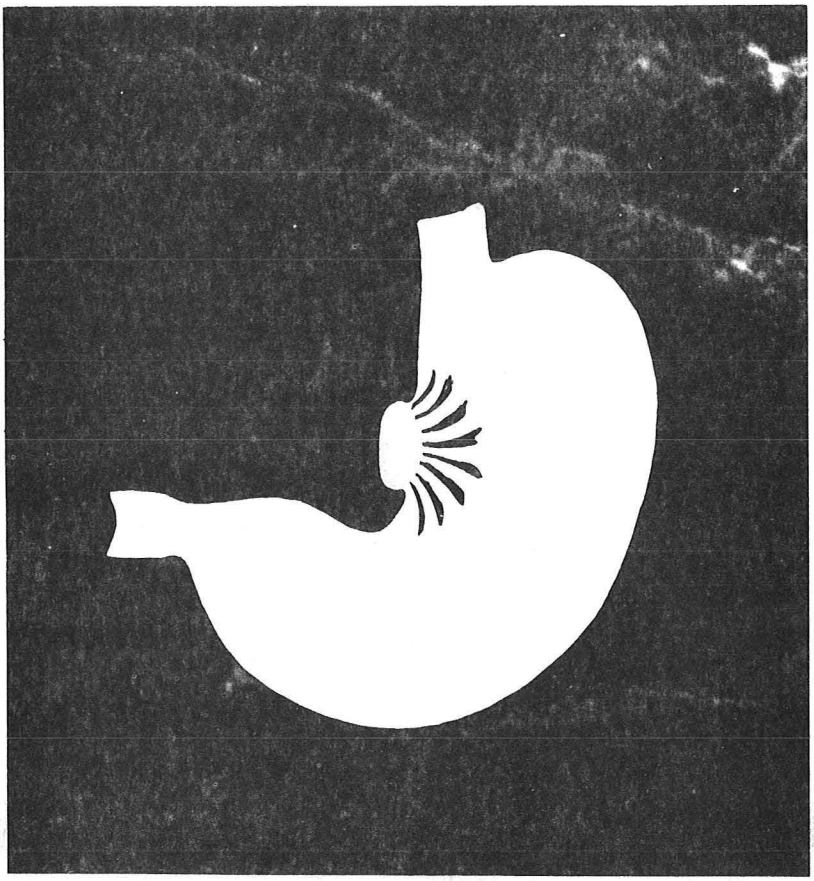
PATHOGENESIS, DIAGNOSIS AND TREATMENT OF GASTRIC ULCER



MEDICAL GRAND ROUNDS

February 12, 1976

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Case 1

E. G. is a 55 year old school teacher who presented with epigastric pain. He described this pain as an "aching" and "nagging" pain which radiated through to the back and occasionally to the sternum. The pain usually occured within 30 minutes of completion of a meal and was relieved immediately by eating food or taking antacid. He stated that he occasionally had nocturnal pain which occurred 1-2 hours after going to bed. Additional complaints included mild anorexia, occasional nausea, and a 5 pound weight loss. Physical examination was normal except for slight epigastric tenderness. Upper gastrointestinal x-ray examination revealed a benign-appearing ulcer on the lesser curvature 3 cm proximal to the pylorus. Endoscopic examination showed a benign-appearing ulcer in the same location as described on x-ray. Biopsies of the ulcer margin - chronic inflammation. Basal acid output was 0.5 meq/h and peak acid output was 12.3 meq/h. Cytology was negative for malignant cells.

What caused the gastric ulcer in this patient?

There are a number of factors that probably play a role in the pathogenesis of gastric ulcer and in each patient with gastric ulcer one or several of these factors may be important. The following is a review of most of these factors.

Gastric Histology and Anatomy

A histological study of gastrectomy specimens from 185 patients with gastric ulcer showed a narrow junctional area separating parietal cell mucosa from antral mucosa (1). In all patients the ulcer occurred in the antral mucosa and 96 percent of the ulcers were adjacent to the acid-secreting mucosa. This finding was confirmed in another study in which 95 percent of gastric ulcers occurred in the antrum in an area adjacent to parietal cells (2). In this same study 2 gastric ulcers were found in the acid-secreting area. When these non-conforming ulcers were examined histologically, it was discovered that they had occurred in islets of ectopic antral mucosa.

Most gastric ulcers occur on the lesser curvature. In the V.A. cooperative study on gastric ulcer, 88 percent were located in this area (3). This predilection for the lesser curvature is difficult to explain. In the study by Oi and co-workers (2) the musculature of gastrectomy specimens was carefully examined, and a series of oblique bands of muscle were found on the lesser curvature. Ninety-seven percent of ulcers occurred in an area where these bands overlap with a prominent circular band of muscle; when deep contractions occur such an arrangement of muscle may distort the lesser curve and in some way account for ulceration at this site.

The term "dual control mechanism" has been coined for the principle that in order for a gastric ulcer to develop both mucosal and muscular factors

must coexist. This "dual control mechanism" may be a factor in the pathogenesis of some gastric ulcers, but certainly not all gastric ulcers.

Conclusions: 1) Most gastric ulcers occur in antral mucosa at or near the junction of antral and acid-secreting mucosa. 2) Most gastric ulcers occur on the lesser curvature perhaps as a result of varying thicknesses in the muscle coat in this area. It is postulated that this arrangement of muscle may distort the lesser curve and in some way account for ulceration.

Mucosal Resistance - "Gastric Mucosal Barrier"

The normal stomach is lined by a membrane which is thought to protect the mucosa from ulceration. This membrane has been labeled the "gastric mucosal barrier".

The exact anatomic location of this barrier and the features that maintain its integrity are not known. Most workers think that the barrier is related to the lipoprotein membrane at the surface of each epithelial cell. Whatever its composition, it functions in an impressive manner in that it maintains a hydrogen ion gradient between lumen and plasma of 1,000,000:1.

A number of substances have been shown to disrupt the "mucosal barrier". A partial list of these so-called "barrier breakers" is shown in Table 1 (4).

