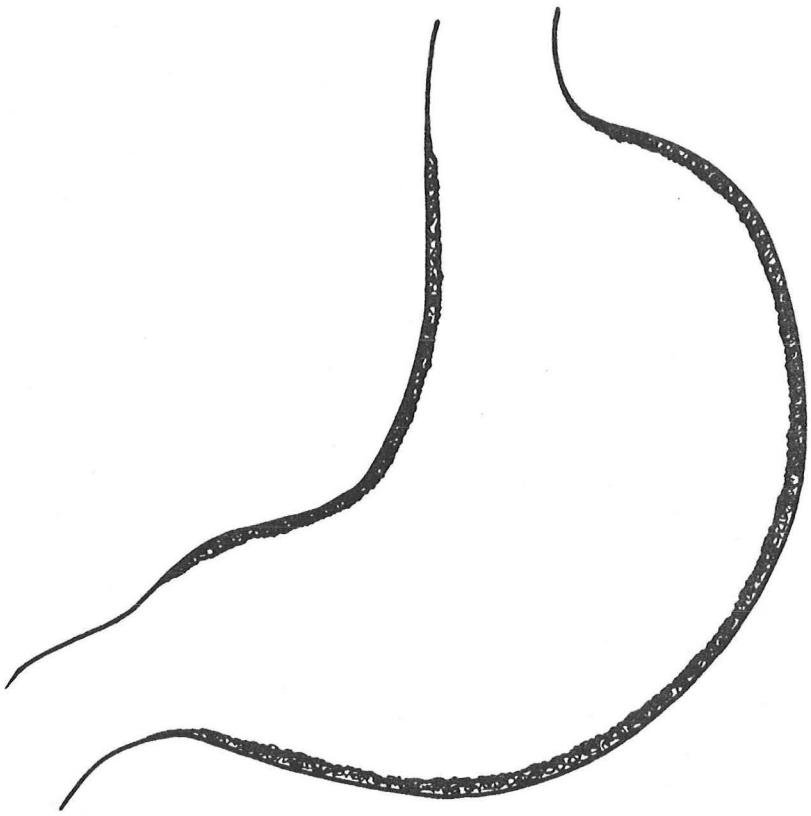
GASTRITIS



MEDICAL GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL

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NORMAL GASTRIC ANATOMY AND HISTOLOGY

The stomach is divided into four major areas - cardia, fundus, body and pyloric antrum (Fig. 1). The mucus membrane of the stomach has

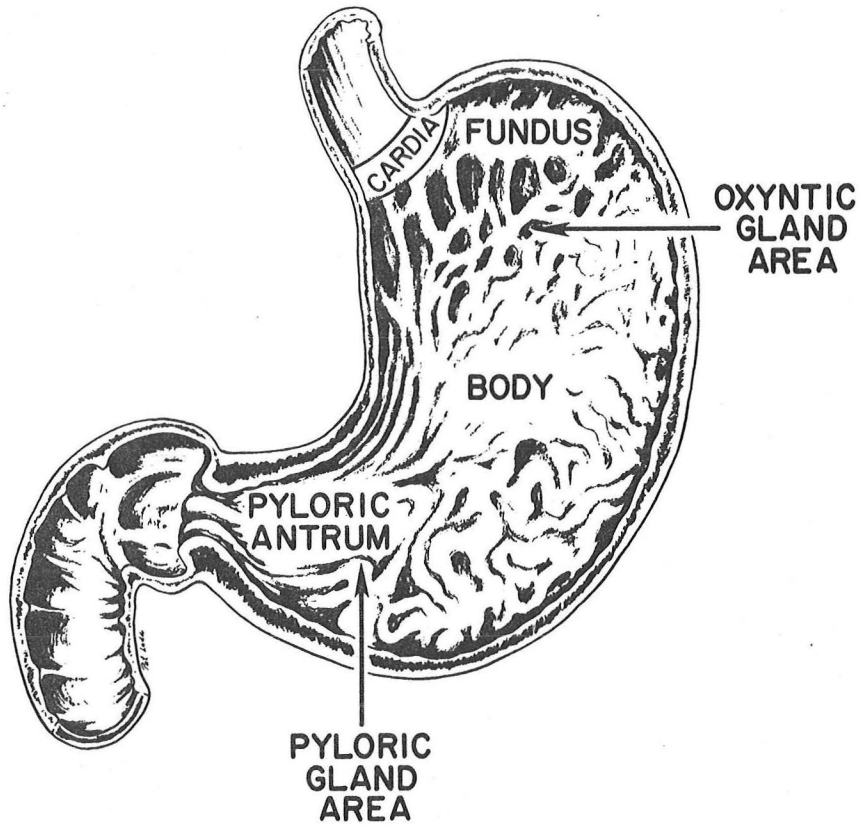

Fig. 1

numerous ridges or folds which are called rugae. The rugae vary in height and number with the degree of gastric distention. When the stomach is fully distended, the rugae become less obvious. The rugae are diminished or absent in patients with gastric atrophy and become enlarged in patients with hypertrophy of cellular or glandular elements (for example, patients with Zollinger-Ellison syndrome or Giant Hypertrophic Gastritis).

The epithelial surface of the stomach is divided by grooves into small irregular areas that are 1 to 5 mm in diameter. These are called the mamillated or gastric areas (Fig. 2). The surface of the mamillated areas is covered with minute depressions, the gastric pits (Figs. 2 & 3).

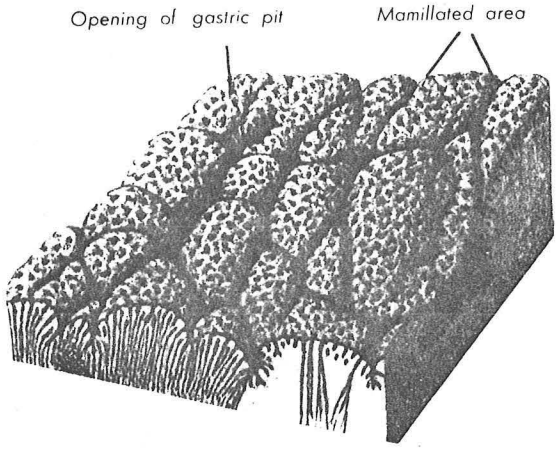

Fig. 2. Diagram of gastric mucosa demonstrating mamillated or gastric areas and gastric pits.

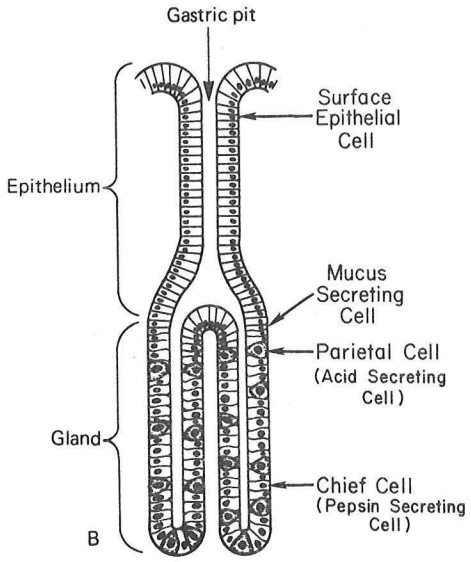

Fig. 3. Schematic representation of gastric pit and gland.

In the cardia, fundus and body of the stomach the gastric pits are relatively shallow and occupy about 1/3 of the thickness of the mucosa while in the pyloric antral region the pits are deeper and occupy 1/2 of the thickness of the mucosa. The lamina propria between the pits contains a few lymphocytes, plasma cells, histocytes and eosinophils.

The surface epithelium and the pits are lined by tall columnar cells (Fig. 3). The columnar cells as well as the mucus secreting cells in the glands secrete mucus which supposedly provides a protective coat over the surface epithelium.

Glands open into the bottom of the pits and occupy the remainder of the mucosa. The glands are branched and several glands may open into one pit (Figs. 3 & 4). The human stomach contains approximately 35 million glands.

The glands found in the mucosa of the fundus and body of the stomach contain chief cells (pepsin secreting cells), parietal cells (acid secreting cells) and mucus secreting cells (Fig. 3). The glands in the cardiac and pyloric antral regions of the stomach contain primarily mucus secreting cells. In addition, the pyloric antral glands contain gastrin (G) cells and an occasional parietal cell.

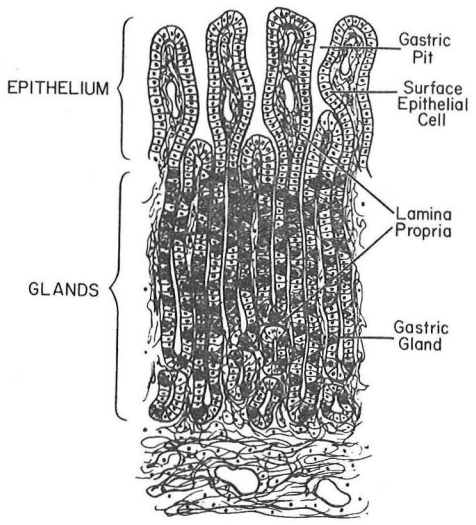

Fig. 4. Gastric pits and glands demonstrating branched nature of glands. Note that 2 or more glands open into 1 pit.

GASTRITIS

Inflammation of the gastric mucosa may be diffuse and involve all parts of the stomach or localized to the fundus and body regions or to the pyloric antral region. Even within a specific area (for example, the antrum), gastritis may be diffuse or localized. Gastritis is classified as acute or chronic based primarily on histologic findings and long-term clinical follow-up. In some forms of acute gastritis (for example, Acute Hemorrhagic Gastritis) endoscopic findings are also important in characterizing the type of gastritis. The term chronic gastritis usually refers to chronic non-specific gastritis.

There are also several specific types of gastritis such as hypertrophic, granulomatous or eosinophilic gastritis. These forms of gastritis can be further classified as acute or chronic based on the duration of the disease. For example, in some patients with hypertrophic or granulomatous gastritis, the disease is self-limited and regresses in a relatively short period of time (1-3 mos.). In other patients the disease continues for long periods (perhaps for life) and thus is classified as chronic.

CLASSIFICATION BASED ON HISTOLOGY

Acute Gastritis

In acute forms of gastritis neutrophils and mononuclear cells are usually found in the lamina propria of the pit and glandular areas.[1,2] In addition, inflammatory exudate is often found in the gastric pits or glands (pit or gland abscesses) (Fig. 5, Appendix). Patchy abnormalities of surface cell structure such as loss of nuclear polarity and decreased cell height also occur. In spite of the inflammatory changes parietal and chief cells usually remain histologically normal.

