINE	50(10)	100(15)	<0.03	20
RANITIDINE	30(25)	70(25)	<0.03	21

* Numbers in parentheses represent number of patients in each group.

If smoking cigarettes predisposes patients to gastric ulceration, the mechanism is not clear. Nicotine has no consistent effect on acid secretion, although it has been shown to reduce pancreatic bicarbonate secretion (18). Theoretically, this could lead to duodenal ulcers by impairing neutralization of gastric acid in the duodenal bulb. However, it is difficult to understand how reduction in pancreatic bicarbonate secretion might contribute to gastric ulcer pathogenesis. Smoking cigarettes has been shown to reduce pyloric sphincter pressure in gastric ulcer patients which may lead to increased duodenogastric reflux of bile and pancreatic juice and subsequent damage to gastric mucosa (22).

Because of the above mentioned associations between smoking cigarettes and ulcer disease, it seems reasonable to advise patients to stop smoking.

Alcohol or Caffeine-Containing Beverages

There is no evidence that drinking alcohol or caffeinated drinks causes gastric or duodenal ulcers. However, results of a recent study (Figure 10) indicate that some alcohol or caffeine-containing beverages stimulate acid

secretion (23). In fact, beer stimulated nearly as much acid as a maximum dose of pentagastrin. Milk, presumably because of its protein and calcium content, was the most potent stimulant of acid secretion.

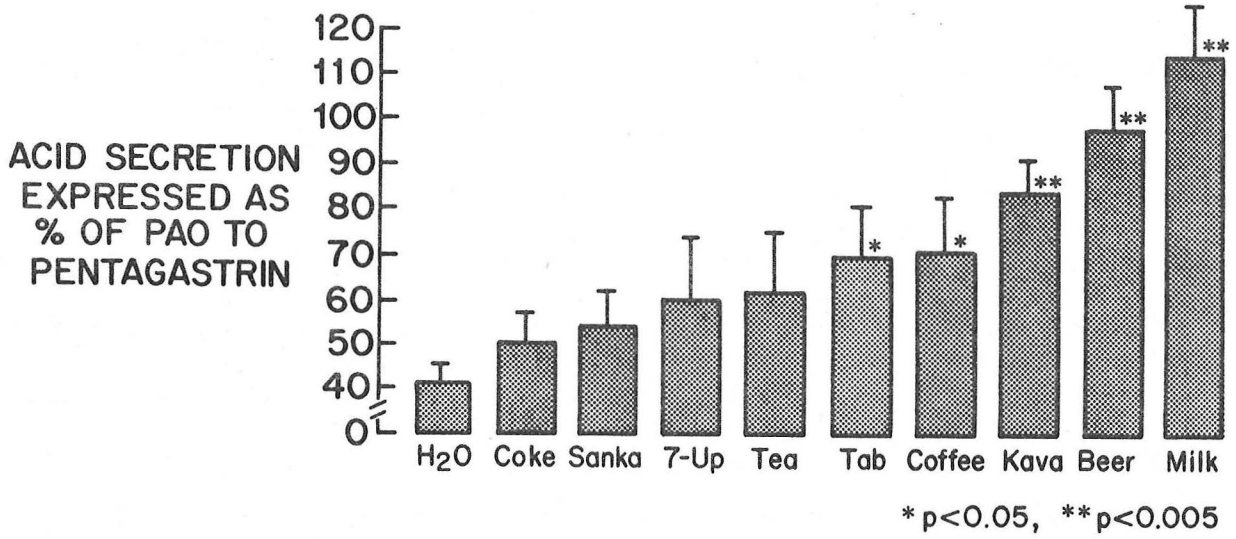

Figure 10. Effect of various beverages on gastric acid secretion (from Ref. 23).

Even though beer and some caffeine-containing beverages stimulate near maximum rates of acid secretion, there is no evidence to support the avoidance of these beverages by ulcer patients. However, it seems reasonable to advise patients to be moderate in their drinking of alcohol or caffeine-containing beverages.

Emotional Stress

The role of emotional stress in the pathogenesis of peptic ulcer disease has remained controversial despite years of research. Some investigators have advocated the classic psychosomatic theory of a specific "ulcer" personality, characterized by an exaggerated dependency-independency conflict. The conflict is believed to remain unconscious and the dependency needs (wishes to be loved and cared for) induce in the patient a sense of shame and reduced self confidence (24). Ulcer patients may display exaggerated self-sufficiency, ambition, and aggressiveness as a defense against an awareness of dependency. Other workers have not supported the concept of the classic psychosomatic theory of ulcer pathogenesis. There are, however, several pieces of evidence suggesting an association between stressful life events and development of ulcers. First, some ulcer patients experience stressful life events more frequently or may be

more sensitive to stress than non-ulcer subjects (25). Second, stressful events frequently precede the onset of ulcer symptoms in both newly diagnosed and chronic ulcer patients (26). Third, severe emotional stress may contribute to ulcer perforation in some patients (27).

The mechanism by which environmental stress might contribute to ulcer disease is unclear. Certain emotions such as hostility, resentment, guilt and frustration have been associated with increased gastric acidity, peristaltic activity, and blood flow. For example, in classic studies of two patients with gastric fistulae, Wolf and Wolff (28) and Beaumont (29) evaluated the acute effects of various emotions on the appearance of gastric mucosa and volume of gastric secretions. Although extensive details were not given, Beaumont observed mucosal hyperemia and increased gastric juice secretion when his subject, Alexis St. Martin, was emotionally upset. Wolf and Wolff conducted detailed studies of their patient, Tom, over a 17 year period and correlated changes in gastric function with specific emotions. They reported that gastric mucosal hyperemia, secretory volume, and acidity were augmented by feelings of anxiety, hostility, and resentment. On the other hand, depression and dispair led to mucosal pallor and diminished secretion. In other studies, basal acid secretion has been reported to increase during stressful interviews and prior to surgery in ulcer patients or before difficult school examinations in healthy subjects. Thus, certain emotions can cause increased acid secretion which, in turn, may lead to ulceration.

The case summaries detailed below represent two patients who had acid hypersecretion and ulcer disease during periods of severe emotional stress. With alleviation of stress, acid secretion diminished, and symptoms and ulcerations disappeared (30).

Patient 2

A 48 year-old man was hospitalized after 4 weeks of severe "burning", mid-epigastric pain which was partially relieved by food and was accompanied by poor appetite, diarrhea and a 23-lb weight loss. He denied prior gastrointestinal symptoms although he was taking insulin for diabetes mellitus. Six members of his immediate family, including his mother and sister, had died in the previous six weeks, and he had attended a funeral on six consecutive weekends. He was grieving over the loss of his relatives but he was also fearful that he himself would soon die; his present illness reinforced this fear. Physical examination was normal except for tenderness in the epigastrium. Upper gastrointestinal barium contrast x-rays revealed hypertrophic gastric folds, a 1 cm, benign-appearing gastric ulcer on the lesser curvature of the stomach, and flocculation of barium in the small intestine. These findings suggested an acid hypersecretory state such as Zollinger-Ellison syndrome. Gastric analysis showed a basal acid output (BAO) of 24.1 mmol/h and a peak acid output (PAO) of 81.3 mmol/h (Figure 11, June, 1970).

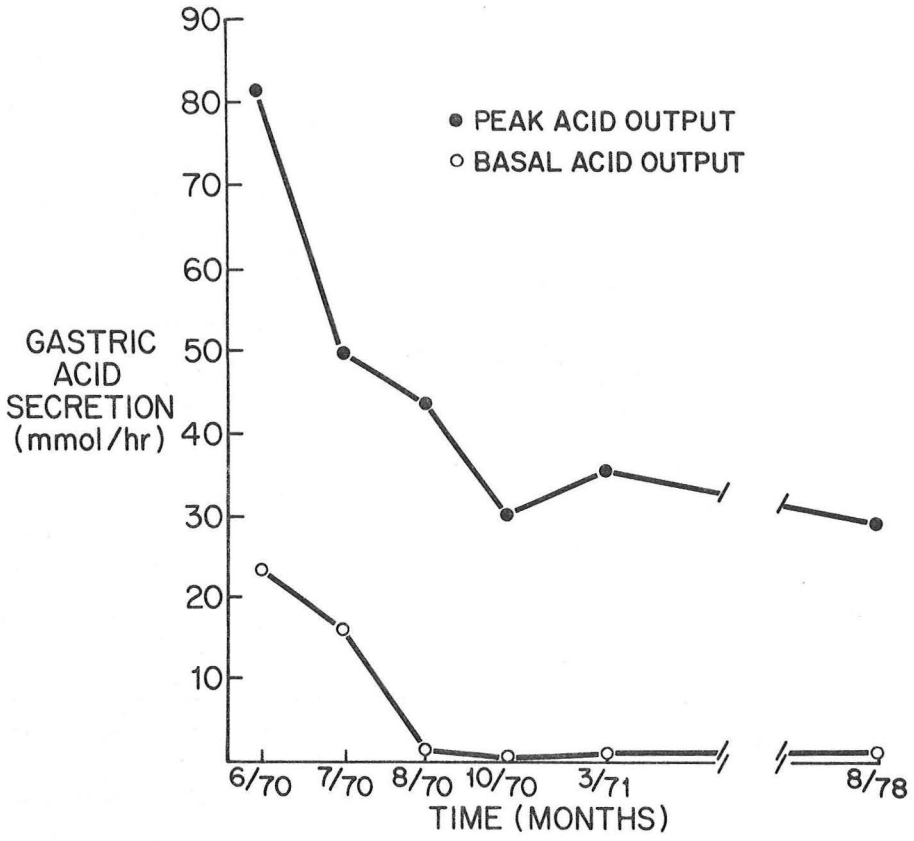

Figure 11. BAO and PAO in patient 1.

Serum gastrin concentration was 144 pg/ml (normal ≤200 pg/ml). He was treated with antacids and an anticholinergic drug but the pain persisted. With hospitalization and reassurance from his physicians, pain, diarrhea, and anorexia gradually disappeared. In July and August, 1970, gastric analysis showed a progressive decrease in BAO and PAO (Figure 11). By October, 1970, BAO had decreased to 1.2 mmol/h and PAO to 30.0 mmol/h. Upper gastrointestinal barium contrast x-rays at that time were normal. In long-term follow-up, BAO and PAO have remained normal and he has had no further episodes of ulcer disease.

Patient 3

A 19 year-old man was evaluated because of severe epigastric pain which had been present for one month. The pain had begun at a time when he had been accused of grand theft, had been told that he had failed two polygraph tests, and had lost his job. He was resentful and angry about the false accusation but also was anxious about conviction and imprisonment. In addition, he was extremely worried about finding another job. Physical examination was normal. Upper gastrointestinal barium contrast x-rays showed a 1 cm, benign-appearing prepyloric ulcer and thickened jejunal folds. Acid secretory studies were performed and results are depicted in Figure 12.