Table 1

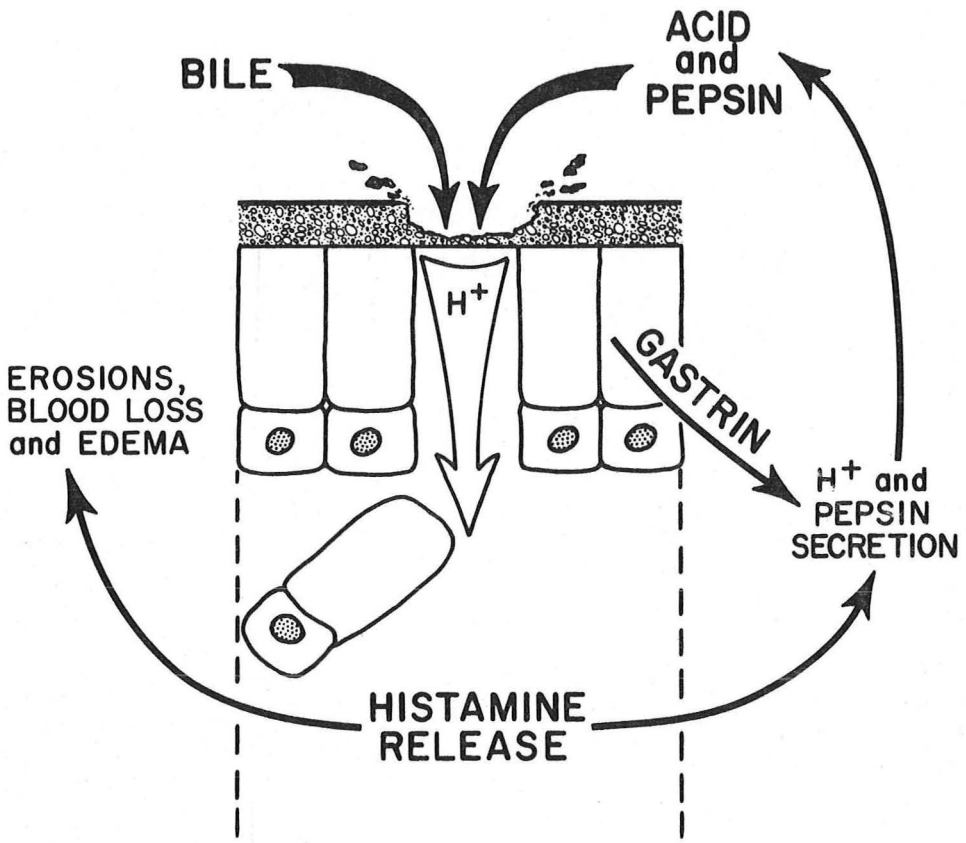
Substances that have been shown to disrupt the so-called "gastric mucosal barrier" (from Ivey, Gastroenterology 1971)

Bile salts (5,6)
Aspirin (7)
Ethanol (8)
Acetazolamide (9,10)
Lysolecithin (11)
Digitonin (11)
Promethazine HCl (12)

Once the barrier is broken by any of the substances in Table 1 a series of events is thought to occur. Figure 1 depicts these events using bile as an example. Hydrogen ions, that heretofore have been confined to the gastric lumen, back diffuse through the damaged mucosa (7). This hydrogen ion back diffusion causes the release of histamine (13, 14) and gastrin (14). Histamine and gastrin cause the secretion of additional acid and pepsin, and histamine causes erosions, blood loss and edema.

Conclusions: The "broken barrier" hypothesis seems plausible and has been accepted as fact by many individuals. There is, however, no proof that the sequence of events occurs.

Fig. 1



Postulated sequence of events that occur after damage to the "gastric mucosal barrier". Bile is used as an example in this figure. The same sequence of events is thought to occur after aspirin and the other substances listed in Table 1.

Bile Reflux

Bile salts have already been mentioned as one of the substances thought to break the "gastric mucosal barrier" (Table 1). The postulated sequence of events in which bile reflux leads to gastric ulceration is as follows: a) Reflux of bile and other duodenal contents lead to b) damage to gastric mucosa via the broken barrier theory and then c) an ulcer in damaged mucosa.

The experimental evidence to support the concept of duodenogastric reflux of bile and pancreatic enzymes is as follows:

1. Reflux of radiopaque material (barium sulfate) and a non-absorbable marker (polyethylene glycol) has been demonstrated in gastric ulcer patients (15-17).

2. When compared with samples of gastric juice from normal subjects, samples from gastric ulcer patients have shown an increased concentration of bile acid conjugates. This has been shown to be true both in the fasting state and also after protein, fat, and carbohydrate meals (18,19). In one of these experiments bile reflux was measured after the ulcer had healed. The same degree of reflux was present after healing as when the ulcer was active. This suggests that if bile reflux is important in the pathogenesis of gastric ulcer, bile reflux precedes ulceration as opposed to being the result of the ulcer.

3. It has recently been shown that patients with gastric ulcer have pyloric sphincter dysfunction (20). In normal subjects pyloric sphincter pressure increases with hormonal stimulation (secretin and cholecystokinin). This is true whether the hormone is given intravenously or released endogenously by the infusion of acid or fat into the duodenum. This, however, is not true in gastric ulcer patients. There was essentially no increase in pyloric sphincter pressure in gastric ulcer patients in response to hormonal stimulation, and this lack of response persisted even after the ulcers healed. This lack of pyloric sphincter responsiveness in gastric ulcer patients is thought to be an explanation for reflux of bile and pancreatic juice.

There are problems with duodenogastric reflux as a factor in the pathogenesis of gastric ulcer.

1. It has <u>not</u> been shown that bile and other components of duodenal juice in the concentrations that are present in the stomachs of patients with gastric ulcer cause damage to gastric mucosa.

2. Patients with pyloroplasty in whom the integrity of the pylorus is destroyed do not get gastric ulcer.

3. The studies showing pyloric sphincter dysfunction must be confirmed.

<u>Conclusions</u>: Duodenogastric reflux of bile and pancreatic juice may occur secondary to pyloric dysfunction. Additional studies, however, are needed to confirm this and also to establish that bile and pancreatic juice in concentrations found in stomachs of gastric ulcer patients actually cause mucosal damage.

<u>Gastritis</u>

Much has been written about gastric ulcer and its association with chronic gastritis. The relationship between the two, however, is controversial. There have been studies suggesting that gastritis is the primary

change with gastric ulceration supervening (21, 22). Conversely, there are an equal number of studies which suggest that the ulcer is the primary lesion and that gastritis is a zonal change around the ulcer (23, 24). In a recent study the presence of gastritis associated with chronic gastric ulcer was evaluated. Biopsies were obtained through a gastroscope prior to and after either medical or surgical treatment (25). Gastritis was found to persist or even worsen after healing of the ulcer. This suggests that gastritis is the basic disease process and that gastric ulceration is a secondary phenomenon.