In severe forms of acute gastritis, such as Acute Hemorrhagic Gastritis (Erosive Gastritis), loss of surface epithelium frequently occurs (Fig. 6, Appendix). Exudate usually covers the base of these superficial ulcerations or erosions. The mucosa is intensely congested with inflammatory cells, the majority of which are neutrophils. Often red blood cells are found in the lamina propria.

Chronic Nonspecific Gastritis

Chronic nonspecific gastritis is divided histologically into three subdivisions: superficial gastritis, atrophic gastritis and gastric atrophy. Superficial gastritis is the earliest and least severe lesion. Inflammatory infiltrate (primarily plasma cells, lymphocytes, neutrophils and eosinophils) is limited to the superficial epithelium and the gastric pits. The glandular area is spared (Fig. 7, Appendix).

In chronic atrophic gastritis the inflammatory infiltrate is extensive and involves both the pit and glandular areas (Fig. 8, Appendix). Glandular tissue is greatly reduced with reduction in mucosal thickness. Glandular structures become simplified and are transformed from complex to simple tubular glands. As atrophic changes progress there is loss of parietal and chief cells. Intestinal metaplasia may occur with goblet and paneth cell formation.

With gastric atrophy the mucosa becomes extremely thin with total or near total loss of glands. The lamina propria is prominent with wide spaces between gastric pits. There is virtually complete absence of chief and parietal cells. Inflammatory infiltrate is greatly reduced with only a few mononuclear cells present. Intestinal metaplasia may be extensive.

ACUTE GASTRITIS

It should be emphasized that finding acute gastritis on biopsy does not necessarily mean that a patient has clinically significant disease. As many as 30 percent of otherwise healthy, asymptomatic individuals can have acute gastritis on biopsy. Also, some forms of acute gastritis with known cause, such as acute irradiation gastritis, are not associated with symptoms.

Acute Hemorrhagic Gastritis (Erosive Gastritis)

This is one of the most common types of acute gastritis and is an important cause of upper gastrointestinal bleeding. When viewed through the endoscope, the mucosa appears severely congested with petechial hemorrhages and superficial ulcerations or erosions. All areas of the stomach may be involved although the fundus and body are most severely affected.

Salicylate ingestion is probably the most common cause of acute hemorrhagic gastritis. Studies in animals suggest that aspirin disrupts the so-called "gastric mucosal barrier"[3,4] (the ability of the gastric mucosa to maintain a high intraluminal pH gradient relative to plasma has been termed the gastric mucosal barrier; the anatomic location of the barrier is unknown[5]). Similar events also occur with alcohol.[6] The exact pathophysiologic mechanism whereby salicylates damage the gastric mucosa is not known. There is evidence to suggest that normal osmotic and pH equilibria within cells may be altered by salicylates.[7] Intraluminal acid and perhaps pepsin are thought to contribute to cellular damage by secondarily diffusing into the cell (Fig. 9). If the insult to mucosal cells is sufficiently severe or prolonged, cell lysis and death may occur.

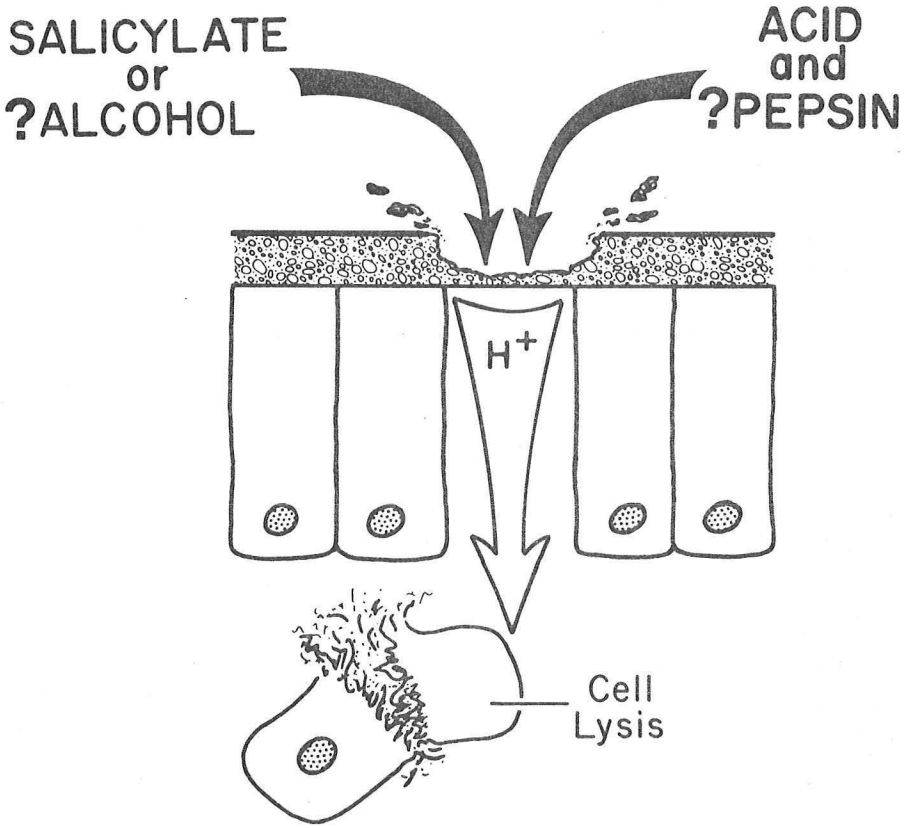

Fig. 9

Endoscopic studies in humans have shown that salicylates (and perhaps other non-steroidal anti-inflammatory drugs) cause mucosal damage and superficial ulcerations.[8-11] Based on in vitro studies and in vivo studies in animals, alcohol theoretically should also cause the same mucosal changes. However, data supporting the pathogenetic role of alcohol in acute hemorrhagic gastritis in humans are not convincing.

Stress associated with severe medical or surgical illnesses ("stress bleeding"; "stress ulceration") is another important cause of Acute Hemorrhagic Gastritis. The risk factors for developing stress induced gastritis include respiratory failure, sepsis, peritonitis, surgery, trauma, burns, renal failure and shock.[12] Massive upper gastrointestinal bleeding with a mortality rate of 80 percent has been reported in as many as 5 percent of critically ill patients.[13]

The pathophysiology of stress induced gastritis is not completely understood but is thought to involve the concomitant presence of acid, duodenal contents (especially bile acids) which have refluxed into the stomach and gastric mucosal ischemia.[14] Evidence to support this includes the fact that acute ulceration can be prevented in animals by increasing mucosal blood flow and by neutralizing bile acids. In addition, ulceration does not occur in the absence of acid.[15] Presumably, ulceration only occurs when the interstitial mucosal pH falls to levels inconsistent with cell survival.

Patients with acute hemorrhagic gastritis, whether due to aspirin or stress, usually have massive upper gastrointestinal bleeding. These patients require fluid and blood replacement and nasogastric lavage (a detailed discussion of the treatment of upper gastrointestinal bleeding is beyond the scope of this protocol). The role of reducing gastric acidity with antacids and/or cimetidine in treating these patients has not been established. However, since it is thought that acid plays a role in the pathogenesis of acute hemorrhagic gastritis it seems reasonable to reduce gastric acidity. The fact that surgical therapy is often associated with inordinately high morbidity and mortality adds further support for vigorous medical therapy.

Initially, antacid (usually 30 ml) is prescribed every hour during the day and night; higher doses or more frequent administration may be needed in some patients. Measurement of intragastric pH every hour and administration of antacid in doses to keep intragastric pH above 3.5 has been suggested. Studies have shown that such a regimen prevents "stress" induced ulcerations and bleeding in a large percentage of critically ill patients.[12] Furthermore, additional evidence suggests that antacid is better than cimetidine in preventing stress induced ulcerations.[16] There is no evidence, however, that maintaining pH above 3.5 controls bleeding or assists in healing acute hemorrhagic gastritis once it occurs.

Epidemic Gastritis with Hypochlorhydria

This form of acute gastritis occurred in a group of normal human volunteer subjects who were undergoing acid secretory studies in our laboratory.[17] In addition to gastritis, they also developed profound hypochlorhydria. The case history of one of the subjects is detailed below.

Case 1

J.B. is a 21 yr. old student who volunteered for a series of gastric acid secretory studies. Just prior to beginning the experiments his basal acid output (BAO) was 2.0 meq/hr and peak acid output (PAO) was 44.8 meq/hr. During the first week of studies basal pH ranged from 1.7 to 1.9 (Fig. 10). Following the initial series of studies, he developed epigastric pain, nausea and vomiting. These symptoms were moderately severe for 1 day and abated after 3 days. When he returned to the laboratory for the next acid secretory study, his basal gastric pH had risen from 1.9 (on the initial study) to 7.0. A repeat BAO and PAO were 0 and 2.9 meq/hr, respectively. Within 2 weeks he developed achlorhydria. The lowest pH after maximal stimulation with pentagastrin was 6.9. Basal and peak acid secretion were measured at 3-to-4-week intervals for several months. As shown in Fig. 10, by 5 months the acid secretory capacity had returned to near pre-illness levels.

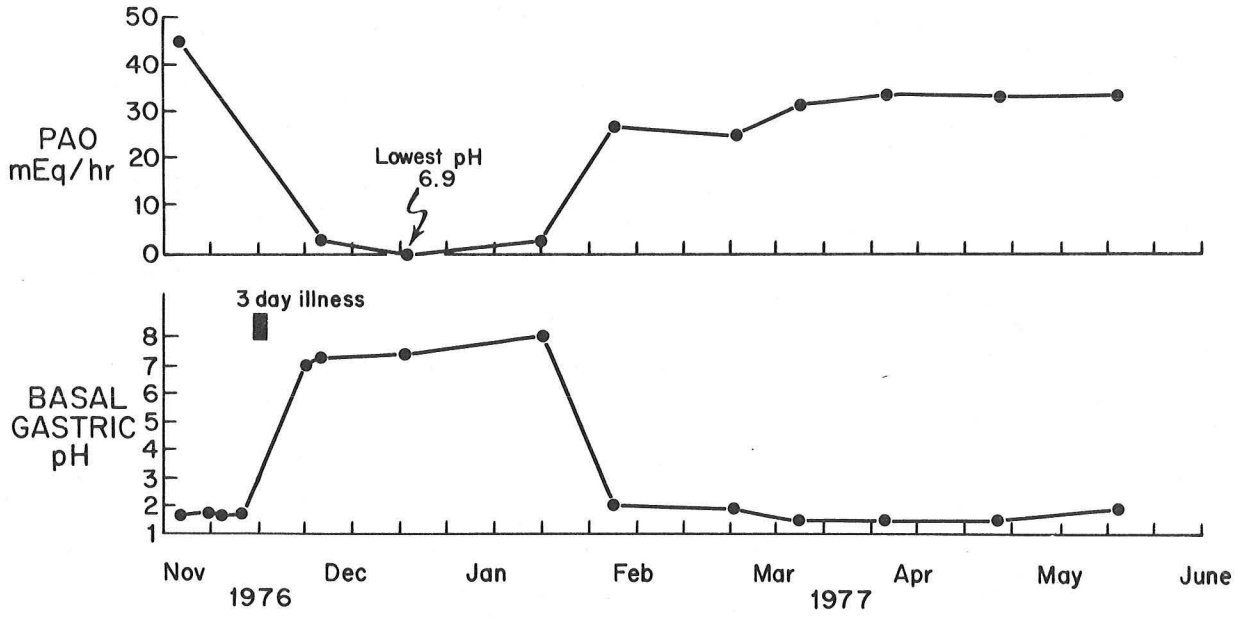

Fig. 10. Peak acid output (PAO) and basal gastric pH in a normal subject before and after development of a 3 day illness (epigastric pain, nausea and vomiting). Gastric biopsy performed following the illness revealed severe acute gastritis (from Ref. 17).

