

Gastritis: Terminology, Etiology, and Clinicopathological Correlations:

Another Biased View

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The histological approach to gastritis, especially the chronic forms, has undergone a series of re-evaluations by different experts over the past decade, mainly because of the recognition of individual disease patterns that have specific clinical and epidemiological implications. The most spectacular of these was the discovery of *Helicobacter pylori* and its common gastritis, its relation to almost all duodenal peptic ulcers and to most gastric peptic ulcers, its potential as a precursor of first multifocal atrophic gastritis and later tubule-forming gastric carcinomas, and its status as a cause of gastric mucosal lymphomas. During this same decade other classes of gastric reaction and inflammations have been recognized, including chemical injury and lymphocytic gastritis. Also in the same decade the importance of non-steroidal anti-inflammatory drugs (NSAIDs) has emerged as a cause of gastric mucosal injuries. To add emphasis to all these discoveries, biopsies are being performed on stomachs in almost epidemic numbers and each biopsy specimen has the potential of having the features of one or more of these injuries as well as injuries that have yet to be described. To cope with this rapidly expanding gastric inflammatory informational extravaganza, pathologists need some way of dealing with the various entities comfortably and some method of cataloging them in ways that are understandable both to them and to the endoscopists with whom they work. However, if emerging data about the chronic gastritides are correct, it is conceivable that the need to diagnose them, from a strictly clinical standpoint, is limited. Either we may know what is in the biopsy specimen before we see it or what we see may not be important, although it may be intellectually challenging. HUM PATHOL 25:1006-1019. Copyright © 1994 by W.B. Saunders Company

"Gastritis" should not be a nasty word, yet it has become one. It is a word that often seems mysterious, a word with too many conflicting meanings, each of which is dependent on who defines it. For the patient gastritis conjures up images of acute epigastric peptic ulcer-type pain, sometimes accompanied by nausea and vomiting, perhaps after an episode of overindulgence with food and drink. Other patients' gastritis accounts for their constant low grade upper abdominal gnawing pain that only temporarily goes away with over-the-counter antacids and then comes back. There is endoscopic gastritis, the erythematous, edematous, friable, slightly eroded mucosa found in stomachs of patients who have the symptoms referred to above and, peculiarly, also in the stomachs of those who are asymptomatic. Finally, for the pathologist gastritis is an annoying collection of pits, glands, acute and chronic forms of inflammation, metaplasias, and bacteria, and

these, in any combination or in no combination at all, may or may not have anything to do with the gastritis of the patient and the gastritis of the endoscopist.¹⁻⁶ To be perfectly frank the correlation between histological and endoscopic gastritis is terrible! When the endoscopist sees spectacular inflammatory changes, even with erosions, a biopsy specimen of such an area, even of an erosion, is almost as likely to be normal as inflamed.^{2,4} Whatever it is that the endoscopists see often has no histological counterpart. Furthermore, a biopsy specimen from an endoscopically normal antrum may be intensely and actively inflamed. In contrast, the endoscopic histological correlation for lumps, masses, or big ulcers is very good. No wonder there have been a bewildering number of classifications of gastritis, some of which attempt to relate endoscopic and histological alterations as well as others that make no pretense at correlation. Some classifications are named after people, such as Whitehead, whereas others are named after cities, such as Sidney.^{7,8} Some use letters to designate types of gastritis, giving us types A, B, AB, and C to play with, whereas others skip letters and use words instead.^{9,10} It is also no wonder that any clinical classification of gastritis is likely to be of little value, considering the lack of correlation between symptoms, endoscopic findings, and histological features.

Nevertheless, we pathologists must contend with gastric inflammatory disease, much as we must deal with inflammations of the esophagus and colon. Our clinical colleagues continue to perform biopsies on stomachs, hoping that we will offer them some help with their patients who have unpleasant upper gut symptoms or striking endoscopic findings. To begin, we have to demystify the word gastritis. This is best accomplished by developing a classification system that is simple and easily applicable to the types of inflammations that we see regularly in our gastric biopsy specimens. In the past 6 years several classifications for gastritis have appeared in independent articles, chapters in books, and gastrointestinal pathology texts (Table 1). All of them include the common gastritides, although the names vary.⁹⁻¹⁴ Furthermore, much of the descriptive work in histological gastritis is still being published and, in addition, it is critical that a classification scheme recognize that there are inflammations that do not fit into predetermined categories; in other words, there are gastritides that have not yet been named. Therefore, any classification system must allow for periodic revisions. Such a system also should recognize that more than one type of gastritis will occasionally occur in stomachs, so that there may be double or triple gastritides.