Whatever the exact relationship between gastritis and chronic gastric ulcer, gastritis appears to be widespread and involves the parietal cell area as well as the antral area (even though the ulcer always occurs in the antral area, see page 1). This widespread gastritis is seen especially in association with ulcers located in the body or corpus of the stomach. The cause of gastritis is not clear. If duodenogastric reflux occurs, gastritis may be secondary to bile salts and/or pancreatic enzymes.

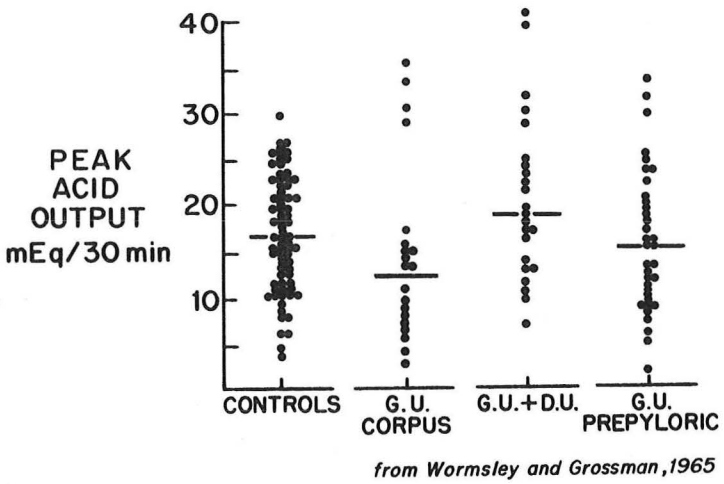
Conclusions: Gastric ulcer occurs in association with gastritis. Gastritis appears to be primary and also to be widespread. The cause of gastritis is unknown.

Acid

The role of acid in the pathogenesis of gastric ulcer is unclear. With the exception of a few isolated cases, acid is present in all patients with benign gastric ulcer (26, 27), although on the average acid secretion is lower than in normal subjects.

Fig. 2

Figure 2 shows acid secretory studies in control subjects and in 3 groups of patients with gastric ulcer (28). Control subjects had a mean peak acid output (PAO) to Histalog of 17 meq/30 min, whereas patients with ulcers in the body of the stomach (corpus) and the prepyloric area had a mean PAO of 12 and 14 meq/30 min, respectively. Only the patients with gastric ulcer combined with duodenal ulcer had a mean PAO that was higher than the control subjects. The overlap, however, between all groups is great.



Peak acid output (Histalog) in control subjects and patients with gastric ulcers.

There are at least 2 reasons why acid secretion in many gastric ulcer patients (especially those with corpus ulcers) is lower than the control population. 1) Since gastritis is thought to involve the parietal cell mucosa as well as the antral mucosa, there

probably are fewer functioning parietal cells. Recall that gastritis is more widespread when the ulcer is located in the corpus and on the average acid secretion is lower in patients with corpus ulcers (page 5 and Fig. 2). 2) Secreted acid may back diffuse through a damaged gastric mucosa (see page 2) so that secreted acid is absorbed rather than collected via a naso-gastric tube.

It would be interesting to know whether acid secretion increases after the ulcer heals. If the study showing persistence of gastritis after healing of an ulcer is accurate (page 5), then low acid secretion may also persist. There are no careful studies in which acid secretion has been measured before and after healing of a gastric ulcer.

Conclusions: Acid probably plays a role in the pathogenesis of gastric ulcer, although the concentration does not appear to be important.

Factors That May Cause Gastric Ulcers in Selected Cases

Aspirin

There is experimental evidence in animals that aspirin damages the gastric mucosa and that this damage involves a direct, toxic action on the mucosal surface. (See page 2 and 3) (29-32). There are ultrastructural changes as well as desquamation of surface epithelial cells. In animals there are 2 types of acute lesions: a) superficial erosions which occur as early as 30 minutes after aspirin exposure and which completely heal within 24 hours, and b) deeper erosions which reach maximum numbers at 4 hours and which heal slowly with a median disappearance time of 5 days. These types of lesions have also been described in humans.

The effects of prolonged administration of aspirin on the gastric mucosa have been studied in animals. Groups of rats were given aspirin by esophageal intubation daily for 6 months (33). Chronic gastric ulcers were found in 9 of 16 rats given 250 or 500 mg/kg/day of aspirin. In addition there were multiple erosions in the glandular mucosa in all of the aspirin-treated rats surviving the treatment period.

In 1961 studies from Australia reported that in humans the regular ingestion of aspirin-containing compounds was associated with the development of chronic gastric ulcer (34). Other reports followed including reports of chronic gastric ulcer in patients with analgesic nephropathy (35-38). In these studies it is impossible to attribute the ulcerations directly to the use of salicylates because many of the patients were taking preparations containing phenacetin and caffeine as well as aspirin, and many of the patients had chronic debilitating diseases which also may be ulcerogenic.

Additional studies in patients who were taking only aspirin-containing compounds have shown an association between aspirin and chronic gastric ulcer (39, 40). In a recent study by Levy (41) an association was established between heavy regular use of aspirin (defined as 4 days/week for 3 months) and both bleeding gastric ulcer and chronic non-bleeding

gastric ulcer. The estimated attributable incidence rates of hospital admissions were very low, however, being 15 for bleeding gastric ulcer and 10 for non-bleeding gastric ulcer per 100,000 aspirin users per year. Remember, that this study evaluated hospital admissions. The incidence may be higher when out-patients are included.

Conclusions: Long-term regular aspirin use causes chronic gastric ulcer in some patients.

Other Drugs

It has been said that treatment with prednisone, ACTH, phenyl butazone and indomethocin may be complicated by gastric and duodenal ulcer (44). Just as with aspirin, prednisone, ACTH, phenyl butazone, and indomethacin reduce the rate of mucus secretion and increase the loss of surface epithelial cells (43, 44) and prednisone and ACTH also reduce the rate of renewal of epithelial cells. In spite of this experimental evidence of damage, it is difficult to incriminate these drugs in humans since many patients are also taking aspirin and since a number of patients have chronic diseases such as rheumatoid arthritis which in themselves may lead to mucosal damage.