A similar phenomenon occurred in 17 of 37 healthy volunteer subjects undergoing studies in our laboratory. Nine of the 17 subjects developed a clinical illness prior to detection of hypochlorhydria. Symptoms consisted of mild to moderate epigastric pain, nausea and vomiting. The illness persisted from 1-4 days. The pain was not relieved by antacid but was relieved by food in two cases. Physical examination was normal.

The PAO before, during and 1 yr. after the onset of hypochlorhydria in the 17 subjects is shown in Fig. 11. The mean reduction in PAO was 93 percent and 3 patients were achlorhydric. Acid secretion returned to baseline values in 14 subjects during the one year follow-up. However, 3 subjects remained hypochlorhydric at the end of a year.

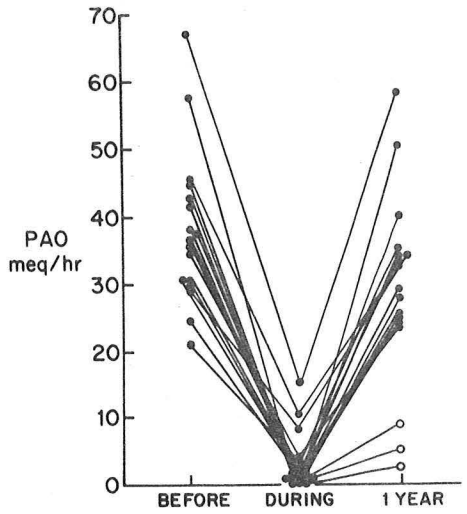

Fig. 11. Peak acid output (PAO) in 17 subjects before, during and 1 year after development of hypochlorhydria and gastritis (from Ref. 17).

Twelve of the 17 subjects had a gastric biopsy while they were hypochlorhydric. All twelve had 2-3+ gastritis in the fundus and body (Fig. 12) [moderate to severe infiltrate of mononuclear cells and neutrophils in the lamina propria; abscesses in the pit and gland areas (Fig. 5, Appendix)]. Parietal cells and chief cells were abundant and appeared normal in all fundal biopsies. Only 3 of 8 control subjects had gastritis (Fig. 12).

It is thought that gastritis was the cause of hypochlorhydria; however, the mechanism whereby this occurred was not determined. The etiology of gastritis also was not found. Since gastritis occurred in a number of different individuals who were in contact with each other over a relatively brief period of time, an infectious etiology was suspected; however, an organism was not found.

The three subjects who were still hypochlorhydric at the end of one year (Fig. 11) have been followed and acid secretory studies have been performed every 6 to 12 mos. Acid secretion in one patient returned to normal. However, two patients remain hypochlorhydric. Acid secretory data in one of the subjects who is still hypochlorhydric is shown in Fig. 13.

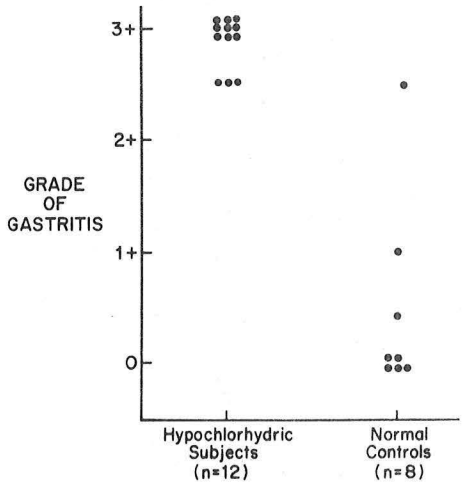

Fig. 12. Grade of gastritis in 12 subjects with hypochlorhydria and 8 normal control subjects.

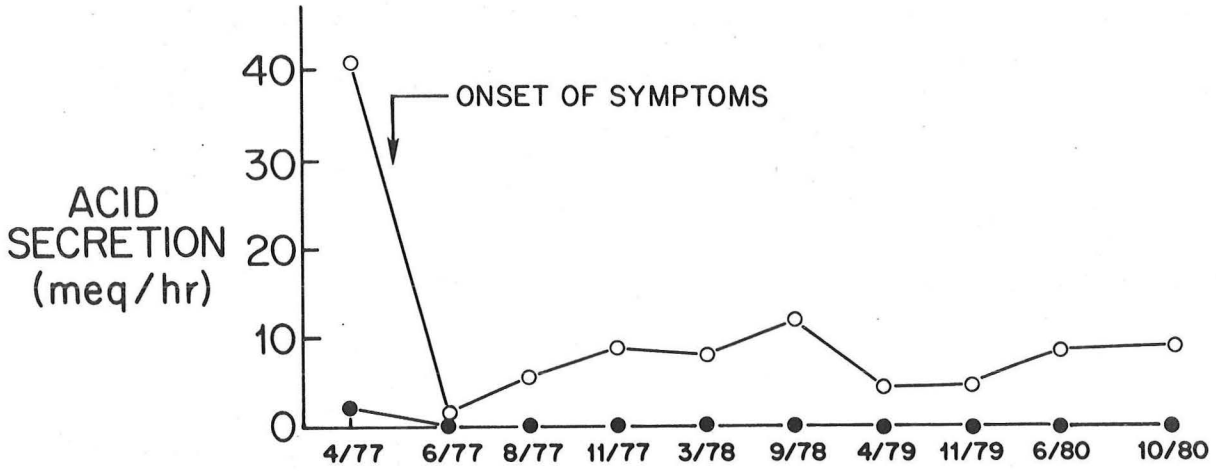

Fig. 13. Basal acid output (BAO) (●—●) and peak acid output (PAO) (o—o) in a subject with hypochlorhydria and gastritis who has been followed for 2 1/2 years.

It is generally accepted that acute gastritis is a reversible lesion and thus, does not progress to atrophic gastritis and gastric atrophy. However, persistent hypochlorhydria in our subjects suggests that functional abnormalities may persist for months in some patients with acute gastritis. Whether acute gastritis in these subjects will progress to chronic atrophic gastritis and gastric atrophy remains to be determined.

Other Causes of Acute Gastritis

Acute gastritis can occur as a result of irradiation, corrosive ingestion and bacterial infections (Acute Phlegmonous Gastritis). Acute Phlegmonous Gastritis is a rare, but fulminant and often fatal, form of acute gastritis.[18] Streptococci are most commonly the cause although staphlococci, Escherichia coli and proteus have been cultured from stomachs of patients with Acute Phlegmonous Gastritis.

CHRONIC GASTRITIS

Causes of Chronic Nonspecific Gastritis

The causes of chronic nonspecific gastritis are not known although a number of mechanisms have been postulated. For example, radiation injury, nutritional deficiencies, endocrine disorders and infectious diseases have been implicated. However, there is no proof that any of these factors cause chronic gastritis. Repeated insults to the gastric mucosa by mechanical, thermal or chemical agents also have been said to cause chronic mucosal changes. Some studies have suggested that long-term alcohol or aspirin ingestion can lead to chronic gastritis although there is no proof of this. The most likely causes of chronic nonspecific gastritis are thought to be reflux of duodenal juice into the stomach or immunologic abnormalities. Genetic influences are also thought to play a role in the pathogenesis of chronic gastritis in some patients.

Reflux of Duodenal Juice. Bile, pancreatic juice and lysolecithin (which is formed when phospholipase A from pancreatic juice reacts with lecithin from bile) are postulated to initiate the process leading to gastritis by somehow damaging the "mucosal barrier" (Fig. 14).[19,20] It is likely that these substances cause damage in a manner similar to that of salicylates. Damage to the so-called "mucosal barrier" occurs allowing diffusion of acid and pepsin into the mucosa. This, in turn, leads to further mucosal damage. Experimental bile damage appears to be greater at a low intragastric pH suggesting that gastric acid is important in the development of the lesion.[21] Both chronic superficial and atrophic gastritis have been produced experimentally in dogs following infusion of bile and pancreatic juice.[22] However, it has not been shown that the amounts of bile and pancreatic juice found in the stomachs of humans with chronic gastritis are similar to those that cause mucosal damage and gastritis in animals.

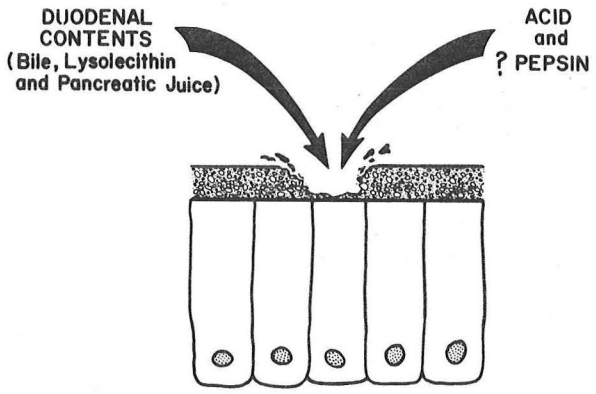

Fig. 14

Immunologic Mechanisms. The fact that antibodies to parietal cells[23] and intrinsic factor[24] have been found in some patients with chronic nonspecific gastritis (especially those with pernicious anemia) has led to speculation that immunologic factors may be important in causing chronic gastritis. Studies in animals have shown that injection of sera from patients with atrophic gastritis and pernicious anemia can lead to a thinning of the gastric mucosa, a reduction in peptic and parietal cell masses and gastric secretory failure.[25] It has been postulated that humoral immune mechanisms are responsible for these changes. Against antibodies being involved in the pathogenesis of

atrophic gastritis is the fact that adults with acquired hypogammaglobulinemia (common variable immunodeficiency) can develop gastric atrophy and pernicious anemia. Furthermore, antibodies to intrinsic factor are not present in at least 40% of patients with pernicious anemia.