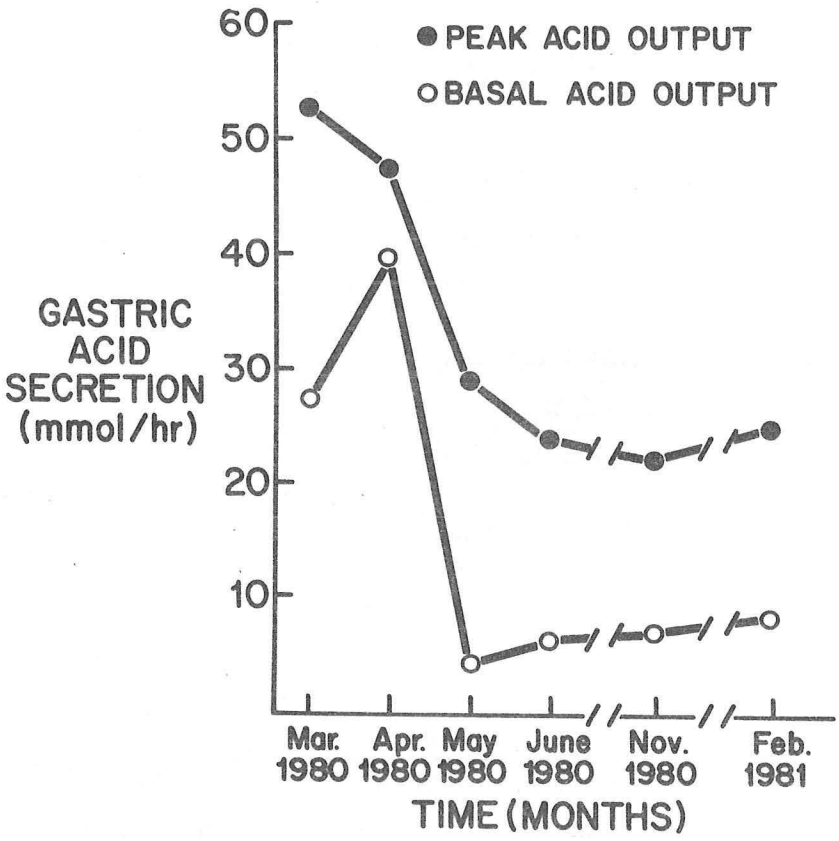

Figure 12. BAO and PAO in patient 3.

BAO's in March, 1980 (when he was initially evaluated) and again in April (while he remained under police surveillance) were abnormally high, suggesting a basal hypersecretory state such as Zollinger-Ellison syndrome. However, serum gastrin concentration was normal (70 pg/ml). During the next month, his legal problems were resolved, he found work, and his symptoms abated. Simultaneously, BAO decreased by 89 percent, from 38.8 to 3.4 mmol/h, while PAO decreased by 40 percent, from 47.2 to 29.0 mmol/h (Figure 12, May, 1980). Repeat upper gastrointestinal contrast x-rays, performed in May, 1980, were normal. He has continued to be asymptomatic and BAO and PAO have remained normal.

Comments: Although it cannot be proven, it seems likely that emotional stress caused increased acid secretion which led to ulcer disease in these patients. Alleviation of stress led to reduced acid secretion, disappearance of symptoms, and healing of ulcerations. It is also possible that emotional factors alter mucus secretion, bicarbonate secretion, mucosal blood flow or gastric motility, and that emotional stress leads to ulcerations via defects in mucosal defense. The role of emotional stress (if any) in the pathogenesis of ulcer disease in most patients is not known.

GENETICS AND ULCER DISEASE

For a number of years, hereditary factors have been postulated to play a role in the pathogenesis of ulcer disease. Doll and Kellock reported that relatives of gastric ulcer patients had a threefold increased prevalence of gastric ulcers compared to the general population, whereas duodenal ulcers occurred no more frequently than expected (31). Similarly, relatives of duodenal ulcer patients had an increased prevalence of duodenal ulcers but no increased risk of gastric ulcers. These studies suggested that, at least in some instances, the tendency to develop a gastric or duodenal ulcer was inherited and that, from the genetic standpoint, gastric and duodenal ulcer diseases were separate entities.

It was believed originally that familial aggregations of ulcer disease represented polygenic inheritance since the genetics of peptic ulcer could not be explained by a single, simple autosomal or sex-linked, dominant or recessive defect. Polygenic or multifactorial disorders are believed to be caused by the interaction of several genes with environmental factors. Thus, the hereditary component in ulcer disease was believed to reflect the combined contribution of many different genes in an individual.

More recently, it has been recognized that polygenic inheritance is not likely to be the mechanism explaining familial aggregation of ulcer disease (32). Instead, ulcer disease is believed to represent a heterogeneous group of disorders with a common clinical manifestation - a hole in the mucosa of the stomach or duodenum. Thus, ulcer disease is not one disease but many different diseases, some of which are inherited. There are several reasons to believe that peptic ulcer disease represents many different disorders. First, several pathophysiologic abnormalities have been found in various groups of patients (see Table 2 for a partial list). It is believed that these defects contribute to ulceration in these subgroups of patients. Second, several of these defects have been found in "ulcer families" (Table 6) (33,34).

TABLE 6. SUBTYPES OF FAMILIAL PEPTIC ULCER DISEASE

1. Hyperpepsinogenemia I*
2. Antral G-cell hyperfunction
3. Normopepsinogenemia I
4. Rapid gastric emptying
5. Childhood or early onset duodenal ulcer
6. Immunologic forms of duodenal ulcer (Antibody to secretory IgA)

* Presumably these patients also would have acid hypersecretion.

Third, several rare genetic syndromes associated with ulcer disease have been discovered (Table 7).

TABLE 7. RARE GENETIC SYNDROMES ASSOCIATED WITH PEPTIC ULCER DISEASE

1. Multiple endocrine neoplasia, Type I
2. Systemic mastocytosis
3. Ulcer-tremor-nystagmus syndrome (35)
4. Amyloidosis, Type I (36)
5. Stiff skin syndrome* (37)
6. Pachydermoperiostosis* (38)
7. Multiple lentigenes-ulcer syndrome* (39)
8. Leukonychia-gallstone-ulcer syndrome (40)

*Association with ulcer disease not firmly established

How genetic factors contribute to ulceration in most patients is unclear. It is likely that patients with multiple endocrine neoplasia, Type I (increased gastrin) syndrome and systemic mastocytosis (increased histamine) get an ulcer because of too much acid and pepsin. Other patients, perhaps, get an ulcer because of inherited defects that lead to decreased mucosal defense.

Although several genetic ulcer syndromes have been described and a number of different abnormalities that are believed related to the pathogenesis of ulcer disease have been discovered, the true importance of these findings has not been ascertained. It has been postulated that further definition of various subgroups of patients will have prognostic and therapeutic implications. In other words, physicians will be able to prescribe specific medical or surgical treatments for specific types of ulcer patients. Whether or not this will occur remains to be determined.

OTHER FACTORS IN THE PATHOGENESIS OF ULCER DISEASE

Delayed Gastric Emptying

It has been postulated that delayed gastric emptying might cause retention of food in the stomach which, in turn, would lead to increased gastrin release, higher rates of acid secretion, and gastric ulceration (41). It also has been said that prolonged gastric emptying, perhaps due to antral hypomotility, might cause stasis and delayed clearing of duodenal contents (bile and pancreatic enzymes) which have refluxed into the stomach. This, in turn, could damage gastric mucosa and lead to ulceration. For a number of years delayed emptying was thought to be a major factor in the pathogenesis of gastric ulcer. Now, however, delayed emptying is believed to be related to ulceration in only a minority of patients.

Incompetence of the Pyloric Sphincter

This has been postulated as a cause of gastric ulceration, and pyloric sphincter abnormalities have been identified in small groups of gastric ulcer patients (42). It has been suggested that an abnormal sphincter mechanism allows increased reflux of bile and pancreatic juice into the stomach which, in turn, leads to mucosal damage and ulceration. So far, there is little evidence either confirming duodenogastric reflux in gastric ulcer patients or relating bile and pancreatic juice to the pathogenesis of gastric ulcer disease.

Infectious Agents

Cytomegalovirus has been isolated from gastric ulcers in patients receiving immunosuppressive drugs after renal transplantation. Herpes simplex type I virus has been implicated as a cause of ulceration in a few patients with duodenal ulcers. One study has reported that antibodies to herpes type I virus occur more frequently and in higher titer in patients with duodenal ulcers than in controls. Herpes virus has not been isolated from gastric or duodenal ulcers but it has been found in vagal ganglia (43-45).

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THERAPY

Even though there may be a number of different causes of gastric or duodenal ulcers, therapy, at the present time, is the same for most patients. Controlled clinical trials indicate that ulcers will heal in 70 to 80% of patients if acid is inhibited by conventional doses of H_2-receptor antagonists or acid and pepsin are prevented from reaching the ulcer crater by drugs that coat ulcer craters. The 20 to 30% of patients who do not heal with conventional doses of currently available medications are discussed in the section entitled "cimetidine resistance."

Drugs used to treat patients with ulcer disease are divided into several categories: 1) drugs that inhibit acid secretion; 2) drugs that neutralize acid; 3) drugs that coat ulcer craters and protect ulcers from acid and pepsin; and 4) drugs that enhance mucosal defense. Specific drugs in these categories and the mechanisms of action of these drugs are listed in Table 8 and are discussed below.

TABLE 8. DRUGS EITHER AVAILABLE OR UNDERGOING INVESTIGATION FOR TREATMENT OF PEPTIC ULCER DISEASE

DRUG CLASSIFICATION	EXAMPLES	MECHANISMS OF ACTION
Drugs that inhibit acid secretion		
Histamine H_2-receptor antagonists	Cimetidine (Tagamet, Smith Kline and French Laboratories, Philadelphia, PA) Ranitidine (Zantac, Glaxo, Inc., Raliegh, NC) Oxmetidine* (Smith Kline and French Laboratories, Philadelphia, PA) Etintidine* (Ortho Pharmaceutical, Raritan, NJ)	Block the action of histamine on H_2-receptors on parietal cells (see Fig. 18).
Muscarinic Receptor Antagonists	Classic Anticholinergic Drugs (These are listed in Ref. 1) Pirenzepine* (Boehringer Ingelheim, Ltd.,Ridgefield,CT) Trimipramine*+ (Surmotil, Ives Labs, Inc., New York, NY) Doxepin*+ (Sinequan, Roerig Div. of Phizer, Inc., NY, NY; Adapin, Penwalt, Rochester, NY)	Block the action of acetylcholine on muscarinic receptors on parietal cells (See Fig. 23).

Substituted Benzimidazols	H 149/94* H 83/69*	Inhibit a hydrogen/potassium adenosine triphosphatase enzyme located on the acid secretory surface of parietal cells (See Fig. 26).
Gastrin Receptor Antagonists	Proglumide*	? Block the action of gastrin on mast cells or on parietal cells
Drugs that neutralize acid		
Antacids	Commonly used antacids are described in Ref. 2 and 3	
Drugs that coat ulcer craters		
Sulfated Disaccharides	Sucralfate (Carafate, Marion Labs, Kansas City, MO)	Attaches to necrotic ulcer tissue in base of ulcer and prevents pepsin from further degrading ulcer tissue; may prevent hydrogen ions from reaching ulcer base; may adsorb bile salts (see Figure 28)
Colloidal Bismuth Compounds	Tripotassium dicitrate bismuthate* (De-Nol; Brocades Ltd., Delft, Netherlands)	See sucralfate
Drugs that enhance mucosal defense		
Prostaglandins	Primarily E type*	Increase mucus and bicarbonate secretion; increase mucosal blood flow; reduce acid secretion (see page 13 and 47 and Fig. 27).
Licorice Extracts	Carbenoxolone++ (Biogastron, Beck Pharmaceuticals, Ltd., Great Britain)	Increase mucus secretion; increase life span of gastric mucosal cells; reduce peptic activity

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* Undergoing clinical trials either in the United States or other countries.