Delayed Gastric Emptying

Historically, delayed gastric emptying as a result of antral hypomobility or pyloric stenosis has been considered an important factor in the pathogenesis of gastric ulcer (45-47). Dragstedt and co-workers (48, 49) have shown in animals that acid secretion increases and gastric ulcers develop when the pylorus is occluded. It is postulated that antral stasis secondary to the occluded pylorus causes distention and this leads to increased acid secretion.

There is no evidence in the literature to support delayed emptying as a factor in the pathogenesis of gastric ulcer in humans. It is possible, however, that delayed emptying with subsequent antral stasis may be a factor in the pathogenesis of gastric ulcer in selected patients, for example, patients with long-standing duodenal ulcer disease as illustrated by the next case.

Case 2

J. G. is a 62 year old lady who has had duodenal ulcer disease since 1942. She was recently admitted with epigastric pain and frequent episodes of nausea and vomiting. Physical examination revealed moderate epigastric tenderness. Upper gastrointestinal x-ray examination revealed a benign-appearing gastric ulcer on the greater curvature and a deformed bulb. Saline load test was abnormal with 275 ml removed at the end of 30 minutes (normal < 150 ml). Endoscopy showed a benign-appearing gastric ulcer. The endoscope could not be passed through the pylorus. At surgery a large gastric ulcer was found on the lesser curve. The pylorus was narrowed and would admit only a #12 catheter.

Conclusion: Delayed gastric emptying may be a factor in the pathogenesis of gastric ulcer in a few selected patients.

How are gastric ulcers discovered and how are benign ulcers differentiated from malignant ulcers?

X-ray

Patients with gastric ulcer most often present to the physician with the chief complaint of pain. In these patients the single most widely used diagnostic tool is the barium x-ray.

What are the x-ray criteria suggesting a benign ulcer? The presence of at least one sign indicating benignancy is of importance, but the presence of two or more signs is strong evidence of a benign ulcer. The most reliable signs of benignancy are as follows:

1. Penetration beyond the contour of an otherwise normal gastric lumen.

2. Mucosal folds radiating into the orifice of a crater.

3. A smooth "mound" of edema surrounding a sharply defined crater.

4. Signs of undermining: a. "Hampton's line"
   b. Ulcer "collar"

What are the x-ray criteria suggesting a malignant gastric ulcer? The following are the radiological signs of malignant gastric ulcer:

1. "Abrupt transition" sign and crater within a mass - crater does not usually project from lumen.

2. Outer margins of mass form acute angles with the gastric wall, in contrast to the obtuse angle produced by an edematous benign ulcer mound.

3. Nodular, thickened, and irregular margins.

If an ulcer is interpreted by x-ray as benign, what is the chance that it is malignant? The percentage of "apparently benign" gastric ulcers on x-ray that are malignant at the time of surgery ranges from 1.6 to 18 per cent (50-53). Most of the studies, however, do not adequately answer the question posed above. In some studies, patients in whom the radiologist equivocated or raised the question of malignancy were also included. At the time many of the studies were performed, x-ray techniques were not as advanced as they now are and this may have contributed to a high incidence of wrong interpretation. In all of the studies the diagnosis of benign or malignant ulcer was confirmed by surgery, but many of the patients were sent to surgery after a long period of time (months to years) after the diagnosis of benign ulcer.

The results of 3 of the better and more recent studies are summarized in Table 2.

Table 2

Frequency of Patients With Radiologically Benign-Appearing Ulcers Found to be Malignant at Surgery

	Total No. Patients With Benign-Appearing Ulcer	No. Patients With Malignant Ulcer at Surgery	%
Gear, et al (54)	70	5	7
Montgomery, et al (55)	210	9	4
Wenger, et al (56)	574	19	3

There are also problems with these studies. The first study included a small number of patients. In the second study, a delay of 18 and 20 months occurred in two patients between the x-ray diagnosis of benignancy and surgery. In these cases the cancers may have been separate lesions from the benign-appearing ulcers. If these 2 cases are eliminated, the percent of malignant ulcers initially interpreted as benign would be 3%.

Conclusion: The incidence of cancer in ulcers that have been intrepreted by the radiologist as benign ranges from 3-7%.

Gastroscopy

With the introduction of fiberoptics, the addition of photography, and the development of biopsy capabilities, gastroscopy is now considered an important tool in the diagnosis of gastric ulcer and in the differentiation of benign from malignant ulcer. It is said that the differential diagnosis between a benign and malignant ulcer can be made on gross appearance with an accuracy of approximately 90% (57). This accuracy can be improved by taking multiple directed biopsy specimens at the edges of the lesions. The diagnostic accuracy rate is said to be more than 99% when x-ray, gastroscopy and biopsy are combined (57).

What are the gastroscopic criteria that suggest a benign ulcer?

1. A clean ulcer base with regular edges.

2. Radiating folds that terminate at or near the ulceration.

What are the gastroscopic criteria that suggest a malignant ulcer?

1. Ulceration within a tumor mass.

2. Irregular nodules surrounding lesion.

Indications for gastroscopy. There are two unequivocal indications for gastroscopy in patients with gastric ulcer.

1. If on x-ray there is a question that the ulcer might be malignant, the patient should be gastroscoped and the ulcer biopsied. At least 6 biopsies should be obtained from the ulcer margin.

2. If a narrowed non-distensible antrum is present on x-ray (Case 3) the patient should be gastroscoped and if an ulcer is present, biopsies should be obtained.

Case 3

L. I. is a 40 year old woman who presented in October 1974 with epigastric pain which was relieved by food. There was no history of nausea or vomiting. An UGI series revealed a narrowed, non-distensible antrum which was suggestive of an infiltrating neoplasm; no ulcer was seen on x-ray. Endoscopy - pre-pyloric gastric ulcer which appeared benign. Biopsy - adenocarcinoma.

Should all radiologically benign-appearing gastric ulcers be endoscoped?

Many gastroenterologists think that all gastric ulcers should be endoscoped regardless of whether or not their appearance is benign on x-ray. As stated on page 9, if gastroscopy with multiple biopsies is combined with x-ray, the diagnostic accuracy rate is said to be 99%. We have recently reviewed our experience at Parkland. During the past 2 years, 21 patients have had an UGI x-ray prior to an endoscopic procedure. Only these patients were included in this review. There were a much larger number of patients with gastric ulcer who had endoscopy. Many of these, however, were gastroscoped because of gastrointestinal bleeding, and therefore, had endoscopy prior to x-ray. These were excluded.