There are several observations that suggest that cellular rather than humoral immune reactions may be responsible for mucosal damage. First, lymphocyte transformation occurs when lymphocytes from patients with pernicious anemia are cultured with preparations of human intrinsic factor.[26] Second, several studies have shown that lymphocytes from patients with pernicious anemia respond to intrinsic factor by releasing migration inhibitory factor.[27] Third, administration of steroids to patients with pernicious anemia leads to reappearance of parietal cells and secretion of small amounts of acid.[28] Fourth, there is a marked infiltrate of lymphocytes and plasma cells in the mucosa of patients with atrophic gastritis.

The presence or absence of parietal cell antibodies (PCA) in patients with atrophic gastritis led to the classification of atrophic gastritis into two types.[29,30] It was observed that patients whose sera was positive for PCA usually had diffuse gastritis, markedly reduced acid secretion and a large number eventually developed impaired B_{12} absorption. On the other hand, patients whose sera was negative for PCA had a less advanced gastritis, moderate reduction in acid secretion and rarely had problems with B_{12} absorption. Strickland and Mackay[31] followed 70 patients during a 24 year period and further refined the classification of chronic nonspecific gastritis (Table 1). They called the two types of gastritis: Type A and Type B.

Table 1

Characteristics of Patients with Type A or Type B Gastritis
(adapted from Strickland & Mackay, Ref. 31)

	Type A Gastritis	Type B Gastritis
Number of Patients	30	40
Positive Test for PCA	30	0
Fundic and Body Gastritis	30	40
Antral Gastritis	4	37
Acid Secretion		
Achlorhydria	26	23
Hypochlorhydria	4	17
Intrinsic Factor Antibody	9	0

Thus, the distinctive features of Type A gastritis are 1) presence of antibodies to parietal cells, 2) gastritis primarily of the fundal and body mucosa, and 3) achlorhydria. In addition, there is a tendency for these patients to develop pernicious anemia and there is an increased incidence of endocrine disorders.[31-33] The features of Type B gastritis are 1) absence of parietal cell antibodies, 2) involvement of antral mucosa in addition to fundal and body mucosa and 3) no association with pernicious anemia or endocrine disorders. Recently,

one study has shown that a few patients with Type B gastritis have antibodies to gastrin cells.[34] These patients do not have parietal cell or intrinsic factor antibodies and do not develop pernicious anemia.

Although patients with Type A gastritis have parietal cell antibodies, not all develop pernicious anemia (perhaps most would if followed for a long enough time period). On the other hand, almost all patients with pernicious anemia have parietal cell antibodies (80 to 90 percent) and many patients with pernicious anemia also have intrinsic factor antibodies (about 50 to 60 percent of established cases).

Genetic influences. Hereditary factors also have been implicated in the development of chronic gastritis. Several studies have reported a higher incidence of atrophic gastritis, achlorhydria, vitamin B_{12} malabsorption and parietal cell and intrinsic factor antibodies in family members of patients with pernicious anemia than in the general population.[35] The role of genetics in patients with chronic gastritis who do not have pernicious anemia has not been adequately explored.

Clinical Manifestations

As with acute gastritis, many patient with chronic gastritis and no other underlying disease are asymptomatic and have a normal physical examination. For example, it is rare for patients with pernicious anemia to have symptoms related to gastric atrophy or gastritis. In fact, in the study by Strickland and Mackay[31], only 4 of the 30 patients with Type A gastritis had symptoms. On the other hand, 26 of 40 patients with Type B gastritis had either anorexia, vomiting, epigastric pain, indigestion or a combination of these symptoms. Some studies have shown a poor correlation between the presence or absence of symptoms and histologic evidence of gastritis. Thus, a biopsy diagnosis of chronic gastritis should not be used as the sole explanation for upper gastrointestinal symptoms and other causes such as peptic ulcer disease, irritable colon or cholelithiasis should be excluded.

Other clinical findings in patients with chronic gastritis relate to abnormalities in laboratory studies. Because of gastric atrophy, rugal folds usually appear flat on the upper gastrointestinal x-ray (Fig. 15, Appendix). Gastric acid secretion usually is lower than normal in patients with either Type A or Type B Gastritis and decreased secretion of pepsin also occurs. Patients with gastritis involving the fundus and body but sparing the antrum (type A gastritis) usually have elevated serum gastrin concentrations presumably secondary to an alkaline antral pH and lack of acid inhibition of gastrin release. In some patients, serum gastrin concentrations are as high as in patients with Zollinger-Ellison syndrome as illustrated in Fig. 16 and by Case 2.

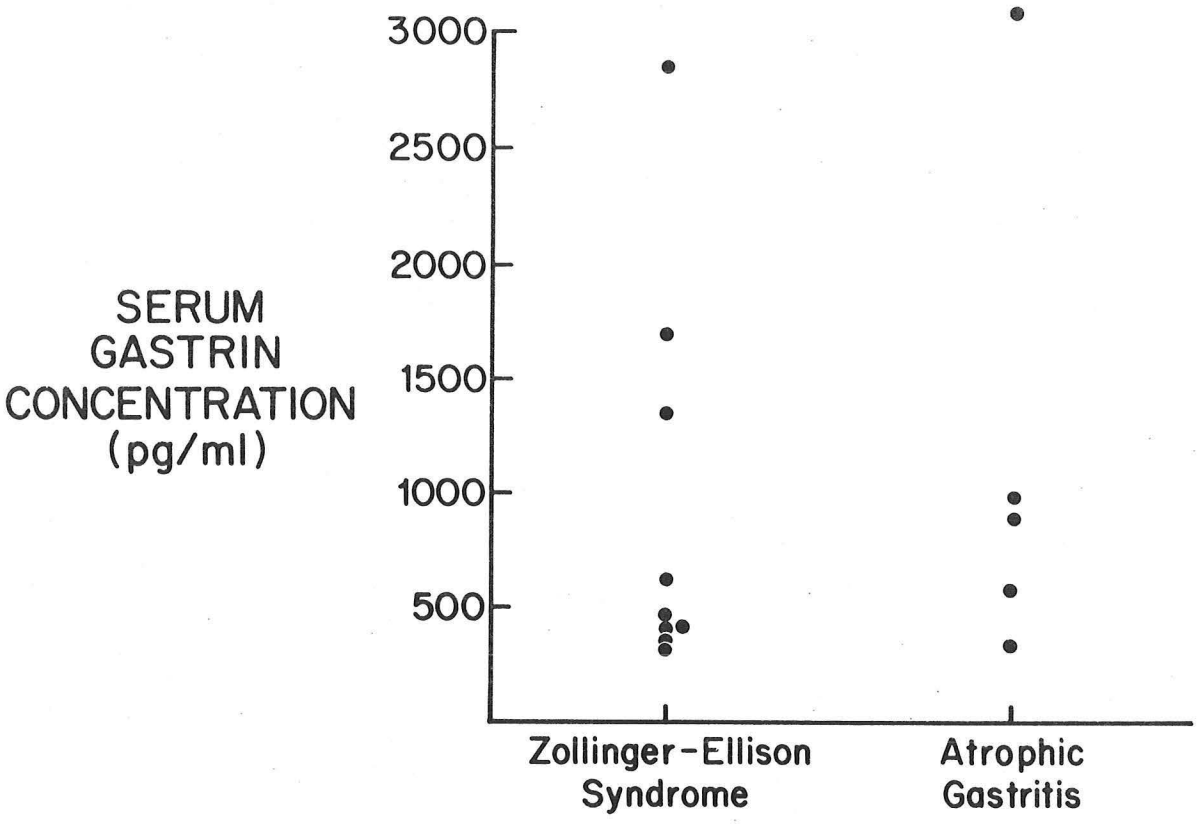

Fig. 16. Serum gastrin concentration in patients with Zollinger-Ellison syndrome or atrophic gastritis.

Case 2

A 57 year old lady was referred to Parkland Memorial Hospital for evaluation. The referring physician suspected Zollinger-Ellison syndrome because she had epigastric pain, an elevated serum gastrin concentration (480 pg/ml, nl < 200 pg/ml) and diarrhea.

At the time of her evaluation at Parkland, basal serum gastrin concentration was 393 pg/ml (performed by Dr. John Walsh in Los Angeles, Calif., nl < 100 pg/ml). Acid secretory studies were performed and basal acid output was 0 as was the peak acid output to pentagastrin. The lowest gastric pH after pentagastrin was 7.1 Thus, achlorhydria is the most likely explanation for the increased serum gastrin concentration in this patient. Irritable colon syndrome was the explanation for diarrhea and symptoms abated with Metamucil.

When gastritis involves the antrum as well as the fundus and body (Type B Gastritis), serum gastrin concentration is usually normal even though patients usually have hypochlorhydria and the pH of the antrum is usually alkaline. Normal serum gastrin concentrations presumably result from the fact that the gastrin cells are damaged by gastritis and thus, cannot generate an elevated serum gastrin concentration even though the pH of the antrum is alkaline.

In patients with pernicious anemia, the vitamin B_{12} absorption test (Schilling Test) is abnormal when performed in the absence of exogenous intrinsic factor and in untreated patients signs and symptoms of vitamin B_{12} deficiency may develop. Also, some patients with pernicious anemia have clinical and laboratory evidence of other diseases such as Hashimoto's thyroiditis, hypothyroidism, hyperthyroidism, insulin-dependent diabetes mellitus or vitiligo.

Natural History

Chronic gastritis is believed to be a longstanding disease which increases in frequency with advancing age. Studies have suggested that with time there is progression in an individual patient from superficial gastritis to chronic atrophic gastritis to gastric atrophy. In one study, patients with superficial gastritis were followed for 18 years.[36] Superficial gastritis persisted, relatively unchanged, in approximately half of the patients whereas progression to atrophic gastritis occurred in most of the remainder. In this same study normal subjects were also followed for 18 years. The mucosa remained normal in spite of advanced age in 48% of the subjects whereas 39% developed superficial gastritis and 12% developed atrophic gastritis. In another study[37] patients with atrophic gastritis were followed for 10-15 years. The disease regressed in 15%, progressed in 18% and remained unchanged in 67%. These studies suggest that superficial gastritis can progress to atrophic gastritis in some patients but that atrophic gastritis infrequently progresses to gastric atrophy.