We have known for years that there are acute gastric injuries and inflammations that include small super-

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TABLE 1. Recent Classifications of Most of the Common Chronic Gastritides

Correa ⁹ 1988	Owen ¹³ 1989	Yardley ¹⁴ 1990	Dixon ¹⁰ 1990	Goldman ¹¹ 1992	Lewin et al ¹² 1992
Diffuse antral gastritis	Chronic nonspecific gastritis, type B	H pylori gastritis	Type B gastritis	Chronic antral gastritis	Nonerosive, nonspecific gastritis, H pylori-associated gastritis subtype
Multifocal environmental gastritis	Chronic nonspecific gastritis, type B	Metaplastic atrophic gastritis, type B [environmental]	No specific category	Chronic antral gastritis	Nonerosive, nonspecific gastritis, no specific subtype
Diffuse corporal [autoimmune] gastritis	Chronic nonspecific gastritis, type A	Metaplastic atrophic gastritis, type A [autoimmune]	Type A chronic gastritis	Chronic fundic gastritis	Nonerosive, nonspecific gastritis, severe atrophic fundic gland gastritis subtype
Lymphocytic gastritis	No specific category	Lymphocytic gastritis	Lymphocytic gastritis	Lymphocytic gastritis [a type of chronic erosive gastritis]	Lymphocytic gastritis
Postgastrectomy gastritis	No specific category	Chemical gastritis	Type C gastritis	No specific category	Alkaline reflux gastritis

ficial ulcers, or erosions, with no plasma cells, scars, or granulation tissue to indicate chronicity. Sometimes, these injuries lead to extensive superficial mucosal necrosis accompanied by hemorrhage. These reactions are the acute types of gastritis, and they have been given names like "acute erosive gastritis" or "acute hemorrhagic gastritis." Precipitating injuries include alcohol, steroids, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Such acute processes have not been part of the gastritis mystery unless they were superimposed on a chronic inflammation. These will be discussed in more detail below.

It is the variety of inflammations with overtones of chronicity that is the problem. In the past it was assumed that chronic gastritis was a single disease with a collection of histological characteristics that were present in various combinations. Different forms of chronic gastritis differed only in the intensities of these histological characteristics and in their mix.⁷ Furthermore, the stomach was looked on as a single organ; yet we know that there are several distinctive mucosae, as different from each other as the mucosa of the small intestine differs from that of the colon. This approach was aided by the fact that no studies identified a precursor lesion and systematically followed it with sequential biopsies through intermediate stages to the full-blown end-stage chronic gastritis. As a matter of fact, this giant hole in our knowledge and understanding persists because we still have no proof of how each chronic gastritis evolves and what the precursor or precursors are. A frequent suggestion implicates a ubiquitous mild inflammation known simply as "superficial gastritis" as the common precursor, but there is no proven support for that contention, only some questionable evidence based on population studies.^{7,11,13} However, this should not deter us. We also have no idea of the histological evolution of most other chronic inflammations of the gut, including ulcerative colitis, collagenous colitis, and Crohn's disease. Recent discoveries, aided by the intense use of upper endoscopy and the frequent biopsy specimens obtained by our endoscopic colleagues, have given us insights into the intricacies of the chronic gastritides. We now recognize that several separate chronic entities

exist, although new discoveries seem to relate some of them. Unfortunately, the more we know about the chronic gastritides, the more names we invent for the same diseases. The practicing pathologist must choose which names he or she will use routinely, and that pathologist must ensure that the endoscopists understand what the names mean. It is silly to adopt a nomenclature that has no meaning for the very people on whose business we depend for our livelihood! The following discussion is based on a simple, functional classification of gastritis, concentrating mostly on the chronic forms, that has proven useful in a busy endoscopic biopsy practice in a large teaching hospital (Table 2). It incorporates many attributes of other classifications, hopefully the best ones, and thus is not a fanciful invention of the author. In fact, it is really a simplified version of the classifications proposed by Correa and Yardley.^{9,14} It affirms the existence of several distinct entities, but it offers several choices of names for most entities, recognizing that dif-