\+ Tricylic compounds; these drugs are believed to be useful in treating ulcer disease primarily because of their antimuscarinic property.

++ Marketed in several countries but not in the United States.

DRUGS THAT INHIBIT ACID SECRETION

Prior to discussing individual drugs and their mechanisms of action, methods whereby acid secretion is stimulated under normal conditions will be discussed.

Endogenous Stimulants of Acid Secretion

Three endogenous chemicals stimulate acid secretion from parietal cells. These chemicals are 1) gastrin, 2) histamine and 3) acetylcholine (Figure 13).

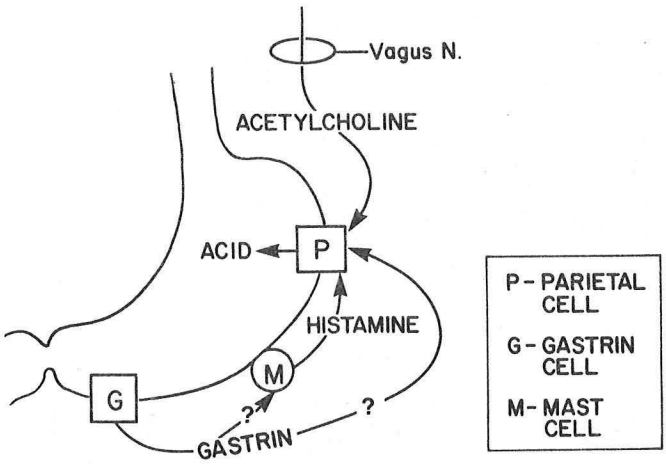

Figure 13. Model illustrating the origin of three endogenous chemical stimulants of acid secretion.

Whether gastrin, histamine, and acetylcholine stimulate acid secretion by interacting with separate receptors on parietal cells is not known (Figure 14). Evidence suggests that there is a parietal cell receptor for histamine and acetylcholine but evidence supporting the existence of a gastrin receptor on parietal cells is weak (see below).

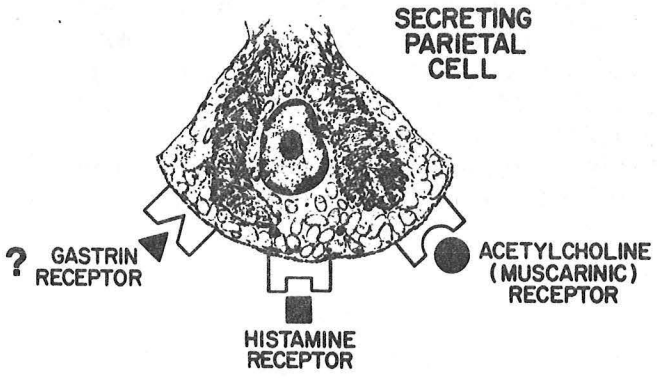

Figure 14. Model illustrating receptors on parietal cell.

Parietal cell function in vitro.

This has been studied by measuring aminopyrine uptake or oxygen consumption from gastric mucosal cell preparations containing a preponderance of parietal cells (4). Aminopyrine uptake in response to gastrin, histamine, or acetylcholine is shown in Figure 15. Uptake of aminopyrine was enhanced by putting histamine and carbachol (acetylecholine) in the preparation. However, when gastrin was placed in the system, there was only a slight stimulation of aminopyrine uptake. These findings suggest that histamine and acetylcholine stimulate acid secretion by interacting directly with receptors on parietal cells (Figure 14), whereas gastrin acts by some other mechanism. Histamine receptors on parietal cells are called H_2-receptors while acetylcholine receptors are called muscarinic receptors.

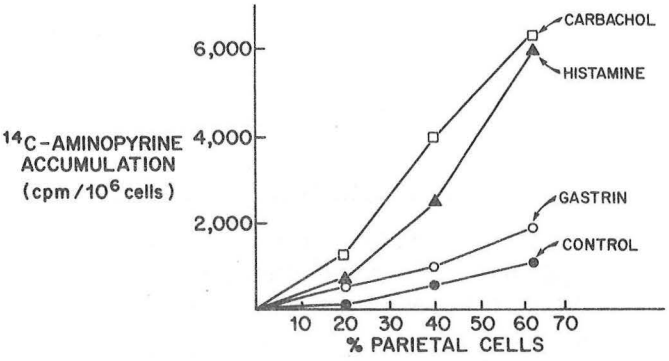

Figure 15. Effect of gastrin, histamine and acetylcholine on aminopyrine uptake in parietal cells in vitro. (Modified from Ref. 4).

Gastrin Stimulation of Parietal Cells.

There is increasing evidence that gastrin releases histamine from mast cells and histamine, in turn, stimulates acid secretion from parietal cells via H_2-receptors (Figure 16).

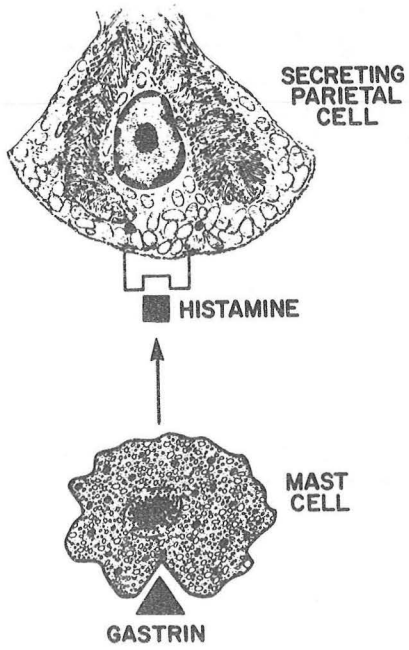

Figure 16. Hypothetical model of mast cell and parietal cell, illustrating gastrin release of histamine from mast cell. Histamine stimulates the parietal cell to secrete acid. If this model is correct, histamine is the major mediator of gastrin-stimulated acid secretion. This does not, however, exclude a separate receptor for gastrin on parietal cells (see Figure 14).

Histologic examination of gastric mucosa reveals that mast cells are located in close proximity to parietal cells (5). Furthermore, studies in rats, dogs and humans indicate that pentagastrin (synthetic form of gastrin) causes release of histamine from histamine containing cells (6-8). (In dogs and humans histamine-containing cells in the gastric mucosa are mast cells. In rats, enterocromaffin cells contain histamine.) Presumably histamine, acting as a paracrine substance, interacts with a receptor on parietal cells to cause secretion of acid.

Acetylcholine Stimulation of Parietal Cells.

In vitro studies (Figure 15) indicate that acetylcholine causes uptake of aminopyrine by parietal cells, thus supporting the concept of a muscarinic receptor on parietal cells. However, recent studies in dogs (R. Thirlby, M. Feldman, M. Tharp, and C. T. Richardson, unpublished observations) suggest that acetylcholine also releases histamine from mucosal mast cells. Therefore, acetylcholine may stimulate acid secretion by two mechanisms: 1) direct stimulation of parietal cell receptors and 2) release of histamine from mast cells which, in turn, stimulates acid secretion via a histamine receptor.

Intracellular Mechanisms of Acid Secretion.

There is little known about intracellular mechanisms leading to acid secretion. However, the available information is illustrated in Figure 17.

Histamine is believed to stimulate acid secretion via activation of cyclic AMP (4). Acetylcholine stimulated acid secretion, on the other hand, is believed to be dependent on entry of calcium ions into the parietal cell. Secretion of hydrogen ions from the apical (luminal) membrane of parietal cells is believed to be via a hydrogen/potassium (H^+/K^+) ATPase enzyme (9,10). The intracellular steps from cyclic AMP (histamine stimulated secretion) or from entry of calcium ions (acetylcholine stimulated secretion) to activation of H^+/K^+ ATPase are not known.

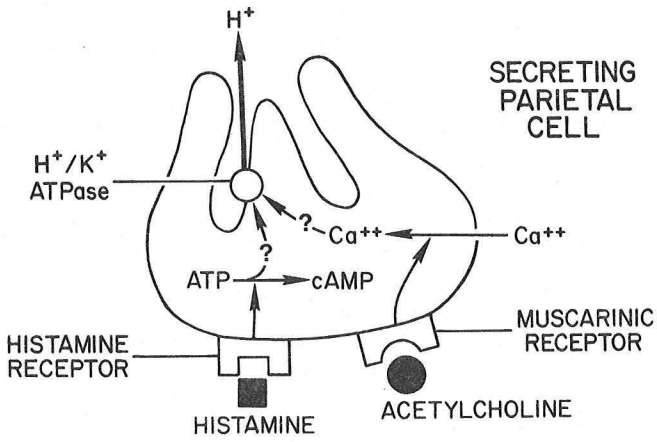

Figure 17. Model illustrating intracellular mechanisms of acid secretion.

Inhibition of Acid Secretion

This can be accomplished by blocking either the histamine or muscarinic receptor (Figure 14) on parietal cells or by inhibiting one of the intracellular mechanisms of acid secretion (Figure 17).

H_2-Receptor Antagonists

These drugs block histamine receptors on parietal cells (Figure 18) and inhibit acid secretion stimulated not only by histamine but also by gastrin and

acetylcholine. The fact that H_2-receptor antagonists block gastrin and acetylcholine stimulated acid secretion lends further support to the idea that histamine may be a major mediator of gastrin and acetylcholine-stimulated acid secretion.

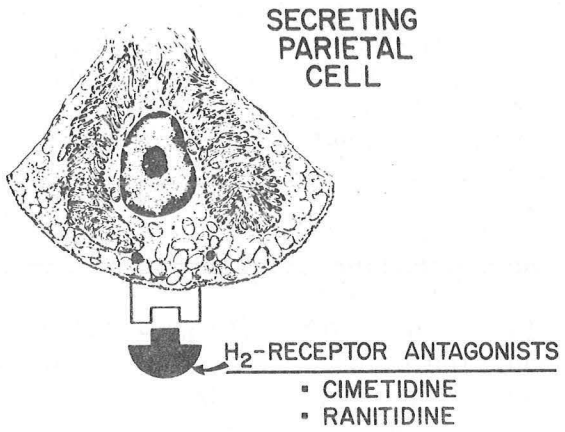

Figure 18. Model of parietal cell showing antagonists of H_2 receptors.

Cimetidine.

The clinical pharmacology of cimetidine has been described in numerous reviews and, therefore, will not be discussed in this protocol. Similarly, controlled clinical trials evaluating cimetidine in the treatment of patients with duodenal ulcers also will not be discussed in detail. However, the reader is referred to Refs. 11 to 13 for a discussion of these aspects of cimetidine therapy and to the summary below. In this protocol new studies evaluating the effect of cimetidine in the treatment of patients with gastric ulcers and several other topics related to the clinical use of cimetidine will be discussed.