The incidence of atrophic gastritis, achlorhydria and parietal cell antibodies is higher in family members of patients with biopsy-proven atrophic gastritis than in the general population[38,39] and data suggest that genetic rather than environmental factors are primarily responsible for this familial aggregation.[40] In addition, other diseases associated with pernicious anemia such as diabetes mellitus, vitiligo and thyroid disease also occur with increased frequency in relatives of patients with pernicious anemia.[39]

Diseases Thought to be Associated with Chronic Non-specific Gastritis

Associations have been reported between chronic gastritis and benign gastric ulcer, gastric polyps and gastric cancer. Benign gastric ulcers usually occur in an area of chronic superficial or atrophic gastritis. However, it is not known whether gastritis precedes and perhaps leads to gastric ulcer formation or whether gastritis develops in response to ulceration. Chronic gastritis also can occur in patients with Sjögren's syndrome.

In a 10 to 15 year follow-up study of 116 patients with atrophic gastritis, 9 developed gastric carcinoma and 2 developed gastric polyps.[36] On the other hand, only 1 of 93 patients with superficial gastritis and none of 168 normal subjects developed gastric cancer. In another study of 70 patients with gastritis, gastric carcinoma occurred in 4 patients.[41] These findings have been confirmed by other studies.[42-44]

Most of these studies have involved patients from countries other than the United States. Whether or not patients in this country who have atrophic gastritis or gastric atrophy are at increased risk for developing gastric carcinoma is controversial.

Treatment

Since the pathogenesis of chronic nonspecific gastritis is poorly understood, it is difficult to design therapy for symptomatic patients. A number of drugs (antacids, Oxaine M, anticholinergics) have been prescribed; however, there is no evidence that any of these agents are beneficial.

Although pernicious anemia cannot be prevented, it seems reasonable to follow patients with known gastric atrophy for development of either signs of pernicious anemia or low serum B_{12} levels. Once there is evidence of pernicious anemia, patients should receive monthly injections of vitamin B_{12}. One study has shown that steroid therapy can partially reverse the gastric mucosal changes in patients with pernicious anemia.[28] However, it is impractical and perhaps dangerous to maintain pernicious anemia patients on chronic steroid therapy.

Some investigators have suggested that patients with pernicious anemia should be evaluated for other diseases such as thyroid disease and diabetes mellitus and their relatives should be screened for pernicious anemia. Also, some have suggested that patients with known gastric atrophy and/or pernicious anemia should be screened periodically for gastric cancer. In practice, however, these screening procedures have not been rewarding.

SPECIFIC TYPES OF GASTRITIS

Giant Hypertrophic Gastritis

Several relatively uncommon clinical syndromes are characterized by gastric mucosal hypertrophy. These syndromes are usually included under the heading of giant hypertrophic gastritis although inflammatory cells are not always present. The most commonly recognized syndrome is Menetrier's disease which is characterized by gastric mucosal hypertrophy, hyposecretion of gastric acid, increased loss of protein from the stomach, edema, weight loss and occasionally pain, nausea and vomiting.[45,46] Another syndrome, hypertrophic hypersecretory gastropathy, is similar but is associated with hypersecretion of acid.[47] These syndromes are more commonly found in men than in women and

usually occur between the ages of 30 and 50 although a childhood variety has been described. In children the large rugal folds and protein loss may resolve spontaneously whereas in adults the disease is usually persistent and progressive. Gastric atrophy and parietal cell antibodies have been reported as late developments in a few patients.[48] Adenocarcinoma of the stomach has also occurred in a few patients.

Diagnosis is based on clinical findings, appearance of large rugal folds on upper gastrointestinal x-ray series (Fig. 17, Appendix) or endoscopy and histologic appearance of mucosal biopsies. Large rugal folds are usually limited to the fundus and body of the stomach although the antrum may be involved. Mucosal biopsy reveals hyperplasia of all three glandular elements - parietal, chief and mucus-secreting cells. Cystic appearing structures are found in the mucosa and the submucosa (Fig. 18, Appendix and Case 3). Because of the enlarged rugal folds, other diseases such as Zollinger-Ellison syndrome, infiltrating carcinoma, lymphoma or amyloid must be excluded.

Case 3

A 45 yr. old man was admitted to the Dallas VA Medical Center because of abdominal pain and edema of his feet and ankles. Laboratory studies were normal except for an albumin of 2.4 gms.%. Upper gastrointestinal x-ray revealed large rugal folds in the fundus, body and antrum of the stomach (Fig. 17, Appendix) and gastric biopsy was compatible with the diagnosis of Menetrier's Disease (Fig. 18, Appendix). The patient was treated with Probanthine, 15 mg. four times daily and Maalox every hour while awake. After 4 weeks symptoms abated. Repeat albumin was 3.4 gms.%.

In some patients medical therapy with anticholinergic drugs has led to reduced gastric secretion, decreased protein loss and clinical improvement.[49] It has been postulated that anticholinergic drugs decrease the width of tight cellular junctions and thus lead to decreased protein loss.[50] Cimetidine also has been reported to decrease protein loss although the mechanism is unknown.[51] One or both of these drugs should be tried prior to surgical intervention. Some patients have been treated successfully with vagotomy and pyloroplasty.[52] However, in a few patients, persistent, severe protein loss or recurrent gastrointestinal hemorrhage (Case 4) may necessitate total gastrectomy.

Case 4

A 49 yr. old man was admitted to the Dallas VA Medical Center for evaluation of upper gastrointestinal hemorrhage. Endoscopy revealed markedly enlarged gastric folds and the endoscopist thought that the patient had lymphoma. The patient continued to bleed massively in spite of medical therapy and was taken to surgery. A total gastrectomy was performed since the entire stomach appeared to be abnormal and since blood was originating from many areas of the gastric mucosal surface. Pathologic examination revealed a diagnosis of Menetrier's Disease.

Granulomatous Gastritis

Granulomas can be found in the stomach as part of generalized diseases such as tuberculosis, histoplasmosis, sarcoidosis, syphilis or Crohn's disease, or may be limited to the stomach and unassociated with other diseases.[53] Two examples of the latter are eosinophilic granuloma (a separate disease from eosinophilic gastritis)[54] and isolated (idiopathic) granulomatous gastritis.[55]

On upper gastrointestinal x-ray the involved portions of the stomach appear rigid and narrowed and the x-ray appearance is often similar to that of malignancy (Fig. 19, Appendix and Case 5). The antrum is most often involved although granulomas can be found also in the mucosa of the body and fundus. Mucosal biopsies reveal granulomas in the mucosa and submucosa, and in surgical specimens, granulomas have been found in the muscular layer and serosa, (Fig. 20, Appendix). Ulcerations can also occur. Because of the malignant appearance on x-ray, cancer must be ruled out in all patients by multiple biopsies and/or cytology.

Case 5

A 53 yr. old man was admitted to the Dallas VA Medical Center because of nausea, vomiting and abdominal pain. An upper gastrointestinal x-ray was obtained which revealed a non-distensible and narrowed gastric antrum (Fig. 19) and linitus plastica of the stomach was diagnosed on the basis of the x-ray appearance. An endoscopy was performed which also demonstrated a non-distensible antrum. Biopsies revealed granulomas in the mucosa (Fig. 20, Appendix). VDRL, skin test for tuberculosis and special stains for tuberculosis and fungi were negative. After 3 weeks symptoms had abated and after 3 mos. the upper gastrointestinal x-ray appearance was improved (the antrum was distensible although enlarged folds were present).

Because of problems with differentiating granulomatous gastritis from malignancy, most patients are diagnosed at the time of surgery. If, however, the diagnosis of granulomatous gastritis is made pre-operatively, a search should be made for a primary disease. If a primary disease, for example, tuberculosis, is found, therapy should be tailored to the specific disease. However, if an etiology can not be found and malignancy has been exluded (Case 5), the patient should be observed for several weeks since spontaneous resolution of isolated granulomatous gastritis has been reported.[56] If resolution does not occur, surgical therapy is indicated.

Eosinophilic Gastritis (Gastroenteritis)

Eosinophilic infiltration of the gastrointestinal tract can involve the stomach and/or small intestine.[57] Peripheral eosinophilia also commonly occurs. The pathogenesis is poorly understood although allergic or immunologic factors are thought to be involved. Both IgE-mediated and IgE-independent mechanisms have been implicated.[58]

Gastric involvement is limited usually to the antrum. On biopsy eosinophils infiltrate the mucosa and the muscular layer. This leads to antral rigidity and thickening of mucosal folds. Delayed gastric emptying and/or gastric outlet obstruction may occur. On x-ray it is often difficult to differentiate eosinophilic gastritis from granulomatous disease or neoplasm (Fig. 19, Appendix). Clinically, patients usually present with pain, nausea and vomiting. Occasionally, eosinophils may invade the serosa leading to ascites.

Eosinophilic gastritis is often a self-limited disease. However, in some patients symptoms persist or recur. Corticosteroid therapy has been useful in alleviating obstructive signs and symptoms as well as ascites.[57]

Gastritis Following Gastric Surgery

Gastritis is a common histologic or endoscopic finding after ulcer surgery (antrectomy or subtotal gastrectomy).[59] The pathogenesis of post-gastrectomy gastritis has not been established although the most widely accepted theory is that bile and/or pancreatic juice which reflux into the gastric remnant leads to gastritis (See p.__). Thus, gastritis after ulcer surgery is often referred to as bile reflux or alkaline gastritis. This syndrome is said to include the following: 1) signs and symptoms such as epigastric pain, heartburn, vomiting (often vomiting of bile containing material) and weight loss; 2) presence of bile in the gastric remnant; 3) endoscopic evidence of gastritis; and 4) histologic evidence of gastritis.

None of the above features, however, are specific for the diagnosis of bile reflux gastritis since all can be found in most patients after antrectomy or sub-total gastrectomy. For example, symptoms frequently occur following ulcer surgery and often occur in patients who do not have histologic or endoscopic evidence of gastritis.[60,61] Furthermore, histologic and endoscopic changes can occur in post-operative patients who are asymptomatic. Thus, symptoms, histologic findings or endoscopic changes can not be used with any degree of certainty to diagnose Bile Reflux Gastritis.

The presence of bile in the gastric remnant also does not necessarily mean that the patient has bile-induced gastritis. Bile is a common finding in the stomachs of many patients who do not have histologic or endoscopic evidence of gastritis.[63] When an antrectomy or sub-total gastrectomy is performed, the remaining stomach is anastomosed to either the duodenum (Billroth I) or jejunum (Billroth II) (Fig. 21). Because the pylorus has been removed, it is very easy for bile and other duodenal contents to reflux into the remaining stomach. Thus, bile in the gastric remnant is a non-specific finding and cannot be used to support the diagnosis of Bile Reflux Gastritis.