TABLE 2. A Simplified Classification of Gastritis for 1994

Acute	Erosive, hemorrhagic: some of these are not inflammations but simply hemorrhages
Chronic	<i>Helicobacter pylori</i> type (1,000 synonyms, including chronic active, chronic nonspecific, diffuse antral)
Atrophic	Type A, autoimmune, diffuse body, diffuse corporal Type B, non-autoimmune, multifocal, environmental
	Lymphocytic, sprue-like, Menetrier-like
	Focal and miscellaneous, diagnostic and nondiagnostic
	Crohn's disease of the stomach
	Granulomatous, not Crohn's
	Allergic
	Specific infectious for which agents have been identified
	Miscellaneous, including pimples: those gastritides that do not fit into the other categories. The number of these is in direct proportion to the number of gastric biopsy specimens.
	Chemical gastropathies: those induced by bile-reflux, NSAIDs, and other direct surface-damaging agents.

NOTE. The entities are important; the names are negotiable.

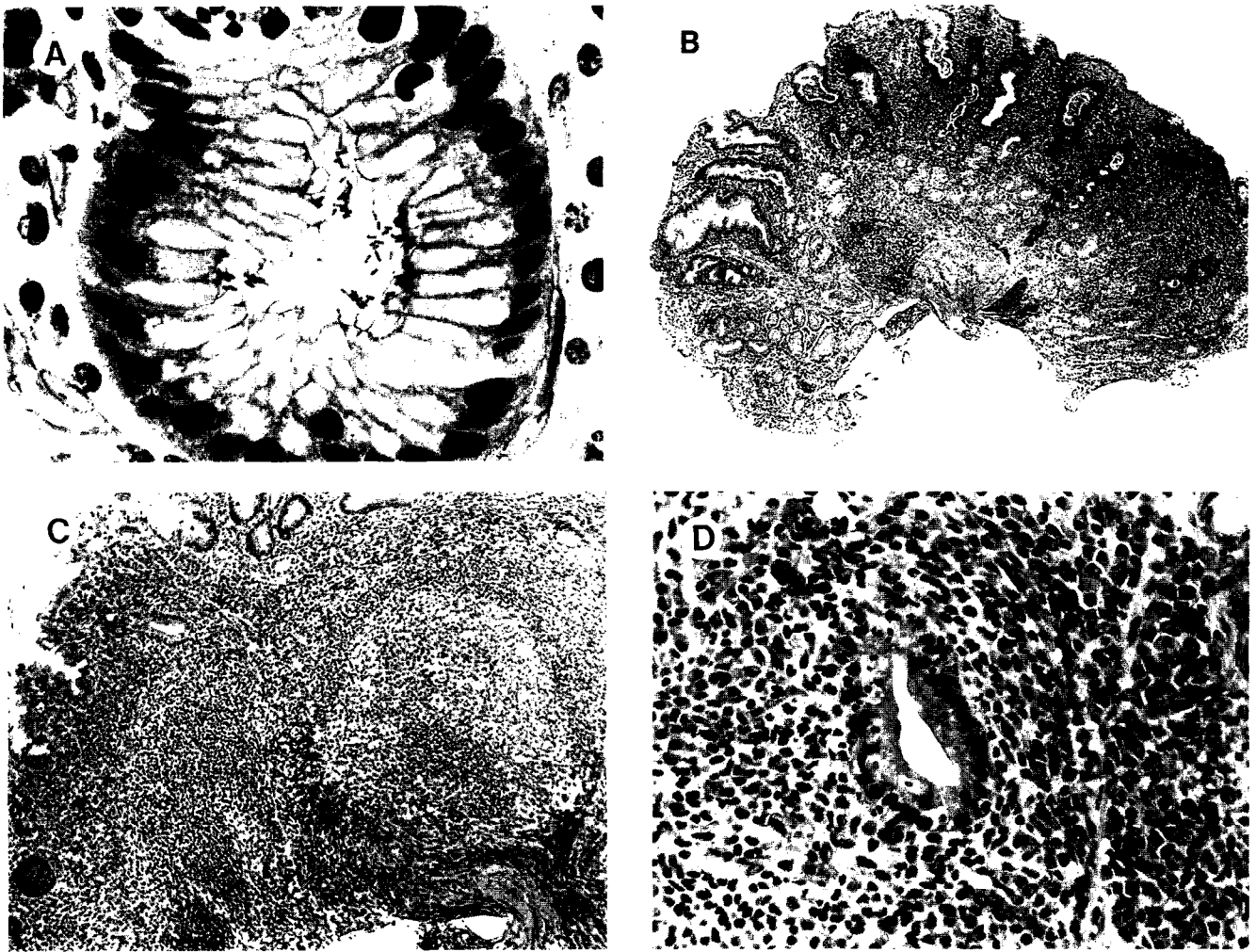


FIGURE 1. *Helicobacter pylori* and its gastritis. (A) The organisms are the slightly curved rods clustered close to the epithelium in this superficial pit. (Warthin-Starry; original magnification $\times 825$.) (B) The typical low power appearance of the active and chronic antral gastritis of *H pylori*. The mucosa appears dark because of an infiltrate of plasma cells in the superficial and mid lamina propria that spread apart the tubules. There is a small crushed lymphoid nodule at the base. The pits are elongated and tortuous. (HE; original magnification $\times 53$.) (C) Prominent lymphoid hyperplasia is an integral part of this gastritis. (HE; original magnification $\times 83$.) (D) The mid mucosa of intense *H pylori* gastritis has dense plasmacytosis. The tubule with neutrophils migrating through its epithelium is a neck. (HE; original magnification $\times 330$.)

ferent names are used by different pathologists, all of whom are capable and accomplished. This classification system can be used easily when more than one type of gastritis occurs in a single stomach, each of which may have an independent cause or epidemiological association. The following discussion analyzes each item, not necessarily in its order in the Table but in order of its importance in the evolution of the classification system.

HELICOBACTER PYLORI AND ITS GASTRITIS

For decades chronic gastritis was more of a pain in the neck than in the stomach. Then approximately 10 years ago Marshall and Warren gave us the great gastritis gift, their discovery that one type of chronic gastritis was an infectious disease, and the responsible organism was a bacillus that now goes by the name of *Helicobacter pylori* (Fig 1A).^{15,16} In fact, Dr Marshall even infected himself with *H pylori* and developed an acute