Summary of Controlled Clinical Trials in Patients with Duodenal Ulcers.

There have been numerous controlled clinical trials evaluating the effect of cimetidine in treating patients with duodenal ulcers. These studies have shown:

1. Cimetidine, 300 mgs four times daily, is more effective than placebo in healing active duodenal ulcers. Average healing incidences after 4 weeks of therapy are approximately 75% in patients treated with cimetidine compared with 45% in patients treated with placebo. The percent of patients with healed ulcers can be increased to over 85% by continuing treatment for 6 to 8 weeks.

2. Cimetidine, 400 mg at bedtime, has been shown to prevent duodenal ulcers from recurring in 70 to 80% of patients if cimetidine therapy is continued for 6 to 12 months. However, a recent study has suggested that 400 mg at bedtime may be inadequate and that patients should be treated with 800 mg at bedtime (14). This must be evaluated in additional studies before the best dose for prophylaxis is determined. Regardless of the dose, when cimetidine is stopped, ulcers recur. Thus, cimetidine treatment does not alter the natural history of ulcer disease. (See page 40 for recommendations relative to maintenance therapy with cimetidine.)

Treatment of gastric ulcer patients. Initial studies in the United States evaluating the effect of cimetidine in treating patients with gastric ulcers did not show benefit of cimetidine compared with placebo. Therefore, cimetidine was not approved by the FDA for use in treating patients with gastric ulcers. However, two controlled clinical trials comparing the effect of cimetidine with that of placebo have been completed recently in the United States. Results are summarized in Table 9.

TABLE 9. EFFECT OF CIMETIDINE OR PLACEBO ON HEALING OF GASTRIC ULCERS

	% Ulcers Healed at Various Weeks of Therapy				P	Ref.
	4	6	8	12		
Cimetidine*		66			<0.05	15
Placebo		45				
Cimetidine	53		86	89	<0.05	16
Placebo	26		58	70	at 4, 8 and 12 weeks	

* Dose of cimetidine was 300 mg four times daily, with each meal and at bedtime.

Results of these studies indicate that cimetidine is more effective than placebo in healing benign gastric ulcers and that benign gastric ulcers in most patients (>80%) will heal if patients are treated for 12 weeks. Additional studies have shown that cimetidine is effective in preventing recurrences of gastric ulcers.

Cimetidine plus Antacid. The effect of antacid plus cimetidine is no better than either drug given alone in healing gastric ulcers (1). The effect of both drugs given together in treating patients with duodenal ulcers has not been evaluated. However, it is unlikely that the drug combination would be necessary in treating most patients with duodenal ulcers. Combining the drugs might be helpful in treating patients who do not respond to either drug alone.

A recent article indicated that antacid, when given with cimetidine, may reduce the blood concentration of cimetidine (2). Although statistically significant, the reduction in blood concentration was small and probably of no clinical importance.

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"Cimetidine Resistance". This term has been used to refer to patients with rates of acid secretion which are not adequately reduced by cimetidine (17-21). Case histories of patients with "cimetidine resistance" are summarized in Table 10.

TABLE 10. PATIENTS WITH HIGH RATES OF ACID SECRETION UNRESPONSIVE TO CIMETIDINE

PATIENT	ASSOCIATED DISEASE OR CONDITION	DOSE OF CIMETIDINE	TREATMENT	REF.
A 63 y/o man	Antral ulcer; normal gastrin; cholecystectomy and excision of ulcer; pancreatitis; NG aspirate: 1400 ml/24 h	300 mg. cimetidine IV, (bolus)*	No specific therapy; improved after 4 mos.	18
B 40 y/o man	Zollinger-Ellison syndrome; partial gastric outlet obstruction; gastrin: 3,500 pg/ml; NG aspirate: 7200 ml/24 h.	300 mg. cimetidine IV, (bolus) q4h	Total gastrectomy	19
C 55 y/o woman	MEN-I (Zollinger-Ellison syndrome; hyperparathyroidism); gastrin: 950 pg/ml; "cimetidine resistance" disappeared after parathyroidectomy.	300 mg. cimetidine p.o. q4h	Parathyroidectomy	20
D 83 y/o man	Three month history of persistent vomiting; pyloric stenosis secondary to peptic ulcer; gastrojejunostomy performed; NG aspirates: 5000 ml/24 h; gastrin: 80 pg/ml.	600 mg cimetidine, I.V. (bolus), q4h	Ranitidine 150 mg IV, q12h	21
E 59 y/o man	Right hemicolectomy for bleeding secondary to angiodysplasia; uremia; gastrin: 450 pg/ml; NG aspirate after surgery: 1600 to 6000 ml/24 h.	600 mg IV (bolus) q6h	Ranitidine 150 mg IV, q12h	21
F 76 y/o man	Small bowel obstruction; NG aspirate from 4th through 14th post-operative day: 1400 to 4200 ml/24 h.	300 mg IV (bolus) q6h	Ranitidine 150 mg IV, q12h	21
G 75 y/o woman	Zollinger-Ellison syndrome; gastrin: 650 pg/ml; NG aspirate: 7600 ml/24 h	600 mg PO q4h	Cimetidine, 100 mg continuous IV infusion+	++
H 54 y/o woman	Zollinger-Ellison syndrome; Diabetes Mellitus; nephrectomy for renal stones; renal failure; stricture in second portion of duodenum; NG aspirate - 3,000 to 4,000 ml/24 h.	600 mg IV (bolus) q4h	Cimetidine 150 mg/h continuous IV infusion	+++

* Bolus is defined as slow IV infusion over a 5 to 10 min period; a few patients have developed bradycardia with rapid injection of cimetidine intravenously.

\+ This patient developed hypocalcemia possibly secondary to continuous cimetidine infusion (see Ref. 22).

++ Patient referred by Dr. Lannie Hughes, Medical City Dallas Hospital.

+++ Patient referred by Dr. Bruce Smith, John Peter Smith Hospital, Ft. Worth, TX.

Case histories of patients listed in Table 10 suggest an association between "cimetidine resistance" and several diseases or conditions. These include:

1) Zollinger-Ellison syndrome (Patients B, C, G and H).
2) Hyperparathyroidism (Patient C).
3) Recent abdominal surgery (Patients A, D, E, F, and H).
4) Delayed gastric emptying from pyloric obstruction (Patients B and D); from narrowed duodenal C-loop (Patient H); or from gastric stasis and ileus secondary to pancreatitis (Patient A).

Patient H had Zollinger-Ellison syndrome plus recent abdominal surgery. Sepsis also has been listed as a possible factor contributing to "cimetidine resistance".

Possible Reasons for "Cimetidine Resistance". Why cimetidine fails to reduce acid secretion in some patients is not known. However, a review of some of the factors that alter drug effects in the body suggests several possible explanations (23).

A. Factors that may alter the effect of a prescribed oral dose of drug (23):

1. Patient compliance
2. Drug absorption
   a. Delayed gastric emptying may slow the rate of cimetidine absorption. For example, a 300 mg dose of cimetidine given every 6 h may be emptied so slowly that a blood level sufficient to inhibit acid secretion adequately may not be achieved even though all medication is eventually emptied from the stomach and absorbed.
   b. Malabsorption of cimetidine as a result of a mucosal defect (e.g., Some patients with Zollinger-Ellison syndrome are known to have damaged jejunal mucosa; see discussion below).
3. Body size and composition
4. Distribution of drug in body fluids
5. Binding of a drug in plasma and tissues.

B. Factors that may alter the effect of a drug at receptors (23):

1. Drug tolerance (This might explain why ranitidine which has a structure different from cimetidine is effective when cimetidine is not).
2. Genetic factors
3. Drug-drug interactions
4. Excessive concentration of agonist (Cimetidine and ranitidine are competitive antagonists of histamine at H_2-receptors; see discussion below)

Gastric emptying (A-2a, above) is a variable in drug absorption. Thus, if a patient has delayed gastric emptying, the drug may be emptied so slowly from the stomach that a blood level sufficient to achieve an adequate effect is never reached even though the total amount of drug absorbed over a given period (i.e., the area under the drug blood concentration curve) is normal for a given patient and dose of medication. Proper absorption of drug is also an important determinant of adequate blood concentrations. This is illustrated by additional information (Table 11, below) from Patient G (Table 10).

TABLE 11. EFFECT OF CIMETIDINE AND RANITIDINE ON ACID SECRETION IN PATIENT G, Table 10

DATE	MEDICATION	VOLUME (ml/hr.)	pH	ACID OUTPUT (mmol/hr.)	PLASMA CONC.* (ng/ml)
6/29/81	None	430	1.00	55.0	
6/30/81	300 mg Cimetidine P.O.	400	1.10	42.0	
7/1/81	150 mg Ranitidine P.O.	315	1.15	30.3	119
7/1/81	300 mg Cimetidine IV (bolus)	136	2.00	2.2	
7/14/81	150 mg Ranitidine P.O.	66	1.50	2.6	314

* 2 hours after medication

It should be possible to overcome delayed emptying or malabsorption of a drug as a cause of "cimetidine resistance" by treating patients with cimetidine intravenously. The fact that Patient G (Tables 10 and 11) did not respond to oral cimetidine or ranitidine but did respond to IV cimetidine suggests that delayed gastric emptying or malabsorption of drug was the cause of "cimetidine resistance" in this patient. This was confirmed by ranitidine concentrations obtained on July 1, 1981 and July 14, 1981 (Table 11). On July 1, the plasma ranitidine level 2 hours after medication was 119 ng/ml. As shown in Table 11, acid secretion was reduced by intravenous cimetidine. Therefore, the patient was treated with I.V. cimetidine for 2 weeks. On July 14, plasma ranitidine concentration again was measured 2 hours after medication. Plasma concentration was 314 ng/ml. Since there was no evidence of delayed gastric emptying, these results suggest that patient G was malabsorbing drug on July 1 and this was corrected by July 14 after treatment with I.V. cimetidine for 2 weeks. Presumably, malabsorption in this patient was secondary to damage to jejunal mucosa by increased acid secretion. The mucosal defect was corrected following treatment with I.V. cimetidine.

Acid secretion in most patients in Table 10 was not reduced by I.V. cimetidine. Thus, delayed emptying or decreased absorption of drug was an unlikely explanation for "cimetidine resistance" in these patients. Patients D, E, and F were subsequently treated with ranitidine (see pages 37 to 47) and acid secretion decreased dramatically. Ranitidine has a structure that differs from that of cimetidine and when given intravenously, ranitidine is about 8 times more potent than cimetidine (when given orally, ranitidine is 3 to 4 times more potent than cimetidine). The fact that patients responded to ranitidine

and not to cimetidine suggests that "cimetidine resistance" in these patients might have been secondary to tolerance to cimetidine (B-1, above), excessive concentrations of histamine (B-4, above) in the gastric mucosa or to some other factor. It is possible that ranitidine has a greater affinity for H_2-receptors than does cimetidine. Also, since ranitidine, when given intravenously, is 8 times more potent than cimetidine, it theoretically could compete with larger histamine concentrations at H_2-receptors in the stomach than could cimetidine. At present these are only hypotheses, but they seem plausible.