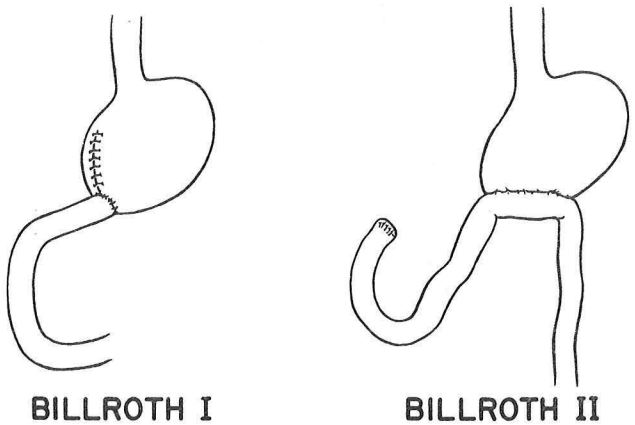

Fig. 21

Cholestyramine or aluminum hydroxide antacids have been given to patients with post-gastrectomy gastritis in hopes that the binding of bile acids by these medications will lead to improvement in gastritis. Unfortunately, these agents have been unsuccessful in improving the symptoms and the histologic appearance of gastritis in most patients.[62]

Surgical procedures have also been performed in patients who have what is thought to be bile reflux gastritis. These procedures are designed to divert the duodenal contents away from the gastric remnant and thus, improve gastritis. Just as with medical therapy (cholestyramine or aluminun hydroxide antacids), the assumption is made that reflux of bile and other duodenal contents into the stomach is the explanation for gastritis. The most commonly used procedure is called a Roux-en-Y diversion (Fig. 22). Several studies have found this procedure to be successful in relieving symptoms thought secondary to bile reflux gastritis.[63,64] However, all studies have not reported success.[65] Since it is not known whether bile reflux is the explanation for the clinical findings in patients after ulcer surgery and since diversionary surgical procedures are not uniformly successful, these procedures are usually reserved for those patients who are incapacitated by symptoms.

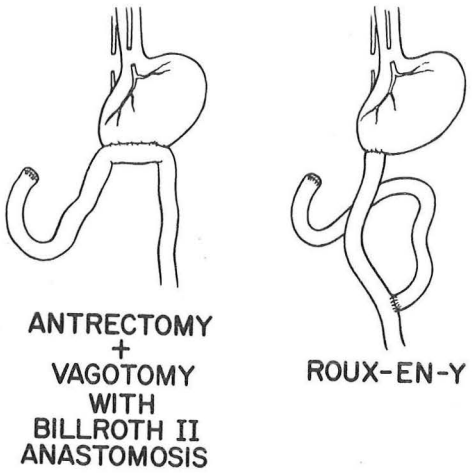

Fig. 22

BIBLIOGRAPHY

1. Owen DA: The diagnosis and significance of gastritis. From Pathology Annual:1979. Edited by SC Sommers, PP Rosen. New York, Appleton-Century Croft. 1979.

2. MacDonald WC, Rubin CE: Gastric biopsy - A critical evaluation. Gastroenterology 53:143, 1967.

3. Davenport HW: Fluid produced by the gastric mucosa during damage by acetic and salicylic acids. Gastroenterology 50:487, 1966.

4. Davenport HW: Gastric mucosal hemorrhage in dogs: Effects of acid, aspirin and alcohol. Gastroenterology 56:439, 1969.

5. Teorell T: Electrolyte diffusion in relation to the acidity regulation of the gastric juice. Gastroenterology 9:425, 1947.

6. Davenport HW: Ethanol damage to canine oxyntic glandular mucosa. Proc Soc Exp Biol Med 126:657, 1967.

7. Martin BK: Accumulation of drug anions in gastric mucosal cells. Nature 198:896, 1963.

8. Douthwaite AH: Effect of aspirin on the stomach. Lancet 2:917, 1954.

9. Weiss A, Pitman ER, Graham EC: Aspirin and gastric bleeding: gastroscopic observations with review of the literature. Amer J Med 31:266, 1961.

10. Lanza FL, Royer G, Nelson R: An endoscopic evaluation of the effects of non-steroidal anti-inflammatory drugs on the gastric mucosa. Gastrointest Endosc 21:103, 1975.

11. Lanza FL, Royer GL, Jr, Nelson RS: Endoscopic evaluation of the effects of aspirin, buffered aspirin and enteric coated aspirin on gastric and duodenal mucosa. N Engl J Med 303:136, 1980.

12. Hastings PR, Skillman JJ, Bushnell LS, et al: Antacid titration in the prevention of acute gastrointestinal bleeding. N Engl J Med 298:1041, 1978.

13. Skillman JJ, Bushnell LS, Goldman H, et al: Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Amer J Surg 117:523, 1969.

14. Ritchie WP, Jr: Pathophysiology of erosive gastritis and stress ulceration. From Gastrointestinal Hemorrhage. Edited by RG Fiddian-Green, JG Turcotte. New York, Grune and Stratton, Inc., 1980.

15. Skillman JJ, Gould SA, Chung RK, et al: The gastric mucosal barrier: clinical and experimental studies in critically ill and normal man and in the rabbit. Ann Surg 172:564, 1970.

16. Priebe HJ, Skillman JJ, Bushnell LS, et al: Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 302:426, 1980.

17. Ramsey EJ, Carey KV, Paterson WL, et al: Epidemic gastritis with hypochlorhydria. Gastroenterology 76:1449, 1979.

18. Bron BA, Deyhle P, Pelloni S, et al: Phlegmonous gastritis diagnosed by endoscopic snare biopsy. Dig Dis 22:729, 1977.

19. Davenport HW: Effect of lysolecithin, digitoxin and phospholipase A upon the dog's gastric mucosal barrier. Gastroenterology 59:505, 1970.

20. Rees W, Rhodes J: Bile reflux in gastro-esophageal disease. Clin Gastroenterol 6:179, 1977.

21. Eastwood GL: Effect of pH on bile salt injury to mouse gastric mucosa. Gastroenterology 68:1456, 1975.

22. Delany JP, Broadie TA, Robbins PL: Pyloric reflux gastritis: the offending agent. Surgery 77:764, 1975.

23. Taylor KB, Roitt IM, Doniach D, et al: Autoimmune phenomena in pernicious anemia: gastric autoantibodies. Brit Med J 2:1347, 1962.

24. Taylor KB: Inhibition of intrinsic factor by pernicious anemia sera. Lancet 2:106, 1959.

25. Inada M, Glass GJ: Effect of prolonged administration of homologous and heterologous intrinsic factor antibodies on the parietal and peptic cell masses and the secretory function of the rat gastric mucosa. Gastroenterology 69:396, 1975.

26. Tai C, McGuigan JE: Immunologic studies in pernicious anemia. Blood 34:63, 1969.

27. Rose MS, Chanarin I, Doniach D, et al: Intrinsic factor antibodies in the absence of pernicious anemia. Lancet 2:9, 1970.

28. Jeffries GH, Todd JE, Sleisenger MH: The effect of prednisone on gastric mucosal histology, gastric secretion and vitamin B_{12} absorption in patients with pernicious anemia. J Clin Invest 45:803, 1966.

29. te Velda K, Hoedemacker PJ, Anders GJPA, et al: A comparative morphological and functional study of gastritis with and without autoantibodies. Gastroenterology 51:138, 1966.

30. Fisher JM, Mackay JR, Taylor KB, et al: An immunological study of categories of gastritis. Lancet 1:176, 1967.

31. Strickland RG, Mackay IR: A reapprasial of the nature and significance of chronic atrophic gastritis. Dig Dis 18:426, 1973.

32. Doniach D, Roitt IM: An evaluation of gastric and thyroid autoimmunity in relation to hematologic disorders. Semin Hematol 1:313, 1964.

33. Sleisenger MH: Illuminating the antrum. N Engl J Med 300:1436, 1979.

34. Vandelli C, Bottazzo GF, Doniach D, et al: Autoantibodies to gastrin-producing cells in antral (Type B) chronic gastritis. N Engl J Med 300: 1406, 1979.

35. Varis K, Ihamäki T, Härkönen M, et al: Gastric morphology, function and immunology in first degree relatives of probands with pernicious anemia and controls. Scand J Gastroent 14:129, 1979.

36. Siurala M, Salmi HJ: Long-term follow-up of subjects with superficial gastritis or normal gastric mucosa. Scand J Gastroent 6:459, 1971.

37. Siurala M, Varis K, Wiljasalo M: Studies of patients with atrophic gastritis: a 10-15 year follow-up. Scand J Gastroent 1:40, 1966.

38. te Velde K, Abels J, Anders GJPA, et al: A family study of pernicious anemia by an immunologic method. J Lab Clin Med 64:177, 1964.

39. Whittingham S, Ungar B, Mackay IR, et al: The genetic factor in pernicious anemia: a family study in patients with gastritis. Lancet 1:951, 1969.

40. Ihamäki T, Kekki M, Varis K, et al: Family patterns of antro-fundal gastritis. Acta Hepatogastroenterol 23:345, 1976.

41. Walker IR, Strickland RG, Ungar B, et al: Simple atrophic gastritis and gastric carcinoma. Gut 12:906, 1971.

42. Imai J, Kubo T, Watanabe H: Chronic gastritis in Japanese with reference to high incidence of gastric carcinoma. J Natl cancer Inst 47:179, 1971.

43. Mosbech J, Videbaek A: Mortality from and risk of gastric carcinoma among patients with pernicious anemia. Brit Med J 2:390, 1950.

44. Cheli R, Santi L, Ciancamera G, et al: A clinical and statistical follow-up of atrophic gastritis. Amer J Dig Dis 18:1061, 1973.

45. Butz WC: Giant hypertrophic gastritis. Gastroenterology 39:183, 1960.

46. Maimon SN, Bartlett JP, Humphreys EM, et al: Giant hypertrophic gastritis. Gastroenterology 8:397, 1947.

47. Overholt BF, Jeffries GH: Hypertrophic, hypersecretory protein-losing gastropathy. Gastroenterology 58:80, 1970.

48. Frank BW, Kern F, Jr: Menetrier's disease, spontaneous metamorphosis of giant hypertrophy of the gastric mucosa to atrophic gastritis. Gastroenterology 53:953, 1967.

49. Smith RL, Powell DW: Prolonged treatment of Menetrier's disease with an anticholinergic drug. Gastroenterology 74:903, 1978.

50. Kelly DG, Miller LJ, Markowitz H, et al: Effect of secretagogues and inhibitors on protein leakage and tight junction width in protein-losing gastropathy. Gastroenterology 78:1193, 1980.