gastritis that began approximately a week after ingestion.¹⁷ At this time we are in the midst of an information explosion about *H pylori* and its epidemiological, histological, genetic, and cancer-associated aspects. There are studies of prevalence in different populations and in different diseases, some using histological diagnosis as proof of infection, whereas others use serum antibodies as evidence of prior exposure. Whole books have been dedicated to the organism and its praises have been sung during week-long symposia. Obviously, the information presented here must be an abbreviated version of what is known. However, even this shortened version of the *H pylori* story must by necessity dominate this entire article because of the importance of the organism.

Briefly, *H pylori* is a worldwide pathogen that has different infection rates in different populations, the greatest rates occurring in developing countries where infection usually occurs in childhood.¹⁸ In developed countries the infection rate increases with age, is more

common in lower socioeconomic populations, and is greater in men than in women. Thus, there is a huge population of asymptomatic infected individuals who not only have the infection but also have its associated gastritis.¹⁹ Recent studies have cast doubt on adult acquisition of the infection and suggest that now in Western societies *H pylori* is usually an infection acquired in childhood and that it is decreasing in frequency.²⁰

It was well known that duodenal peptic ulcers were almost always accompanied by a significant chronic gastritis that involved the antral mucosa.^{21,22} Furthermore, this gastritis was characterized by three components: (1) diffuse plasmacytosis of the superficial mucosa, (2) lymphoid nodules deep in the mucosa, and (3) neutrophils invading the proliferative zone of the mucosa, the neck region (Figs 1B to 1D).^{21,22} In addition, pit hyperplasia in which the pits were longer than normal and often mucin-depleted was common. This complex was called "hypersecretory gastritis" by Correa.²¹ It also involved the body mucosa, especially if the ulcers were in the stomach instead of the duodenum. In such cases the gastritis occurred proximally to the ulcer as well as in the antrum so that the more proximal the ulcer, the more extensive the gastritis.^{7,21} It even can involve the cardia that has a mucosa much like antral. Subsequently, this gastritis has been given several different names, including "diffuse antral gastritis," "type B chronic gastritis," "chronic active gastritis," and "chronic nonspecific gastritis."^{9,13,14}