The x-ray reports from the 21 patients and the results of gastroscopy and biopsy are summarized in Table 3.

Table 3

Parkland experience: Only those patients who had x-ray prior to endoscopy are included in this survey.

X-ray Results	Number of Patients	Gastroscopy and Biopsy Results
Ulcer benign; no question of malignancy	17	all benign
Ulcer benign; no question of malignancy (inadequate study)	1	malignant
Gastric ulcer; cannot tell whether benign or malignant	3	2 benign 1 malignant

The patient in whom the ulcer was interpreted as benign by x-ray, but who had a malignant ulcer, had an inadequate x-ray examination. The patient could not cooperate with the radiologist because she had had a stroke. It is, therefore, difficult to know whether or not to include her in this series. If she is included, gastroscopy with biopsy was helpful in finding 1 malignant ulcer out of 18 radiologically "benign-appearing" ulcers. Whether or not this statistic will be the same when 100 or even 1,000 cases are reviewed is not known. If, when many more cases are reviewed, gastroscopy and biopsy does find cancers in 5% of patients who have benign-appearing ulcers on x-ray, then there is no question that all of these patients should be gastroscoped unless there is a medical contraindication. Considering the cost of gastroscopy and biopsy (especially if follow-up procedures are included), it is imperative that an answer be found to the question,"Should all radiologically benign-appearing gastric ulcers be endoscoped?".

There are some patients with a radiologically benign-appearing gastric ulcer that also have other significant medical problems (Case 4). These patients should not be gastroscoped.

Case 4

L. M. is a 62 year old woman who was admitted to the Medical Intensive Care Unit at Parkland in October, 1975. The admitting diagnosis was unstable angina. Throughout hospitalization she continued to have chest pain and on occasions had angina at rest. An UGI (prior to admission) revealed a benign-appearing gastric ulcer. A gastroscopy was done and an ulcer with a smooth base and smooth margins was found. Biopsy - no evidence of cancer. UGI x-ray in January,1976 - no evidence of active ulcer.

Conclusion: To adequately answer the question, "Should all radiologically benign gastric ulcers be gastroscoped?", many more patients must be reviewed. Based on available data, I recommend that all patients with radiologically benign gastric ulcers be endoscoped unless the patient has other significant medical problems.

Acid Secretory Studies

There are two reasons gastric secretory studies have been performed in patients with gastric ulcer: 1) to determine if they are achlorhydric when stimulated by histamine or pentagastrin and 2) to determine if they have Zollinger-Ellison syndrome. Supposedly, patients with gastric cancer have a 20-25 percent incidence of histamine-fast achlorhydria, whereas achlorhydria is rarely seen in patients with benign gastric ulcer (58, 59).

The results of acid secretory studies performed at Parkland have been reviewed. The results in patients who were sent to the Gastroenterology Lab with the clinical diagnosis of gastric ulcer are summarized in Table 4.

Table 4

Gastric Secretion in 219 Patients With Clinical Diagnosis of Gastric Ulcer

	No. Patients	Follow-up
Achlorhydria	5	2 surgery - benign ulcer
		3 complete healing on medical therapy
Question of Z-E syndrome (Basal > 15)	2	None had Z-E syndrome

Cost to patient - $50 per study

Total cost of these studies - 219 studies x $50 = $10,950

Conclusion: Based on the review of data from Parkland, acid secretory studies are not helpful in the evaluation of patients with gastric ulcer.

Cytology

In order for cytology to be of any value in differentiating a benign from a malignant ulcer, the technique must be performed by skilled and interested cytologists and cytotechnologists. High accuracy rates in distinguishing a benign from a malignant ulcer are reported in the literature. Most of these studies, however, were performed by experienced cytologists (60, 61). It is impossible to tell from the literature the accuracy of cytology when the technique is performed in routine gastroenterology laboratories. More importantly, it is impossible to answer the question of how many malignant ulcers are diagnosed by cytology when the technique is performed in patients who have a benign-appearing ulcer on x-ray or a benign-appearing ulcer by gastroscopy.

The technique of brush cytology performed at the time of gastroscopy does appear to be a valuable technique. This, however, also remains to be established.

How should a patient with a benign-appearing gastric ulcer be followed and when should follow-up examinations be performed?

If the ulcer is visible by x-ray, this technique should be used in follow-up examinations. On the other hand, if the ulcer is not visible by x-ray and the initial diagnosis was made by gastroscopy, follow-up to complete healing by gastroscopy is essential. The timing and expected results of follow-up examinations are summarized in Table 5.

Table 5

Timing and Expected Results of Follow-up Examinations in Patients With Presumably Benign Gastric Ulcer

Time of Examination	Expected Results	Course of Action
3 weeks*	Absolute rate of healing not important. Ulcer should, however, be smaller.	If ulcer has increased in size or has begun to demonstrate signs of malignancy, the patient should be considered a surgical candidate
6 weeks	Complete healing or 90% reduction in size (see exceptions below)	If ulcer does not meet the expected results and is not included in the exceptions to the rule category, the patient should be considered for surgery.
12 weeks	Complete healing (see exceptions below)	Unless ulcer is in the exception to the rule category, patients should be considered for surgery if ulcer has not healed by 12 weeks.

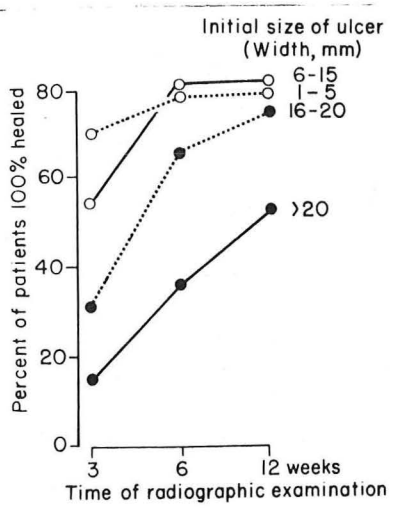
*This examination is not essential.