Treatment of "Cimetidine Resistance". It is important to document that acid secretion is being reduced adequately by cimetidine. Thus, basal acid secretion should be measured following the same dose of cimetidine that an individual patient has been taking. For example, if a patient has been receiving 300 mg. cimetidine four times daily, acid secretion should be measured from 4 to 6 hours after that dose of cimetidine. There are no guidelines defining adequate suppression of acid secretion. In my opinion basal acid secretion should be suppressed to less than 5 mmol/h, especially in patients with active ulcers. If this degree of suppression is not achieved, the frequency of drug administration should be increased (e.g., 300 mg cimetidine q4h while the patient is awake and 600 mg at bedtime). Another alternative would be to prescribe 600 mg cimetidine four times daily or q6h. In patients with Zollinger-Ellison syndrome, 600 mg cimetidine, q4h, or cimetidine plus an anticholinergic drug may be necessary (see page 46).

If increasing the frequency and/or dose of cimetidine does not reduce acid secretion adequately, the effect of intravenous cimetidine should be tested. Intravenous cimetidine should be given over a 5-10 minute period since bradycardia has been reported in a few patients with rapid I.V. cimetidine administration. If the patient responds to intravenous but not to oral cimetidine, delayed gastric emptying or malabsorption of drug should be suspected.

If acid secretion is not suppressed by intravenous cimetidine, there are two alternatives: a) Give cimetidine by continuous intravenous infusion (e.g., with an IMED pump) as in Case H, Table 10. Why this works in some patients is not known. Presumably, plasma concentrations and mucosal concentrations of cimetidine can be maintained at a high level continuously by infusing cimetidine. It is possible that this method leads to higher concentrations of cimetidine at H_2-receptors. b) Obtain ranitidine. This can be done by contacting Glaxo, Inc., 3306 East Chapel Hill-Nelson Highway, Research Triangle Park, NC 27709.

One should also look for special conditions that have been associated with "cimetidine resistance" such as Zollinger-Ellison syndrome, hyperparathyroidism or sepsis.

Patients With Ulcers Which Do Not Heal With Cimetidine. As can be seen from the Summary on page 28 and the data in Table 9, about 10 to 15% of patients with either duodenal or gastric ulcers do not have a healed ulcer at the end of treatment. These results were obtained in controlled clinical trials in which patients were endoscoped at regular intervals to document healing. As will be discussed below, these findings may be important in taking care of patients with gastric ulcers but may have little clinical relevance in treating most patients with duodenal ulcers.

Patients With Gastric Ulcers. In these patients it is important to document healing either by x-ray or endoscopy since a few benign-appearing gastric ulcers are actually malignant. Thus, patients with benign-appearing gastric ulcers that do not heal with cimetidine treatment within 12 weeks (15 weeks in patients with ulcers >2.5 cm in diameter) should be evaluated for gastric cancer. This includes endoscopy with biopsy and cytology even in patients in whom endoscopy with biopsy was performed prior to beginning treatment. If the ulcer is malignant, the patient should be referred for surgery. If the ulcer is benign and if the patient has a concommitant duodenal ulcer, evidence of hypersecretion on x-ray or endoscopy, diarrhea or some other finding suggestive of a hypersecretory state, the patient should be evaluated for basal acid hypersecretion. This includes measurement of serum gastrin concentration and gastric acid secretion. As for further treatment, there are two possibilities: 1) another drug could be added to the treatment regimen (e.g., antacid or sucralfate) and the patient could be treated for an additional 3 to 4 weeks or 2) the patient could be referred for surgery. In my opinion, another drug should be added. If ulcers do not heal by a total of 16 weeks (18 weeks in patients with ulcers >2.5 cm in diameter) and if there is no contraindication to an operation, most patients should be referred for surgery.

Patients With Duodenal Ulcers. In clinical practice, these patients are not endoscoped routinely to document healing. Treatment is continued for 6 to 8 weeks and if a patient is asymptomatic, therapy is stopped. Thus, the fact that controlled clinical trials demonstrate that 10 to 15% of patients with duodenal ulcers have a non-healed ulcer on endoscopy at 6 or 8 weeks of treatment may not be clinically important. Only those patients with persistent symptoms or a reason to suspect a basal hypersecretory state should be further evaluated and treated (See "cimetidine resistance" and discussion of basal hypersecretion above). If a duodenal ulcer patient does not have "cimetidine resistance" or basal hypersecretion but has a persistent ulcer, another drug should be added (e.g., antacid or sucralfate). If the ulcer remains active, in spite of concomitant therapy, the patient should be referred for surgery.

Side Effects of Cimetidine. Considering the millions of patients who have been treated with cimetidine, side effects are exceedingly rare. Side effects have been reviewed recently and will not be discussed in this protocol (24).

Drug Interactions. Cimetidine delays the metabolism of chlordiazepoxide, diazepam, warfarin, theophylline, and propranolol (25-32). In addition, cimetidine may suppress the metabolism of prazepam, clorazepate, and phenytoin. This is believed to occur because cimetidine inhibits cytochrome P_{450}-mediated drug metabolism in the liver (33). Thus, in patients treated concomitantly with cimetidine and drugs known to utilize this metabolic pathway, it may be necessary to reduce the dose of drug. Medications that are metabolized in the liver by glucuronidation, such as lorazepam and oxazepam, are not affected by cimetidine (34). One study has suggested that cimetidine may also reduce hepatic blood flow and this mechanism has been given for the decreased clearance of propranolol. A recent study has shown that cimetidine decreases the clearance and alters the distribution of lidocaine (35).

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Ranitidine

Several new H_2-receptor antagonists have been developed and tested during the past several years (Table 8). However, there is only one, ranitidine, that has been approved by the FDA and will be marketed soon. The structures of histamine, cimetidine and ranitidine are shown in Figure 20. Cimetidine, like histamine, contains an imidazole ring whereas ranitidine contains a furan ring. Etintidine and oxmetidine (Table 8) have structures that are very similar to that of cimetidine.

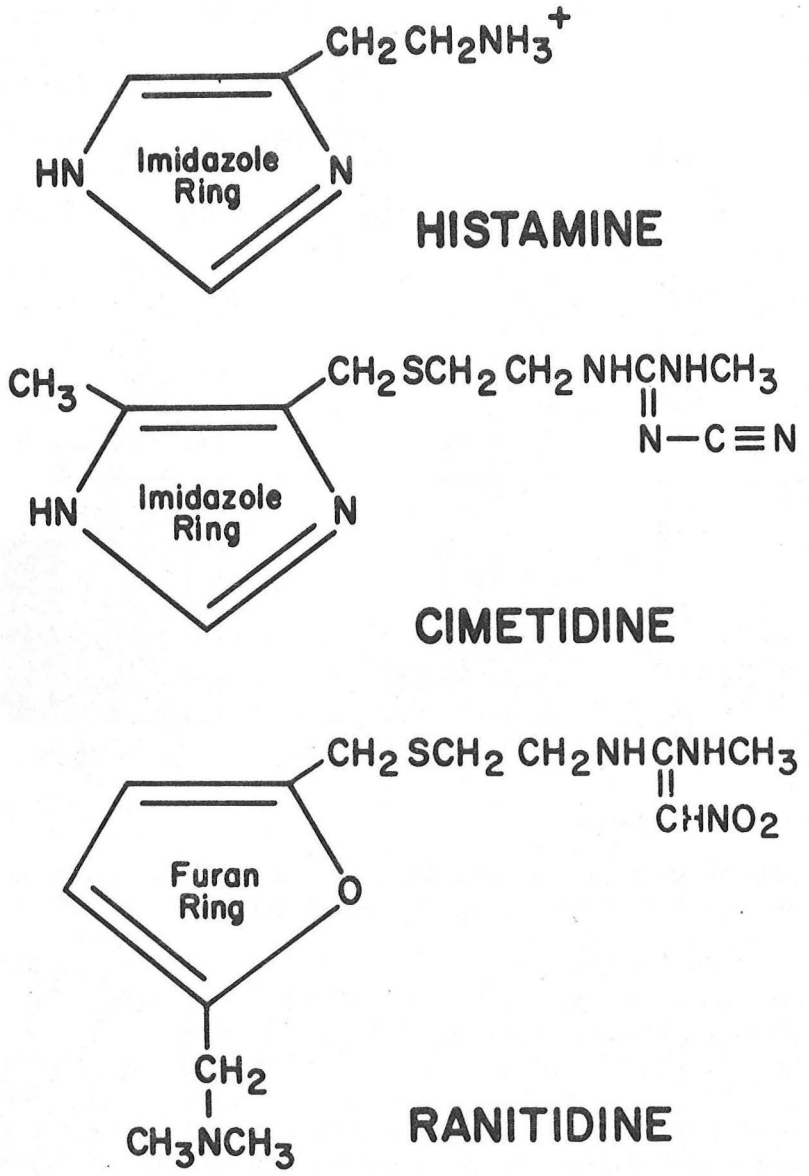

Figure 20. Structures of histamine, cimetidine, and ranitidine.

Clinical Pharmacology of Ranitidine. Ranitidine is well absorbed from the small intestine and has a plasma halflife similar to that of cimetidine (approximately two hours). Ranitidine is excreted in the urine either unchanged or as the N-oxide and S-oxide metabolites (1).

Ranitidine reduces basal, nocturnal, histamine-stimulated, pentagastrin-stimulated and food-stimulated acid secretion to a greater degree than does cimetidine (2-6). Compared with cimetidine, ranitidine, given intravenously, is about 8 times more potent than cimetidine in reducing histamine-stimulated acid secretion and 4 to 5 times more potent in inhibiting food-stimulated acid secretion (5). Because of increased potency, the duration of effect of commonly prescribed doses of ranitidine is longer than that of commonly prescribed doses of cimetidine. This is illustrated in Figure 21. However, when equipotent amounts of ranitidine and cimetidine are given, ranitidine and cimetidine have similar duration of effects (7).