The organisms are found on the surface epithelial cells and less commonly on the superficial foveolar cells. In both locations they lie beneath the mucous coat, mostly over intercellular junctions. They appear as slightly curved short rods. Ultrastructurally they have four flagella at one pole. In almost all cases the organisms are visible with hematoxylin-eosin (HE). The Giemsa stain will darken them and silver stains, such as the Warthin-Starry, will both darken and thicken them (Fig 1). A tissue Gram stain also will make them more obvious. If all else fails there are commercially available antibodies for immunohistochemical detection. How fastidious a pathologist should be in looking for *H pylori* is a matter of individual choice. Our approach has been to use HE only because it has been our experience that a careful search of the HE-stained slide will detect bacteria in almost every case; special stains add little, perhaps increasing the yield by no more than 1%. If the gastritis is totally typical and if we cannot find the bacteria, then we use the Warthin-Starry stain. This situation occurs less than once a month, and we resort to the special stain mostly out of frustration at not finding the bugs in the expected setting. Usually, the Warthin-Starry stain is also negative in these cases. In contrast, some studies have reported a significant infection rate in patients with normal antral biopsy specimens using the special stains or culture or both.²³ We have no idea what it means to have *H pylori* with no disease, but perhaps it indicates first infection or a nonpathogenic strain. In addition, pressures from outside the pathology department may dictate the intensity with which we look for *H pylori*. The gastroenterologists with whom we work may feel it is important for them to know whether *H pylori* is present or absent in every gastric biopsy speci-

men, and in such cases some pathologists have resorted to performing either Giemsa or Warthin-Starry stains routinely on every gastric biopsy specimen.

The lymphoid nodules and the plasma cells are probably the result of chronic antigenic stimulation by the organisms. Genta et al²⁴ found that all individuals with *H pylori* infection, with or without gastric or duodenal ulcers, had lymphoid nodules that were more common in the antrum than in the body, on the lesser rather than the greater curvature, and in ulcer patients rather than in those without ulcers. Treatment of the *H pylori* infection resulted in gradual shrinkage of the nodules. It has been our experience that the density of the plasma cells also diminishes and there is gradual loss of those plasma cells deep in the mucosa.²⁵

The neutrophils generally invade epithelium that is mid-zone in the mucosa, at the level of the necks, whereas the infection is colonizing the surface and superficial pits. This fact is repeatedly illustrated in essentially every publication in which there is a microscopic picture. The epithelium covered by the organisms is never inflamed, whereas inflamed epithelium is never covered by organisms. This discrepancy in location between bacteria and neutrophils has not been adequately explained. Soluble chemotactic factors, either released by the bacteria or by their interactions with host tissues, have been suspected. In patients infected with *H pylori* tumor necrosis factor [TNF]-alpha production by antral mucosa was higher when there was active gastritis than when the gastritis was inactive.²⁶ Tumor necrosis factor-alpha can activate neutrophils. Other neutrophilic chemotactic factors have been identified that appear to come from the bacterium itself.^{27,28}

There are modifications of the typical changes. For instance, the plasmacytosis may be accompanied by lymphocytosis and even by eosinophils, although when they are present the possibility of a second insult might be considered. The infiltrate in the lamina propria also commonly extends into the glandular compartment for unpredictable distances, sometimes reaching the muscularis mucosae. Perhaps this deep extension is an index of severity. The combination of a deeply extending or transmucosal infiltrate plus deep lymphoid nodules results in a histological lesion in which the glands are either spread apart or else are destroyed by the inflammation; in other words, there is loss of glands or atrophy. Unfortunately, we do not know which of these is the correct interpretation. If this is indeed destruction of glands then we should have identified a gland-destructive phase of the inflammation, yet such a phase has not been found. The active epithelial damage with neutrophils involves the necks. Because this is the generative zone of the gastric mucosa from which both pits and glands arise, it is possible that damage to this zone results in selective loss of regenerative capabilities for the glandular compartment. If such is the case then gland loss may be attributed to attrition without replacement.

Helicobacter infection also has been reported to be associated with damage to the colonized surface and foveolar epithelial cells in patients with both duodenal and gastric peptic ulcers or with the typical active chronic gastritis without ulcers.^{29,30} These changes in-

clude irregularities of the apical cytoplasm with indistinct cell borders and loss of apical mucin in almost all cases. Collections of such cells with loss of apical cytoplasm produce surface mucosal depressions or pits. How such changes relate to the ulcers is not clear because many of the ulcers are in the duodenum.