51. Frederiksen HJ, Olsen N, Kraj E: Cimetidine treatment of Menetrier's syndrome. Ugeskr Laeger 140:298, 1978.

52. Russell IJ, Smith J, Dozois RR, et al: Menetrier's disease: effect of medical and surgical vagotomy. Mayo Clin Proc 52:91, 1977.

53. Present D, Lindner A, Janowitz H: Granulomatous disease of the gastrointestinal tract. Ann Rev Med 17:243, 1966.

54. O'Neill T: Eosinophilic granuloma of the gastrointestinal tract. Brit J Surg 57:704, 1970.

55. Fahimi HD, Deren JJ, Gottlieb LS, et al: Isolated granulomatous gastritis: its relationship to disseminated sarcoidosis and regional enteritis. Gastroenterology 45:161, 1963.

56. Weinstock JV: Idiopathic isolated granulomatous gastritis: spontaneous resolution without surgical intervention. Dig Dis Sci 25:233, 1980.

57. Klein NC, Hargrove MD, Sleisenger MH, et al: Eosinophilic gastroenteritis. Medicine 49:299, 1970.

58. Caldwell JH, Tennenbaum JI, Bronstein HA: Serum IgE in eosinophilic gastroenteritis. Response to intestinal challenge in two cases. New Engl J Med 292:1388, 1975.

59. Meyer JH: Chronic morbidity after ulcer surgery. In Gastrointestinal Disease, Pathophysiology, Diagnosis and Management. Sleisenger MH, Fordtran JS, editors, p. 947, 1978.

60. Hoare Am, Keighley MRB, Starkey B: Measurement of bile acid in fasting gastric aspirates: an objective test for bile reflux after gastric surgery. Gut 19:166, 1978.

61. Goldner FH, Boyce HW: Relation of bile in the stomach to gastritis. Gastrointest Endosc 22:197, 1976.

62. Meshkinpour H, Elashoff J, Stewart H: Effect of cholestyramine on the symptoms of reflux gastritis. A randomized, double blind crossover study. Gastroenterology 73:441, 1977.

63. Herrington JL, Sawyers JL, Whitehead WA: Surgical management of reflux gastritis. Ann Surg 180:526, 1974.

64. Kennedy T, Green R: Roux diversion for bile reflux gastritis following gastric surgery. Brit J Surg 65:323, 1958.

65. Halpern NB, Hirshowitz BL, Moody FG: Failure to achieve success with remedial gastric surgery. Amer J Surg 124:108, 1973.

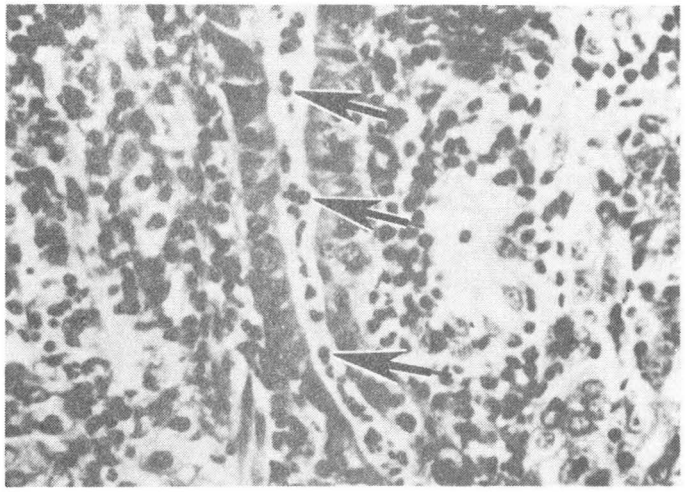

Fig. 5. Histologic picture of Acute Gastritis demonstrating inflammatory cells in the lamina propria and a gland abscess (arrows).

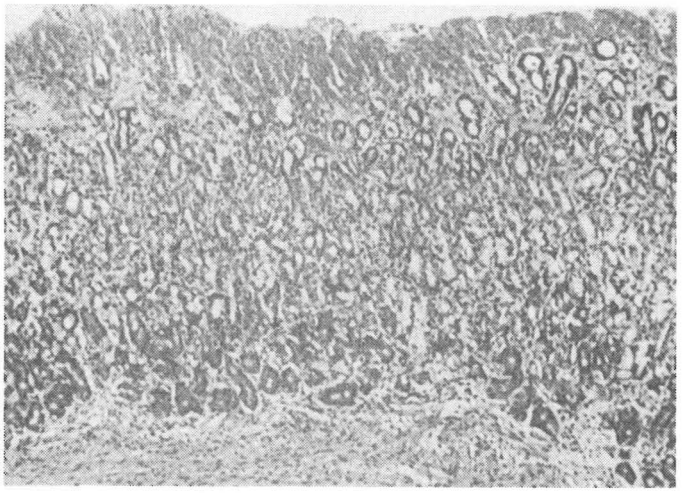

Fig. 6. Acute Hemorrhagic Gastritis (Erosive Gastritis). The surface epithelium is denuded and the mucosa is congested with inflammatory cells.

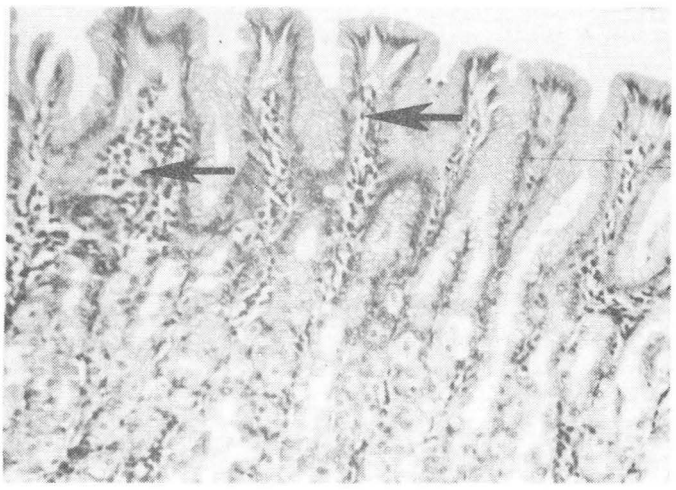

Fig. 7. Chronic Superficial Gastritis. Inflammatory cells are limited to the superficial epithelium and the lamina propria of the gastric pits (arrows).

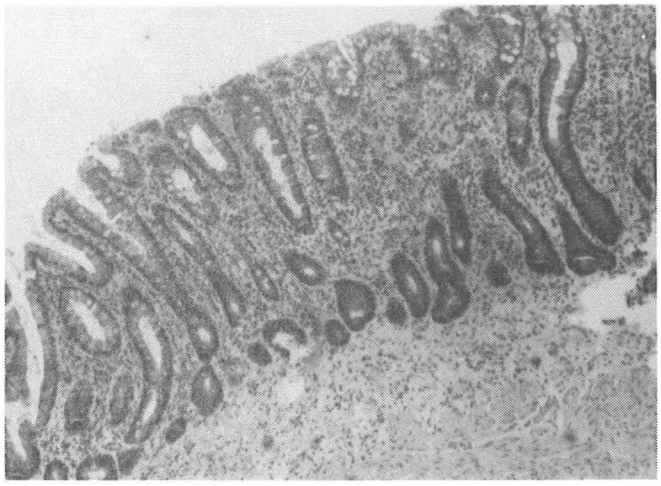

Fig. 8. Chronic Atrophic Gastritis. Inflammatory infiltrate involves both the pit and glandular areas. Glandular tissue is greatly reduced and glands become simplified and are transformed from complex to simple tubular glands. There is loss of parietal and chief cells.

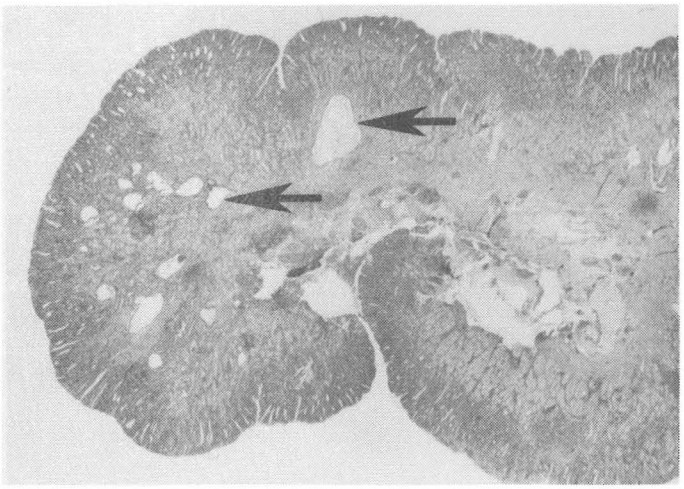

Fig. 18. Giant Hypertrophic Gastritis (Case 3). Note the cystic areas (arrows) that are present in the mucosa and submucosa. Although it can not be seen at this magnification, there is increased numbers of parietal, chief and mucus-secreting cells.

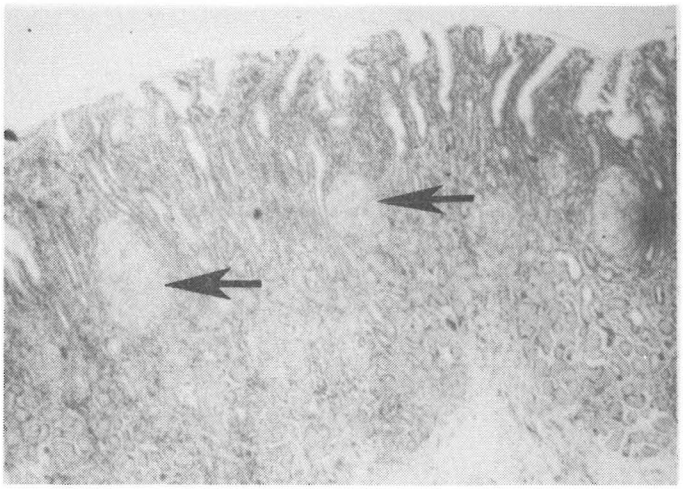

Fig. 20. Granulomatous Gastritis. Note granulomas (arrows) in the mucosa.