Exceptions to the rule:

1. Patient with large gastric ulcer (over 2.5 cm in width).

The rate of healing in both large and small gastric ulcers is approximately 3 mm per week (62). It is obvious therefore that the percentage rate of healing at a given time after beginning therapy will be lower for large than for small ulcers. Large ulcers may require 15 weeks or possibly longer to heal completely rather than the 12 weeks allowed for small and medium sized ulcers. This fact was demonstrated by the Veterans Administration study (3). The percentage of each ulcer size (expressed as width) healed at 3, 6, and 12 weeks is shown in Figure 3. For large ulcers only 15% were healed at 3 weeks, 36% at 6 weeks, and 52% at 12 weeks. Since the percentage of patients with large ulcers that are healed at a given time forms a straight line, it might be assumed that an increasingly larger number of patients might have completely healed if treatment had been

Fig. 3



Percentage of patients with complete healing at 3, 6 and 12 weeks in relation to initial size of ulcer. (from Sun & Stempien, Gastro. 1971)

prolonged beyond 12 weeks. It is also apparent, however, from Figure 3 that it might require as long as 21 weeks for the complete healing of some large ulcers. To observe an ulcer for 21 weeks seems unreasonable and dangerous.

2. Patients who have severe medical problems.

Case 5

E. C. is a 71 year old man who has chronic obstructive pulmonary disease. The patient was seen in November, 1974, with the chief complaint of dysphagia. UGI - normal; endoscopy - revealed a large ulcer high on the lesser curvature; biopsies - no evidence of cancer. He was lost to follow-up and returned to clinic in May, 1975. UGI - benign ulcer. Vigorous medical therapy was reinstituted. UGI was repeated in August - ulcer was still present and appeared benign. The patient was hospitalized to assure intensive medical therapy. He remained in the hospital for one week, but then left the hospital because he could not tolerate being confined in the hospital. Repeat UGI and endoscopy were performed in November - benign-appearing ulcer still present. The surgeons have been consulted and because of his age, chronic lung disease and the benign appearance of the ulcer,recommend continued medical therapy.

3. Patients who refuse surgery.

Case 6

A. J. is a 76 year old man who was diagnosed in February, 1970 as having a benign-appearing gastric ulcer on the lesser curvature. He has been followed in Gastroenterology Clinic for the past 6 years. The ulcer has never healed. Gastroscopy has been performed on 2 occasions. A benign-appearing ulcer was seen at both examinations and biopsies were negative. He has been advised to have surgery on several occasions. Each time he has refused.

Is a trial of medical therapy justified in a patient whose ulcer is presumed to be benign?

This question has been debated for many years, and an answer based on well controlled studies is still not available. There are those who would recommend immediate surgical intervention in all patients with a gastric ulcer whether the ulcer is apparently benign or malignant. A number of surgeons have stated that the current rationale of watchful waiting in patients with a gastric ulcer which may be malignant is more hazardous than that of performing a surgical procedure (53,63,64). These investigators also state that delays encountered by medical observation often lead to great socioeconomic loss, disruption of the patient's normal daily life, and development of complications secondary to the lesion. The possibility also exists that the chance of cure may be lost if the lesion is malignant. Others have advocated early surgery because of a high recurrence rate in patients with initially healed gastric ulcers (65).

There is, however, an equally impressive argument against early surgery (66, 67). First, most gastric ulcers are benign; second, essentially all malignancies can be detected by a lack of complete symptomatic, radiological or gastroscopic response to medical therapy; third, there is an admittedly low but definite mortality rate associated with surgery; and finally, a certain number of patients will experience morbidity in the form of a postgastrectomy syndrome.

Conclusion: A trial of medical therapy is justified in patients whose gastric ulcers are, according to good diagnostic criteria, benign. Medical therapy is also a diagnostic test since healing with medical therapy is utilized as further proof that an ulcer is benign.

What forms of medical therapy are available?

A number of different regimens have been included in trials of medical therapy; some of these regimens have been shown in controlled studies to increase the healing rate of gastric ulcer. The regimens shown to be effective in increasing the healing rate are discussed first.

Carbenoxolone

Historical Development: As with many other drugs (i.e. digitalis, rauwolfia serpentina) the development of carbenoxolone can be traced back to the use of certain plants or their extracts in folklore medicine. The use of carbenoxolone for gastric ulcer originates from the practice of using licorice or its extract in the treatment of dyspepsia. More recently the therapeutic effect of licorice was found to be associated with the glycyrrhizic acid fraction. Carbenoxolone is synthesized from this acid.

Pharmacologic Action: The exact mode of therapeutic action of carbenoxolone has not been elucidated; however, its effectiveness appears to be related to its ability to do one or all of the following (68):

1. Increase the production, secretion and viscosity of mucus (69).

2. Increase the life span of gastric epithelial cells (70).

3. Inhibit back diffusion of hydrogen ions (71).

4. Possibly inhibit peptic activity.

The clinical benefit resulting from the administration of carbenoxolone may be due to all the factors listed above, but increased production of mucus probably plays the most important role in promoting healing.

Carbenoxolone does not effect gastric acid secretion or motility, does not modify the action of histamine, and has no effect on the autonomic nervous system.

Clinical Trials: The first double-blind controlled clinical trial of carbenoxolone was reported in 1962 (72). The ulcer healed completely at the end of 5 weeks in 11 out of 30 patients (37%) on carbenoxolone and in 1 out of 20 patients (5%) on placebo (P = 0.01). From 1962 to 1972, there were a total of 22 European clinical trials involving 684 patients. Most of the trials were performed in ambulatory, working patients. All of the studies except for one demonstrated a beneficial effect of carbenoxolone on the healing rate of gastric ulcer (73).

In most patients symptomatic relief from ulcer pain was prompt and occurred more rapidly in the patients treated with carbenoxolone than in those treated with placebo. A trial of maintenance therapy in the prevention of recurrent ulceration or dyspepsia has shown that carbenoxolone affords better protection than antacid given 3 times a day (74).

The drug is currently being evaluated in Canada and the United States. Preliminary reports indicate that it is effective in increasing the healing rate of gastric ulcer in Canada. Only after further clinical trials will we be certain of its usefulness in the treatment of gastric ulcer in this country.

Method of Administration and Dosage: Carbenoxolone is best administered in a dose of 100 mg 30 minutes before meals and at bedtime for 2-3 weeks; 50 mg four times daily for 4-8 weeks and 50 mg 3-4 times daily for maintenance therapy.

Side Effects: The major side effects of carbenoxolone are its aldosterone-potentiating actions (75). Patients may get hypertension, fluid retention, and hypokalemia. The incidence of side effects have been as high as 30-40% in some studies. Attempts have been made to prevent these side effects by giving thiazide diuretics and/or Aldactone with carbenoxolone. Although Aldactone prevented the side effects, the therapeutic effects of carbenoxolone were abolished. On the other hand, it was found that fluid retention and hypertension could be controlled with thiazide diuretics without interfering with the therapeutic effect of carbenoxolone.