The evolution of the typical chronic and active diffuse antral gastritis that results from *H pylori* infection is not known. As with other forms of chronic gastritis, a superficial inflammatory phase has been postulated in which the superficial mucosa, that part including the pits and necks and surrounding lamina propria but not the glands, contains excess plasma cells and/or lymphocytes. Supposedly, this reaction extends deeper into the mucosa and at some point the lymphoid nodules develop, but this theory has no proof. The acute infection, such as the one Marshall gave himself, may evolve into the typical chronic gastritis if the bacteria are not eradicated or cleared.³¹

Helicobacter pylori is a strange gastroenteric organism. It does not like stagnant stomachs, but it seems to prefer those stomachs in which there is normal motility. In a study of gastroparesis, that is, stomachs with slow emptying, *H pylori* was rarely found compared with stomachs that emptied normally.³² It does not seem to thrive in less acidic environments, such as in bile reflux. In one study 83% of patients with peptic ulcers had *H pylori* before gastric operations, mostly partial gastrectomies. After the operations that led to bile reflux the infection rate decreased to 54%, but after Roux-en-Y biliary diversion that prevented bile reflux the infection rate increased to 92%.³³

Is *H pylori* infection and its resultant gastritis a cause of symptoms, such as nonulcer dyspepsia? The data are conflicting. In one study published before much was known about *H pylori*, active inflammation, that is, neutrophils, in biopsy specimens of either gastric body, antrum, or duodenum was more likely to be found in dyspeptic compared with nondyspeptic patients.⁶ In another study published after *H pylori* was a well-known pathogen, nonulcer dyspepsia, whether associated with *H pylori* gastritis or with no histological inflammation and no bacteria, responded equally to a regimen directed at eradication of the organism.²⁵ In still a third study of patients with nonulcer dyspepsia who were infected with *H pylori*, specific treatment directed against the organism eradicated it and improved the associated gastritis but was not significantly better than placebo in improving symptoms.³⁴

Helicobacter pylori colonizes metaplastic gastric surface cells in the duodenum, and this may be important if it is a cause of duodenal peptic ulcer.³⁵ However, the exact mechanism by which *H pylori* infection leads to duodenal ulcers is not established. Nevertheless, the association is clear. Close to 100% of patients with duodenal peptic ulcers have *H pylori* and its gastritis in the antrum. Eradication of the organism dramatically reduces ulcer recurrence. Why only a tiny fraction of individuals with this incredibly common infection develop peptic ulcers is not known, but perhaps it is related to specific strains of the organism.³⁶

Helicobacter pylori also colonizes gastric type surface epithelial cells almost anywhere else. Infection has been

reported in Barrett's mucosa and in ectopic gastric mucosa in Meckel's diverticula and in the rectum.³⁷⁻⁴¹ When Barrett's epithelium is infected the gastric mucosa is always infected as well, suggesting that the Barrett's epithelium became colonized as a result of reflux. The status of the gastric mucosa in the Meckel's cases was not known, but in a report of *H pylori* in ectopic gastric mucosa in the rectum the stomach also was infected.³⁸

The role of *H pylori* in atrophic gastritis and intestinal metaplasia has been studied in several diverse environments. Data are accumulating rapidly regarding the associations of *H pylori* with carcinoma of the stomach.³⁶ It has been shown that the risk of gastric carcinoma is increased in populations with high infection prevalences, and this relationship is almost linear.⁴² This may explain, at least in part, the high incidence of gastric cancer in Japan where *H pylori* infection seems to be unusually common in older adults. Scores of published studies are appearing monthly linking *H pylori* with gastric cancer, and possibly with certain histological types, but this may depend on the country in which the cancers were studied. For instance, in a study from Japan culture-proven *H pylori* infection occurred in 79% of patients with differentiated, or tubule-forming, early gastric carcinomas but only in 29% of patients with undifferentiated, including signet ring cell, early carcinomas.⁴³ In another study from the United States *H pylori* was found in nonmalignant gastric mucosa in 89% of patients with tubule-forming carcinomas but in only 32% of patients with diffuse carcinomas.⁴⁴ Furthermore, it appears that *H pylori* is associated with noncardiac carcinomas rather than with those that arise in the cardia.⁴⁵ In contrast, in a study from Singapore there was no difference in the rates of histological *H pylori* infection between patients with tubule-forming and diffuse carcinomas.⁴⁶ Similar results were reported from Finland where there was no difference in frequency of antibodies to *H pylori* and in *H pylori*-associated gastritis in patients with both patterns of gastric carcinoma.⁴⁷ As of the time of publication of this article, it is safe to say that the exact role of *H pylori* in causing gastric carcinoma is still not settled. Presumably it is through its relation with multifocal atrophic gastritis that *H pylori* and gastric cancer also are related. This is discussed in more detail in the discussion of multifocal atrophic gastritis.