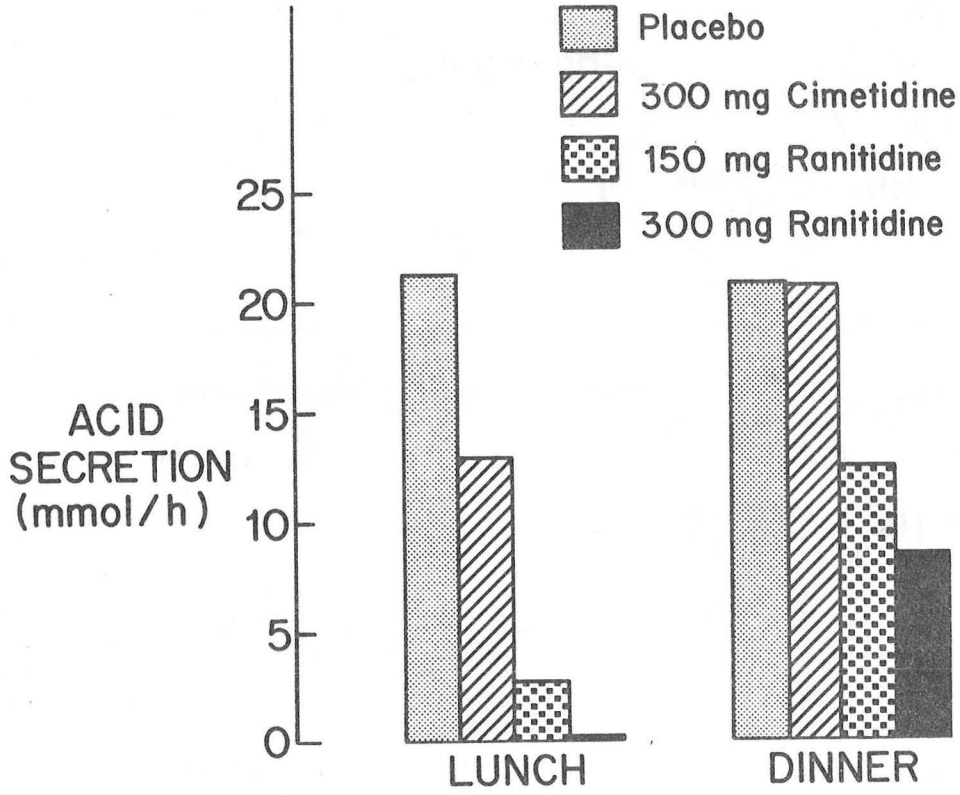

FIGURE 21. Effect of placebo, cimetidine or ranitidine given with a breakfast meal at 7 a.m. on food-stimulated acid secretion measured at lunch and dinner (from Ref. 8).

The recommended dose of ranitidine is 150 mg twice daily, in the morning and evening. The effect of this dose on food-stimulated acid secretion has been compared with the effect of 300 mg ranitidine and 300 mg cimetidine. Results are shown in Figure 21 (8). In these experiments, ranitidine, cimetidine or placebo was given at 7 a.m. with a breakfast meal. Acid secretion was measured in response to a lunch and dinner meal. Ranitidine taken with breakfast reduced acid secretion markedly at lunch, whereas 300 mg cimetidine taken at breakfast reduced acid secretion by only 40% at lunch. At dinner, 150 mg ranitidine taken at breakfast reduced acid secretion by 41%, and 300 mg ranitidine reduced acid secretion by 61%. Cimetidine had no effect on acid secretion in response to the dinner meal. Thus, in doses recommended for treating patients with ulcers, (150 mg ranitidine or 300 mg cimetidine) ranitidine has a longer duration of effect than cimetidine and can be prescribed twice daily.

Clinical Trials. The effect of ranitidine in treating patients with duodenal ulcers compared to that of placebo or cimetidine has been studied in several controlled clinical trials. Only two controlled clinical trials have been performed in patients with gastric ulcers. Results are summarized in Table 11.

TABLE 11. CONTROLLED CLINICAL TRIALS EVALUATING EFFECT OF RANITIDINE IN TREATING PATIENTS WITH PEPTIC ULCERS

MEDICATIONS	% ULCERS HEALED AT VARIOUS WEEKS OF THERAPY				
	4	6	8	P	Ref.
Duodenal Ulcer					
Ranitidine[+]	92			<0.01	9
Placebo	46				
Ranitidine[++]		100		?	10
Placebo		15			
Ranitidine[++]	60			<0.02	11
Placebo	27				
Ranitidine[++]	79			<0.001	12
Placebo	30				
Ranitidine[++]	80			?	13
Placebo	33				
Ranitidine[+++]	78			N.S.	14
Cimetidine[+++]	45				
Ranitidine[++]	77			N.S.	15
Cimetidine[++++]	84				
Ranitidine[+]	63		89	N.S.	16
Cimetidine[++++]	72		94		
Gastric Ulcer					
Ranitidine[++]	76			<0.01	17
Placebo	29				
Ranitidine[++]			77	N.S.	18
Cimetidine[++++]			76		

[+] Ranitidine, 100 mg twice daily.
[++] Ranitidine, 150 mg twice daily.
[+++] Ranitidine, 80 mg four times daily; cimetidine, 200 mg. four times daily.
[++++] Cimetidine, 200 mg with meals and 400 mg. at bedtime.

Summary: Most studies indicate that ranitidine is more effective than placebo and equally as effective as cimetidine in healing duodenal ulcers. Additional studies are needed to evaluate the effect of ranitidine in treating patients with gastric ulcers.

Maintenance therapy. The effect of ranitidine on the prevention of recurrent duodenal ulcers has been evaluated in an open study (not placebo controlled) (19). Patients were treated with ranitidine, 150 mg. at bedtime for 6 months. The cumulative remission data for patients treated with ranitidine compared with results in patients treated with cimetidine or placebo is shown in Figure 22. Data in patients treated with cimetidine or placebo was obtained from Ref. 20.

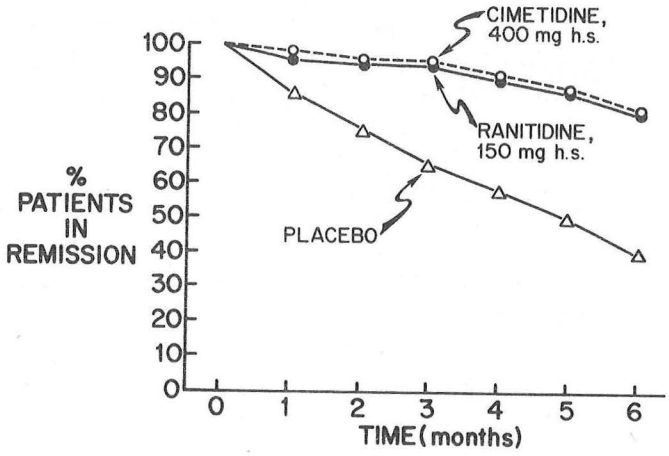

Figure 22. Cumulative remission data for patients receiving maintenance ranitidine, cimetidine or placebo (redrawn from refs. 19 and 20).

Summary: These results suggest that recurrent duodenal ulcer can be prevented by treating patients with either cimetidine or ranitidine at bedtime. A recent study, however, suggests that the recommended dose of cimetidine (400 mg) may be insufficient and that a higher dose (e.g., 600 or 800 mg) may be required to prevent recurrence (21). Maintenance therapy with cimetidine or ranitidine should be limited to 1) patients with frequent ulcer recurrences or complications who would ordinarily be referred for surgery but who prefer medical over surgical therapy; 2) patients with severe medical illnesses (e.g., cardiac, pulmonary, or renal disease) in addition to ulcer disease; 3) patients with acid hypersecretory states such as Zollinger-Ellison syndrome or systemic mastocytosis (These patients require larger doses of cimetidine or ranitidine than are usually prescribed or a combination of H_2-receptor antagonist and anti-muscarinic drug, see page 46).

Side Effects. So far, side effects have been less common with ranitidine than with cimetidine. Early studies in vitro suggested that ranitidine did not have an antiandrogenic effect (22). Thus, it was believed that ranitidine would not cause gynecomastia. However, the case history of a patient who developed gynecomastia while taking ranitidine was reported recently in a letter to the Editor in Lancet (23). Gynecomastia disappeared with withdrawal of ranitidine but recurred with rechallenge. Another patient who developed bradycardia while taking ranitidine was reported recently (24). Since these were only isolated case reports, additional data is necessary to evaluate these side effects of ranitidine.

Drug Interactions. In vitro studies have shown that ranitidine does not bind to cytochrome P_{450} in the liver whereas cimetidine does (25). Other experiments have shown that ranitidine does not inhibit hepatic microsomal drug metabolism as does cimetidine (26-29). Thus, the inhibition by cimetidine of drug metabolism through the cytochrome P_{450} system is likely due to the imidazole ring of cimetidine and not to blockade of H_2-receptors. Drug interactions have not been reported yet with ranitidine.

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Muscarinic Receptor Antagonists

These drugs are antagonists of acetylcholine and block post-ganglionic (muscarinic) receptors. They are believed to reduce acid secretion by blocking a muscarinic receptor on parietal cells (Figure 23).

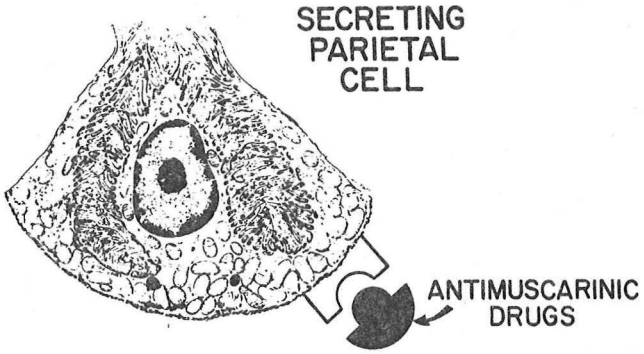

Figure 23. Model of secreting parietal cell illustrating antimuscarinic drugs blocking a muscarinic receptor.

On a molar basis, antimuscarinic drugs are more potent than H_2-receptor antagonists in inhibiting acid secretion. For example, a dose of only 1.39 nmol/kg of atropine will inhibit basal acid secretion in duodenal ulcer patients by 50% whereas a dose of 38 nmol/kg of ranitidine is required for the same degree of inhibition (1). However, most antimuscarinic drugs not only inhibit gastric acid secretion but also reduce salivary and bronchial secretions, dilate pupils and inhibit accommodation of the eye. In addition, atropine and its derivatives cross the blood-brain barrier and also have a central nervous system action. Thus, they are not selective for receptors in the stomach.

Because currently available antimuscarinic drugs are not selective inhibitors of acid secretion and because they produce intolerable side effects, the amounts of drugs that can be given to patients are limited. Thus, in the doses usually prescribed, antimuscarinic drugs are less effective in reducing food-stimulated and nocturnal acid secretion than are H_2-receptor antagonists and are usually not prescribed as the only drugs in treating patients with peptic ulcer disease (see H_2-receptor antagonists plus antimuscarinic drugs, p. 46).

Pirenzepine. This is a new drug (Figure 24) that is undergoing clinical evaluation in the United States.

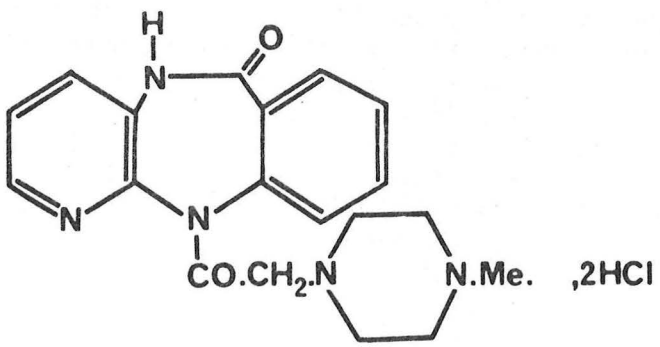

Figure 24. Structure of pirenzepine.

Even though pirenzepine has a structure that is similar to that of the tricyclic antidepressants (compare Figures 24 and 25), pirenzepine does not cross the blood brain barrier, does not have central nervous system side effects and is not an antidepressant.

Pharmacodynamic differences between pirenzepine and atropine are illustrated in Table 12.