Hypokalemia remains a serious adverse effect especially if a diuretic is given concomitantly. It is necessary to monitor serum potassium levels during treatment with carbenoxolone and to administer sufficient potassium to maintain the serum level within normal range.

Conclusion: Carbenoxolone is effective in accelerating the healing of gastric ulcers in ambulatory patients in Europe and Canada. Studies in this country have not been completed. When given in therapeutic doses, carbenoxolone may cause adverse reactions in a large percentage of patients. Although these side effects can be serious, they are predictable, easily recognizable, and controllable by appropriate concomitant therapy.

Bismuth

Pharmacologic Action: Bismuth-peptide complex compounds (De-Nol$^{(R)}$) differ from bismuth-containing antacids in that they act on proteins in an acid medium to form protective bismuth complexes rather than in neutralizing gastric acid (76). The mechanism of action appears to be one of chelation with proteins produced by necrotic ulcer tissue, thus affording protection during the healing phase of ulceration. Supposedly, the formation of a bismuth proteinate coagulum at the site of the ulcer crater protects the ulcer from acid-peptic digestion. Colloidal bismuth has also been shown to have pepsin-binding properties.

Clinical Trials: Several studies have confirmed the clinical impression of the effectiveness of these compounds in the treatment of gastric ulcer (77, 78). Thirty patients with gastric ulcer were evaluated in a double-blind crossover trial (79). Gastroscopy was performed initially and at the end of 4 weeks. Ulcers had healed in 19 out of 24 patients (79%) taking bismuth-peptide complex whereas ulcers had healed in only 6 out of 16 patients (38%) receiving placebo ($P < 0.01$). At the moment there are no studies in the United States evaluating the use of bismuth compounds in the treatment of gastric ulcer.

Method of Administration and Dosage: The compounds are prepared in liquid form. The suggested dose is 5 ml diluted in 20 ml of water and taken 30 minutes before meals and at bedtime. This regimen is continued for 4-6 weeks.

Side Effects: There are essentially no side effects or toxicity when these compounds are taken as prescribed. Bismuth has the disadvantage of causing black stools which may be confused with melena. Milk and antacids may interfere with the action and should be avoided at least an hour prior to and after administration of the drug.

Conclusions: Bismuth compounds appear to be effective in relieving symptoms of gastric ulcer and increasing the healing rate. Additional studies must be done to confirm this. There are no studies being performed in this country at this time.

Antacids

Pharmacologic Action: The pharmacologic action of antacids will not be covered in this protocol. For details of antacid pharmacology see references 80 and 81.

Clinical Trials: One controlled study in outpatients indicates that antacids increase the healing rate of gastric ulcer (82). Other earlier studies, as well as a recent study in hospitalized patients, do not support this finding (83, 84). Not knowing how to interpret the available data, we recommend an intensive program of antacid therapy in an attempt to

neutralize even the small amounts of acid present in most gastric ulcer patients.

Dosage: Thirty ml of Maalox, Mylanta, Riopan or a similarly effective preparation (see ref. 81) should be given every hour while awake until complete healing of the ulcer. Remember, medical therapy is a diagnostic test and every effort should be made to achieve complete healing.

Side Effects: The major side effect of antacid therapy (diarrhea) is well known. Diarrhea usually can be easily treated by alternating Mg-AlOH containing antacids with a pure AlOH containing antacid (Amphojel). Calcium carbonate containing antacids should not be used because of concern about an increase in serum calcium and creatinine in patients treated with large amounts of calcium carbonate and because of calcium-induced gastric hypersecretion (85, 86).

Conclusions: Patients with benign-appearing gastric ulcers should be treated with antacids. Antacids (30 ml) should be given every hour until radiographic or gastroscopic healing is achieved.

Anticholinergic Drugs

Pharmacologic Action: Anticholinergic drugs competitively inhibit the action of acetylcholine on structures innervated by postganglionic cholinergic nerves (i.e., they antagonize the muscarinic action of acetylcholine). In terms of the inhibition of acid secretion, these drugs are thought to act by blocking the acetylcholine receptor on the gastric parietal cell (see Fig. 4). Anticholinergic drugs reduce basal or nocturnal acid secretion by about 60-70% (87) and food-stimulated acid secretion by only 25-30% in duodenal ulcer patients (88).

Clinical Trials: Belladona has been shown to be ineffective in increasing the healing rate of gastric ulcer (89). In this study the anticholinergic was part of a multifactorial trial in which several treatments were being assessed simultaneously, and therefore, it is difficult to interpret the results. In a more recent study the effect of glycopyrronium bromide (Robinul$^{(R)}$) on the healing rate of gastric ulcer in hospitalized patients was evaluated (90). Twenty patients were treated with placebo and 20 with a maximum tolerated dose of Robinul (defined as the dose that gives a slightly dry mouth) (91). A barium x-ray was obtained at the beginning of the trial and at the end of 21 days. In 11 of 20 patients receiving anticholinergic the ulcer was healed completely at the end of 21 days. This is in comparison with 5 patients in the placebo group ($p = 0.02$). There was also evidence that Robinul when taken for prolonged periods might prevent a recurrence.

This study involved a small group of hospitalized patients. Hospitalization alone has been shown to increase the healing rate of gastric ulcer and may have affected the results.

Dosage: When anticholinergic drugs are used, they should be given in a maximum tolerated dose (MTD). The MTD can be determined in each patient by first giving a dose that produces a dry mouth or blurred vision. Once

this occurs the dose should be decreased by 1/2 or 1 tablet. The end point or MTD is that dose that produces a slightly dry mouth.

Side effects: The side effects of blurred vision, photophobia and dry mouth are well known. These can usually be controlled by adjusting the dose. Urinary hesitancy is also an indication to decrease the dose of anticholinergic, and if it is severe, the drug should be discontinued. Anticholinergics should not be used in patients with prostatic hypertrophy.

Conclusions: Until additional studies confirm the finding that anticholinergic drugs increase the healing rate of gastric ulcer, I do not recommend their use during the day. A maximum tolerated dose of anticholinergic should be given at bedtime to decrease nocturnal secretion.