Chronic *H pylori* infection with its induction of gastric lymphoid tissue has been implicated as a precursor of gastric lymphoma of the unique B-cell type that arises from mucosa-associated lymphoid tissue (MALT).⁴⁸ In fact there have been attempts to treat some cases of the low grade variant with anti-*H pylori* regimens, and there has been some success, at least for the limited follow-up period.⁴⁹ Nevertheless, the possibility of treating a malignancy with antibiotics is exciting but also unsettling!

Helicobacter pylori and NSAIDs may interact or potentiate each other's injury, although the published data are not in total agreement. For instance, among nonulcer patients taking NSAIDs who developed endoscopic mucosal damage, *H pylori* infection was much more common than among those who had normal en-

endoscopic findings.⁵⁰ Furthermore, the more severe the endoscopic gastropathy, the more likely there was to be *H pylori* infection. This study suggested that *H pylori* may put NSAIDs users at risk for endoscopic gastropathy. On the other hand, another study found that *H pylori* infection in patients with rheumatoid arthritis taking NSAIDs was only approximately 60% as common as in patients not taking the drugs, suggesting that NSAIDs may protect against *H pylori*.⁵¹

Bile reflux may have some effect in eradicating *H pylori*.⁵² In one study patients with peptic ulcer disease treated with antrectomy, all of whom had *H pylori* infection initially, had more persistent infection if the antrectomy was accompanied by an antibile reflux procedure than by a proreflux procedure. The association between *H pylori*, atrophic gastritis, intestinal metaplasia, and gastric cancer will be discussed later.

Helicobacter pylori is not the only cause of chronic active gastritis. There are biopsy specimens that we encounter from time to time that have all the characteristics of *H pylori* infection, yet have no *Helicobacter*, and no *H pylori* are found by culture or by ancillary tests. There is one other organism that is capable of causing a gastritis resembling *H pylori* gastritis. It is a tightly spiraled bacteria that has been given the name of *Gastrospirillum hominis*.^{53,54} This is a spirochete that has yet to be cultured. It seems to be transmitted from household pets, dogs and cats, and it is a rare human pathogen. In one monumental study the investigators examined more than 15,000 antral biopsy specimens and found only 39 cases of *Gastrospirillum* infection. Two other smaller studies have found these bacteria in roughly the same frequency, with six cases in 1,650 patients in the first study and two cases in approximately 700 patients in the second study.⁵⁴ The inflammation induced by this bacterium is similar to that induced by *Helicobacter*, but the plasmacytosis, activity, and lymphoid hyperplasia all tend to be less intense.

AUTOIMMUNE CHRONIC ATROPHIC GASTRITIS

We have known for years that pernicious anemia, a megaloblastic anemia caused by vitamin B-12 deficiency, is accompanied by a gastritis characterized by total or near total loss of oxyntic mucosa and replacement of that mucosa by elongated pits and metaplastic changes in the pits and in the remaining glands (Fig 2A). The metaplasias include several types of intestinal metaplasia with goblet cells either scattered among altered gastric-type surface epithelium, incomplete intestinal metaplasia, or mixed with other small intestinal cells, including absorptive cells and endocrine cells, complete intestinal metaplasia. Furthermore, another common metaplasia occurs in which the body-type glands are replaced by glands that resemble antropyloric or cardiac glands, the glands in the junctional type of Barrett's mucosa, and the metaplastic pyloric-type glands that occur in the small bowel in segments of Crohn's disease. These epithelial changes often are accompanied by inflammatory changes that include plasmacytosis and lymphocytosis in the lamina propria and

scattered deep lymphoid nodules. This complex involves the body mucosa diffusely but spares the antral mucosa, and many cases also have autoantibodies, particularly those against parietal cells and intrinsic factor. The names "autoimmune gastritis" and "autoimmune chronic atrophic gastritis" clearly are appropriate for this combination. It also goes by the name of "type A chronic atrophic gastritis" and "diffuse corpus gastritis."^{9,14} This disease is most common in Scandinavia and Northern Europe.