TABLE 12. PHARMACODYNAMIC DIFFERENCES BETWEEN PIRENZEPINE AND ATROPINE (Based on animal studies and modified from Refs. 2 and 3)

	EFFECT OF DRUGS ON VARIOUS ORGANS AND FUNCTIONS	
	ATROPINE	PIRENZEPINE
Central Nervous System	Yes	None
Increase in heart rate	Yes	None
Mydriasis	Yes	None
Bladder Contraction	Yes	None
Salivary Secretion	Yes	Slight
Gastric Secretion	Yes	Yes

Thus, pirenzepine does not effect the central nervous system, heart, eyes, or urinary bladder and has only slight effect on salivary secretion. Many of the findings in animals listed in Table 12 also have been confirmed in humans. The differences in effects between atropine and pirenzepine have led some investigators to speculate that there may be more than one type of muscarinic receptor (M_1 and M_2 receptors). It is believed that classical antimuscarinic drugs, such as atropine or propantheline, inhibit M_1 and M_2 mediated responses in the same range of doses and show no preference for either receptor. Studies suggest, however, that pirenzepine acts selectively on M_1 receptors (2).

Clinical Trials. Several controlled clinical trials performed in Europe and Japan indicate that pirenzepine is more effective than placebo in healing duodenal ulcers and results also suggest that the incidence of ulcer healing with pirenzepine is similar to that with cimetidine (3,4). So far, studies in this country have not been as encouraging. Pirenzepine has been used successfully in combination with ranitidine in treating patients with ZollingerEllison syndrome (see page 46, H_2-receptor antagonists plus antimuscarinic drugs).

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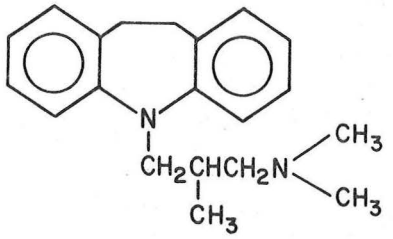
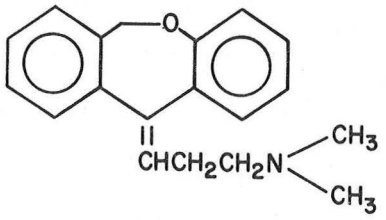
Trimipramine and Doxepin. These two drugs are tricyclic antidepressants (Figure 25). They inhibit acid secretion primarily by blocking muscarinic receptors on parietal cells. They also have been shown to block H_2-receptors in the brain (1) and it has been speculated that they may block H_2-receptors on parietal cells. This, however, has not been established.



TRIMIPRAMINE

Figure 25. Structure of trimipramine and doxepin.



DOXEPIN

Controlled clinical trials have suggested that either trimipramine or doxepine is effective in healing duodenal ulcers (2). These studies, however, must be confirmed before the role of tricyclic antidepressants in the treatment of peptic ulcer disease can be determined.

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H_2-receptor Antagonists plus Antimuscarinic Drugs

Blocking both the H_2-receptor and antimuscarinic receptor on parietal cells leads to a profound reduction in acid secretion in most patients, even in those with very high rates of acid secretion. This concept has been very useful in treating patients with Zollinger-Ellison syndrome (1-3).

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Substituted Benzimidazoles

Studies have indicated that these drugs inhibit a hydrogen and potassium adenosine tryphosphate (H^+/K^+ ATPase) located at the acid secretory surface of parietal cells (Figure 26) (1,2). This H^+/K^+ ATPase is believed to be located only in parietal cells. Thus, the drug may not have effects in other parts of the body. Studies indicate that this compound is a potent inhibitor of acid secretion (3).

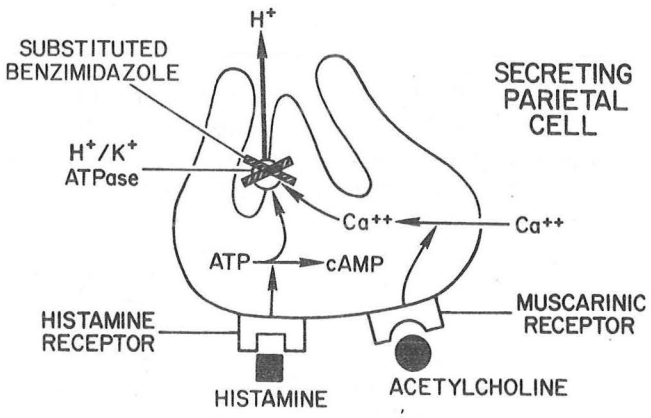

Figure 26. Model illustrating the mechanisms of action of substituted benzimidazoles.

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Prostaglandins

Several prostaglandin analogs of the E, A and I type inhibit gastric acid secretion in animals and humans. Naturally-occurring prostaglandins are active when given intravenously but are inactive when taken orally. Methyl analogues, on the other hand, are effective when given orally or parenterally. One analogue, 15(R)-15-Methyl prostaglandin E_2 reduces food-stimulated acid secretion by 60 to 70 percent.

Mechanism of Action

The methods whereby prostaglandins inhibit acid secretion are not known. There are, however, several possibilities (1). These are listed below:

1) Decreased gastric mucosal blood flow. Some studies have shown reduced mucosal blood flow associated with prostaglandin-induced decreased acid secretion. However, most studies indicate that prostaglandins increase mucosal blood flow. Thus, it is unlikly that changes in blood flow contribute to inhibition of acid secretion by prostaglandins.

2) Cyclic AMP. Although cyclic AMP is believed to be important in secretion of acid, its exact role is unclear. Studies suggest that cyclic AMP may be important in mediating histamine-stimulated acid secretion (Figure 27) and that inhibition of cyclic AMP formation may play a role in inhibition of acid secretion by prostaglandins.

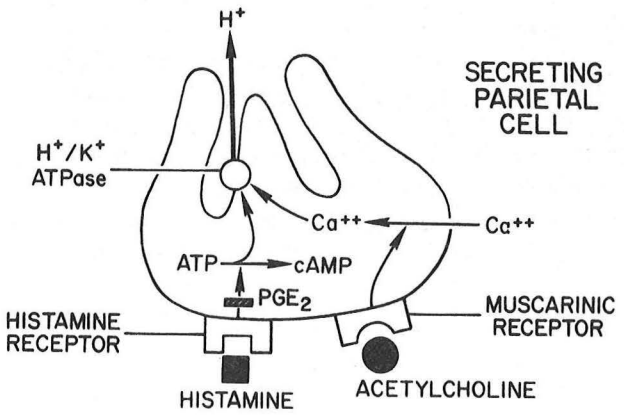

Figure 27. Proposed mechanism of action whereby prostaglandins inhibit acid secretion.

3. Gastrin release. Although oral administration of some prostaglandins block food-induced increases in serum gastrin concentrations, intravenous administration of others do not block post-prandial serum gastrin responses. Furthermore, prostaglandins block pentagastrin-stimulated acid secretion. Thus, it is unlikely that decreased serum gastrin concentration can explain decreased acid secretion associated with prostaglandins.

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Antacids

Pharmacology and clinical results with antacids have been described in numerous reviews (1-3) and will not be discussed in this protocol. In summary, antacid has been shown to be more effective than placebo in healing duodenal ulcers. Results in patients with gastric ulcers have not been as conclusive.

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Coating Agents

Sucralfate

This drug has been approved by the Food and Drug Administration for use in treating patients with active duodenal ulcers. Although sucralfate is new in the United States, it has been used for several years in Japan. Sucralfate neither reduces acid secretion nor neutralizes acid. Instead, it is believed to act primarily at the ulcer crater, forming a protective coat that shields the lesion from pepsin and, perhaps, acid (1-3).

Sucralfate is the salt of sucrose octasulfate$^-$ and $[Al_2(OH)_5]^+$ (Figure 28A). When the drug reaches the acidic environment (pH $\leq$3-4) of the stomach (Figure 28B), some $[Al_2(OH)_5]^+$ ions dissociate from sucrose octasulfate molecules and the residual compound becomes negatively charged. [The occurrence of these physiochemical changes is based primarily on in vitro experiments and in vivo studies in animals[1,2] and has not been verified in humans.] Polymerization of sucrose octasulfate molecules occurs and, simultaneously, a paste-like substance is formed, which is the active form of sucralfate. Although a pH $\leq$3-4 is believed necessary to begin this process, the drug remains active when it reaches the more alkaline environment of the duodenum.

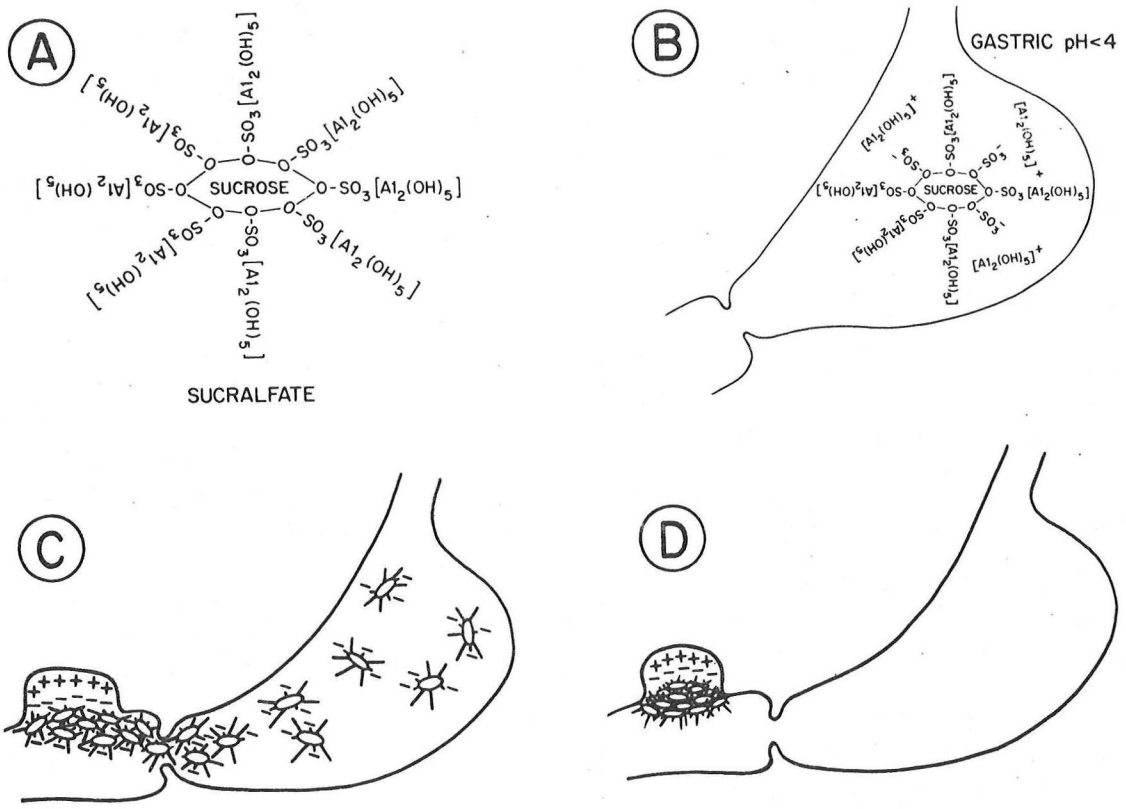

Figure 28. Model illustrating mechanism of action of sucralfate. Sucralfate is a sulfated disaccharide. The structure of the molecule has been drawn as shown in (A) (rather than the conventional method of drawing disaccharide molecules) for clarity and for purposes of demonstrating the mechanism of action.