Hospitalization

Hospitalization has been associated with an increased healing rate of gastric ulcer in 2 studies (92, 93). The first study was a prospective study in which patients were randomized and placed either in an out-patient category or in an in-patient category. The in-patients were hospitalized for 4 weeks. The ulcers in 13 out of 32 patients (41%) in the in-patient group were two-thirds healed at the end of 4 weeks compared with 4 out of 32 patients (13%) in the out-patient group ($p < 0.01$). The other study was a retrospective study. The results of this study also suggest that hospitalization increases the healing rate of gastric ulcer.

Because of the economic impact that three or four weeks of hospitalization can have on the patient and his family, it seems reasonable not to hospitalize every patient with a gastric ulcer. There are some who will require hospitalization to expedite their evaluation and to properly introduce them to a good medical regimen (usually 3-4 days). There is a second group who for psychological reasons must be hospitalized in an effort to isolate them from a stressful home or employment environment. In these patients the hospital can be a very important and necessary adjunct to their therapy. The third group who obviously must be hospitalized are those with complications such as bleeding, perforation, or obstruction.

Smoking

In a study by Doll, the ulcers in 30 out of 40 patients advised to stop smoking were healed by two-thirds or more at the end of 4 weeks compared with 23 out of 40 patients who continued to smoke (94). No p value was given; so, it is not known whether the difference in the number of ulcers healed between the two groups is statistically significant. In a recent study (retrospective) there was no difference in the healing rate of gastric ulcer in a group of patients who smoked as compared to a group who did not smoke (93). Those who were smokers did have larger ulcers than those who were non-smokers.

There is no evidence that smoking is a factor in the pathogenesis of gastric ulcer.

Conclusions: None of the available studies are conclusive. It would obviously be better, for a number of reasons, if gastric ulcer patients stopped smoking.

Cholestyramine

Since it has been suggested that bile reflux may be an etiological factor in the development of gastric ulceration, a double-blind controlled trial was performed, using cholestyramine, an exchange resin that binds bile acids, in the treatment of gastric ulcers (95). The patients treated with cholestyramine had a greater reduction in the size of the ulcer, had less pain, and used fewer antacid tablets than did the patients in the placebo group, but the differences were not statistically significant.

Conclusion: Cholestyramine does not increase the healing rate of gastric ulcer.

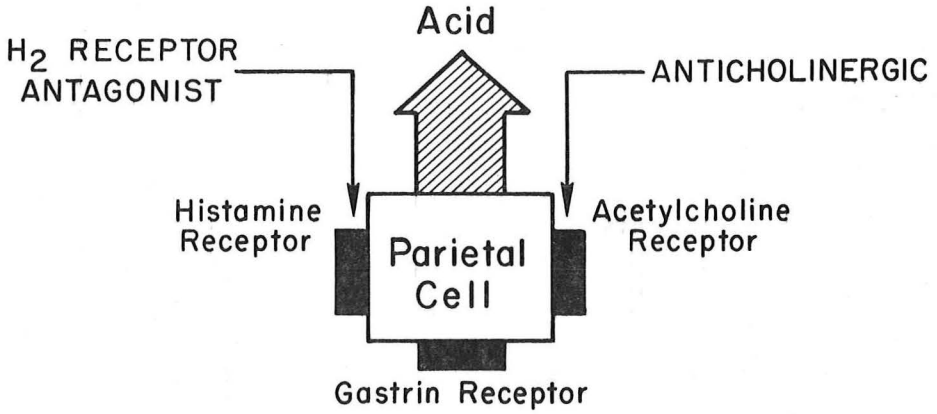
Diet

Two controlled studies in gastric ulcer patients have shown that a bland diet does not increase the healing rate of gastric ulcer (96,97). Therefore, patients with gastric ulcer should be allowed free access to food with the exception of food that specifically causes pain in the individual patient. Patients should be advised not to drink alcohol since alcohol damages the gastric mucosal barrier (Table 1) and in low concentrations stimulates acid secretion (98).

Cimetidine
(Histamine H_2-Receptor Antagonist)

Pharmacologic Action: Histamine exerts physiologic and pharmacologic effects by interaction with at least 2 different receptors. The H_1-receptors mediate the action of histamine on smooth muscle of the gut and bronchi, and this

Fig. 4



Theoretical model of gastric parietal cell showing histamine, acetylcholine, and gastrin receptors.

action is blocked by classic antihistamines (99). In contrast the effects of histamine on the gastric parietal cell, on the guinea pig atria, and on the rat uterus are not blocked by the classic antihistamines. The histamine receptors in the stomach, guinea pig atria, and rat uterus that are not inhibited by the classic antihistamine drugs have been labeled H_2-receptors (100). A theoretical model of the gastric parietal cell with three receptors: histamine, acetylcholine and gastrin is shown in Figure 4 . Three analogues of histamine have been synthesized: burimamide, metiamide and cimetidine. These drugs competitively inhibit the action of histamine on the H_2-receptors. In man these drugs (in recommended doses) suppress basal and nocturnal secretion by 80-95%; suppress pentagastrin- and histamine-stimulated acid secretion by 70-80%; and food-stimulated acid secretion by 75% (88,101-104).

Clinical Trials: Multicenter, double-blind, placebo-controlled trials are now being performed to evaluate the effect of cimetidine on the healing rate of gastric ulcer. So far, none of the results have been published.

Dosage: In clinical trials 300 mg cimetidine is given orally with each meal and at bedtime.

Side Effects: Three of several hundred patients on chronic metiamide therapy developed granulocytopenia, most likely due to the thiourea side chain. The investigational use of metiamide has, therefore, been stopped. Cimetidine has now been given to a number of patients without any reported adverse effects.

Conclusions: The results of clinical trials are necessary before the effect of cimetidine on healing rate of gastric ulcer can be assessed. If cimetidine proves to be effective, its ease of administration and lack of apparent side effects make it an attractive therapeutic candidate.

Medical Therapy Summarized

1. Antacids should be prescribed every hour while the patient is awake and continued until there is radiographic or gastroscopic healing of the ulcer.

2. Anticholinergic drugs should be given at bedtime in a dose sufficient to cause a mild dryness of the mouth.

3. Patients should be given a regular diet except for foods that specifically cause pain.

4. Patients should be advised not to drink alcohol and not to take salicylate-containing drugs.

5. Hospitalization should be used for initial evaluation and introduction to a medical regimen, complications and a few patients that are refractory to other forms of medical therapy.

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