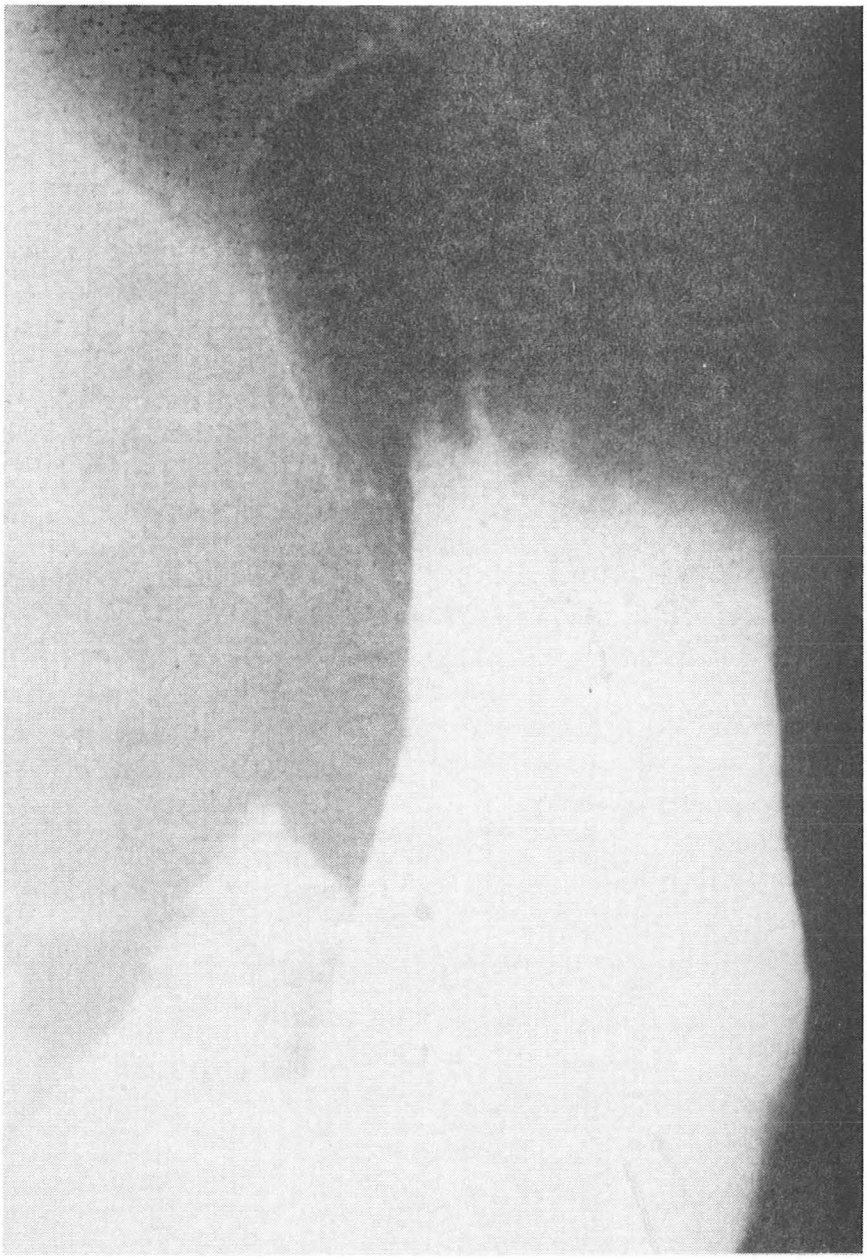

Fig. 15. X-ray showning absent rugal folds in fundus and body of stomach. Patient has atrophic gastritis.

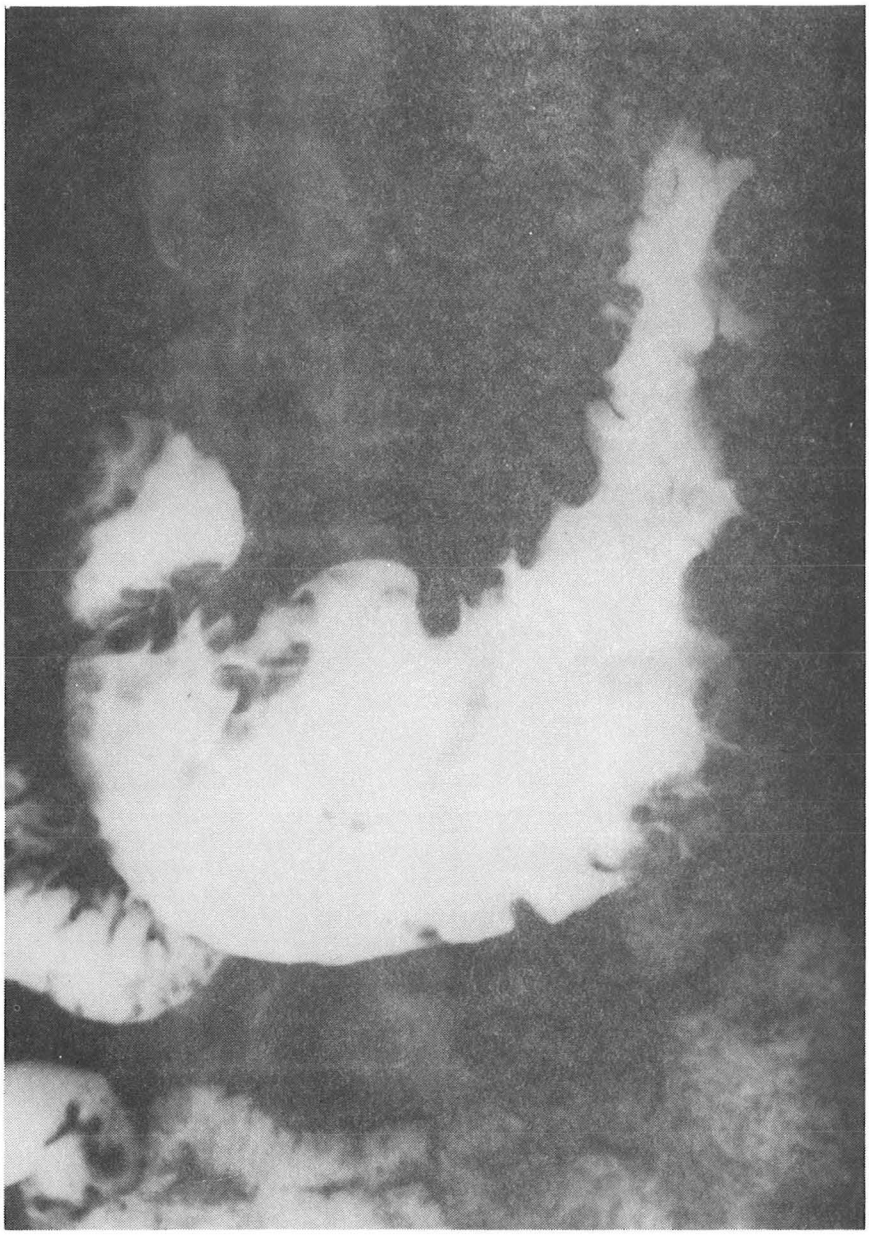

Fig. 17. X-ray of patient (Case 3) with giant hypertrophic gastritis (Menetrier's Disease). Note the large rugal folds in fundus and body. Large folds are also present in the antrum in this patient although in most patients the antrum is spared.

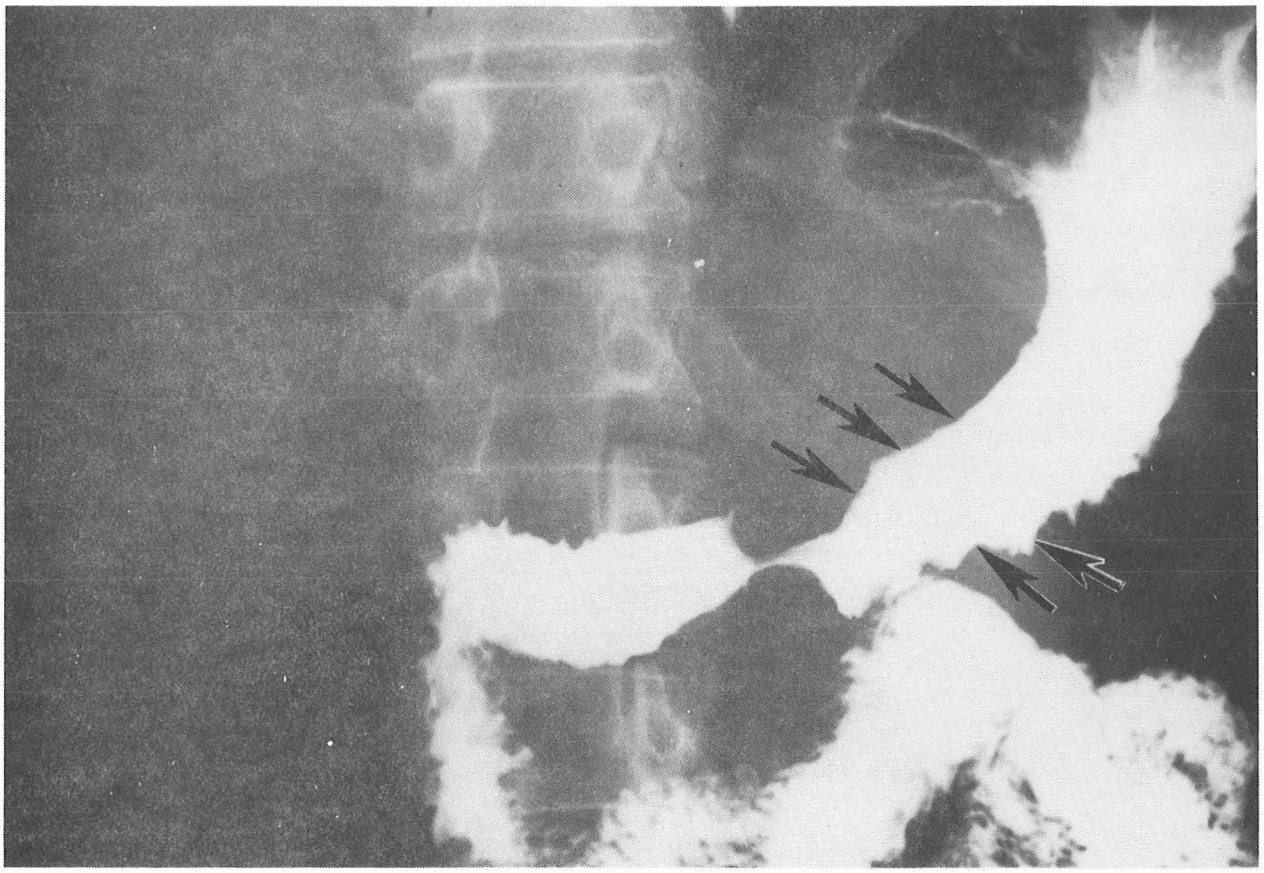

Fig. 19. X-ray of patient with Idiopathic Granulomatous Gastritis (Case 5). Note the narrowed nondistensible antrum (arrows) and large gastric folds. In a patient with this x-ray appearance, infiltrating carcinoma must be considered. A similar x-ray picture can also be found in patients with eosinophilic gastritis.