The paste-like material attaches to necrotic ulcer tissue in both the stomach and duodenum (Figure 28D). This attachment occurs, at least in part, because negatively-charged sucralfate molecules bind to positively charged proteins such as albumin, fibrinogen, damaged mucosal cells, and dead leukocytes in the ulcer base (1,2). Other physiochemical mechanisms may also play a role in the adhesive nature of sucralfate. Binding to ulcer tissue has been shown in animals by measuring the amount of ^{14}C-labeled sucralfate in ulcerated versus normal tissue (4,5). More ^{14}C-sucralfate was found in necrotic than in normal mucosa. Only one such study has been done in humans. Patients with gastric ulcers were given sucralfate before partial gastrectomy, and ulcerated mucosa in the resected specimens contained six to seven times more sucralfate than non-ulcerated mucosa (6).

Sucralfate is absorbed poorly from the gastrointestinal tract. When ^{14}C-labeled sucralfate is given to animals, less than 5% of the compound is absorbed (3). Thus, most of the drug's beneficial effect is believed to occur because sucralfate acts either in the gastric or duodenal lumen or at the ulcer site. Possible mechanisms of action include reduction of peptic activity, protection of the ulcer from acid, and adsorption of bile acids (1-3). Sucralfate reduces peptic activity both in the lumen and at the ulcer crater. For example, luminal peptic activity is reduced by 32% when a 1-g dose is ingested by patients with ulcer disease (3,7). The antipeptic effect of sucralfate at the ulcer site has not been tested in vivo. On the other hand, in vitro studies

using albumin and fibrinogen as protein substrates for pepsin suggest that sucralfate forms complexes with albumin and fibrinogen, preventing peptic digestion of these proteins (8,9). Presumably, similar events occur in humans with ulcers, that is, sucralfate binds to proteins in necrotic tissue, preventing further degradation by pepsin.

Sucralfate has minimal acid neutralizing capability (1). For example, using an in vitro assay (10), a 1-g tablet of sucralfate contains only 2.5 mmol of neutralizing capacity whereas 15 mls of Mylanta II or Maalox Therapeutic Concentrate contains about 75 mmol of buffering capacity. Thus, if sucralfate has a protective effect against acid, it must occur at the ulcer crater and not in the lumen. It has been postulated that the viscous material covering the crater serves as a barrier, preventing hydrogen ions from reaching the ulcer base. This action has been shown only in vitro (2) and it is unclear whether these results are applicable to patients with ulcers.

In vitro studies also indicate that sucralfate adsorbs bile acids and protects against bile acid-induced gastric mucosal injury as assessed by changes in gastric mucosal potential difference (1,2,11,12). This latter finding has been interpreted to mean that sucralfate protects the gastric mucosal barrier. The importance of these findings is uncertain because the role of bile acids in the pathogenesis of gastric mucosal damage in general, and of peptic ulcers in particular, is poorly understood. In addition, cholestyramine, a resin that adsorbs bile acids, is not effective in treating patients with either gastritis or gastric ulcers (13,14). There is little evidence at the present time that adsorption of bile acids is beneficial in treating patients with ulcers.

Several controlled clinical trials have shown that sucralfate (1 g four times daily) results in duodenal ulcer healing more often than placebo (15-18) and as often as cimetidine (Table 13) (19,20).

TABLE 13. EFFECT OF SUCRALFATE, CIMETIDINE OR PLACEBO ON THE HEALING INCIDENCES OF DUODENAL ULCER

	% Ulcers Healed at Various Weeks of Therapy					
	2	4	6	8	12	Ref.
Sucralfate	35	75*				15
Placebo	25	64				
Sucralfate	33	92*				16
Placebo	13	58				
Sucralfate			60*		77*	17
Placebo			24		44	
Sucralfate		80*				18
Placebo		60				
Sucralfate			83		100	19
Cimetidine			71		86	
Sucralfate		80		90		20
Cimetidine		76		86		

* $P < 0.05$ sucralfate vs. placebo

Duodenal ulcer healing with sucralfate has not been compared with antacid therapy. However, comparison of results with sucralfate (Table 14) and results from an earlier study evaluating the efficacy of an antacid regimen (Mylanta II, 30 ml 1 and 3 hours after meals and at bedtime) (21), suggests that sucralfate or antacid produces ulcer healing in a comparable number of patients. The use of sucralfate in treating patients with gastric ulcers is less well documented. Two studies (18,22) found that sucralfate was more effective than placebo, although other studies found no significant differences between sucralfate and placebo (23,24). The efficacy of sucralfate in treating patients with bleeding ulcers, reflux esophagitis, gastritis, or post-operative recurrent ulcers has not been tested. Because sucralfate binds to damaged tissue, the drug might be useful in treating patients with these diseases. However, use must be determined by controlled clinical trials. Sucralfate is not recommended at the present time for treating patients with acid hypersecretory states such as Zollinger-Ellison syndrome, because the drug does not inhibit acid secretion or effectively neutralize acid. Preliminary evidence suggests that maintenance therapy with sucralfate may be effective in preventing recurrent duodenal ulcers (25). This action must be confirmed by other studies before sucralfate can be recommended for this indication.

Can sucralfate and cimetidine be combined in treating ulcer patients? Theoretically, cimetidine, because of its ability to decrease acid secretion and raise intragastric pH, might interfere with the physiochemical activation of sucralfate. However, this possibility has not been evaluated. Another question is whether combining the two drugs is ever necessary. Using the compounds together doubles the cost of therapy. Furthermore, clinical trials suggest that most patients with duodenal ulcer respond to one or the other drug. Combining the drugs might be useful in treating patients with persistent ulcers who do not respond to either drug alone (see "cimetidine resistance").

Side Effects. Sulfated polysaccharides, such as amylopectin sulfate, have heparin-like anticoagulant effects and cause ulcerative colitis in animals. No such abnormalities have been associated with sucralfate. In fact, the overall incidence of side effects in patients treated with sucralfate has been less than 5% (an incidence similar to that seen in cimetidine treated patients) (26-28).

Constipation is the commonest adverse effect, although diarrhea, nausea, and dry mouth also have been reported. Aluminum toxicity has been mentioned as a potential problem, but this seems unlikely. Sucralfate is relatively insoluble after passing through the acidic environment of the stomach. Thus, only a portion of the aluminum contained in sucralfate molecules should be available for absorption. When measured in normal volunteers, mean ($\pm$ SD) plasma aluminum concentrations were slightly higher in those treated for 8 weeks with sucralfate than in those not treated [8.4 $\pm$ 6.0 vs. 6.5 $\pm$ 7.9 µg/L in the two groups, respectively ($P > 0.05$)] (29). [Plasma aluminum concentrations in other control subjects have ranged from 6 $\pm$ 3 to 7 $\pm$ 4 µg/L (30)]. Whether plasma aluminum levels will be higher in patients with renal failure who are treated with sucralfate remains to be tested.

Drug Interactions. The same chemical properties of sucralfate that allow the drug to bind to ulcer craters and to adsorb bile salts may also cause sucralfate to adsorb other drugs. In dogs, sucralfate had no significant effect on intestinal absorption of digoxin, quinidine, propranolol, or aminophylline (31). On the other hand, sucralfate reduced the bioavailability of phenytoin by 38%. Similar results occurred when tetracycline was given with sucralfate. In contrast, when tetracycline was given 1 hour before sucralfate, there was no diminution in the absorption of tetracycline. Whether absorption of other compounds will be reduced by sucralfate remains to be tested.

Bismuth Compounds

De-Nol, a bismuth compound, has a mechanism of action similar to that of sucralfate. Although the drug is not available in the United States, studies have indicated that the compound is effective in treating patients with ulcers. One study suggests that the mechanism of ulcer healing is different with De Nol than with cimetidine (32) while another report suggests that the incidence of ulcer recurrence is less after treatment with De-Nol than after treatment with cimetidine (33).

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MEDICAL TREATMENT OF PATIENTS WITH GASTRIC AND/OR DUODENAL ULCERS SUMMARIZED

Medications.

Four drugs - cimetidine, sucralfate, antacid and ranitidine - which are or soon will be commercially available in the United States have been shown to be more effective than placebo in treating patients with uncomplicated duodenal ulcers (ranitidine should be available in several months). Cimetidine is the only drug conclusively shown to be effective in the treatment of patients with benign gastric ulcers. Thus, patients with benign gastric ulcers should be treated initially with cimetidine. In making a choice among the four agents in treating uncomplicated duodenal ulcers, there are several considerations: cost, side effects, patient compliance, and clinical experience. The cost of a 4-week course of therapy with either sucralfate or cimetidine is approximately the same ($30 to $35). With antacids, the cost differs depending on which compound is prescribed. If a potent liquid antacid that is to be taken seven times a day is selected, the price will probably be more than that of sucralfate or cimetidine. The cost of ranitidine has not been established. Side effects with sucralfate and cimetidine have occurred with similar frequency. Several adverse effects (e.g., gynecomastia, mental confusion, granulocytopenia) reported with cimetidine are more serious than those with sucralfate. However, these more severe side effects rarely occur. Diarrhea, on the other hand, commonly occurs in patients treated with large doses of antacid. Side effects with ranitidine may be less frequent than with cimetidine. Patient compliance with the four drugs has not been evaluated except in clinical trials in which patients were coaxed to take medications regularly. Thus, the frequency with which patients follow directions in routine clinical practice is not known. It would appear that patients prefer taking tablets several times daily rather than liquid antacid seven times daily. Administering ranitidine may have an advantage over cimetidine or sucralfate since ranitidine can be taken twice daily, whereas cimetidine and sucralfate are recommended to be taken four times daily. As far as clinical experience is concerned, the number of patients treated with sucralfate or ranitidine represents only a small fraction of those treated with cimetidine or antacid. Not only have large numbers of patients been treated with cimetidine in controlled clinical trials and in clinical practice, but a postmarket surveillance program evaluating the safety of cimetidine has been carried out in over 20,000 patients in the United States and the United Kingdom. Clinical trials have established the efficacy of cimetidine, and the surveillance program has confirmed the low incidence of side effects. Because of this vast clinical experience, it is difficult not to recommend cimetidine as the drug of choice in treating most patients with duodenal ulcers. However, controlled clinical trials indicate that sucralfate and ranitidine are equally effective in treating patients with uncomplicated duodenal ulcers, and ranitidine is better than cimetidine in treating some patients (see page 29 to 35). Thus, it seems reasonable to recommend cimetidine, sucralfate or ranitidine (when available) in treating patients with uncomplicated duodenal ulcers; and ranitidine in treating patients with increased acid secretion resistant to cimetidine (see "cimetidine resistance", page 29).

Alcohol or Caffeine-Containing Beverages.

There is no evidence that alcohol or caffeine-containing beverages cause ulcers even though some of these drinks stimulate acid secretion. Patients should be told, however, to drink these beverages in moderation (see page 14 and 15).

Cigarettes.

Patients should be advised to stop smoking cigarettes (see page 14).

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