How this gastritis evolves is not known, but there is some suggestion from a Swedish study that early in its evolution the lymphocytic and plasma cell inflammation is mostly in the deep mucosa rather than the superficial mucosa.⁵⁵ Possibly progression of this deep inflammation leads to destruction or atrophy of the glands. In contrast, other investigators have implicated an early phase of superficial inflammation.⁹ Presumably deeper extension of this inflammation leads to loss of body glands. We have no idea why the metaplasias occur.

Patients with autoimmune chronic atrophic gastritis obviously produce no acid and no intrinsic factor, both of which are manufactured by parietal cells. They also have very little *H pylori* gastritis, suggesting that the organisms prefer an acid environment, although they attempt to buffer themselves from that same acid.^{56,57}

This type of diffuse body atrophic gastritis also occurs without the pernicious anemia and without autoantibodies. It is not clear if the anemia- and autoantibody-negative diffuse body gastritis is truly the same as the pernicious anemia-associated type or if it is an unusually diffuse form of the multifocal or type B atrophic gastritis that is discussed next.

Because this type of gastritis results in total destruction of the parietal cells, there is no acid to turn off gastrin production by the antral G cells. Thus, gastrin production goes on unimpeded and at increased levels, and this results, in turn, in stimulation of the gastrin-dependent cells in the body mucosa, specifically the enterochromaffinlike (ECL) population of endocrine cells at the base of the mucosa. These proliferate, first forming small basal nodules of endocrine cells, a feature that is totally predictable in this type of gastritis. Some of these nodules apparently enlarge, resulting in progressively larger endocrine cell lumps, some of which invade as carcinoid tumors. In addition, this type of gastritis has an increased risk for dysplasias and carcinoma. The risk for carcinoma has been estimated at approximately 0.5% per year, so that at the end of 20 years approximately 10% of the patients will have developed a carcinoma. This risk is still small enough and the detection systems, including upper endoscopy with biopsy and cytology, still expensive enough that there is no agreement about the need for a surveillance program to detect the precancerous dysplasias and the carcinomas in their very low stages.

To diagnose this gastritis with confidence the biopsy specimens must come from areas normally covered by body mucosa, there must be no parietal cells or almost none, and there must be no comparable gastritis in the antral mucosa. The characteristic antiparietal cell

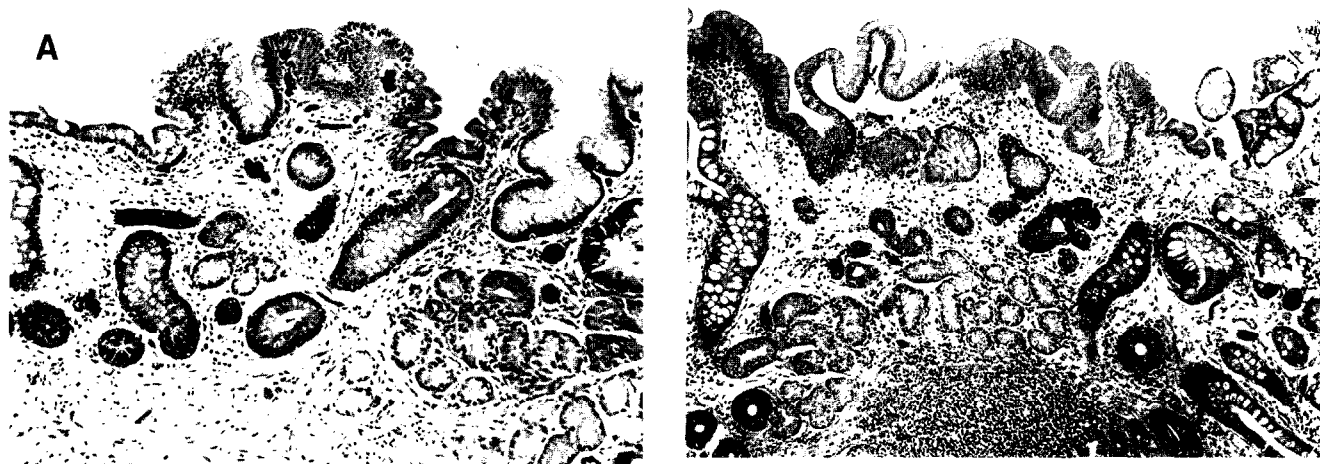


FIGURE 2. The atrophic gastritides. (A) Type A or autoimmune chronic atrophic gastritis involving body mucosa. This is thin mucosa. There are no body-type glands. The only glands at the base of the mucosa are mucous glands that resemble pyloric glands. The pits vary in length, and some of them contain goblet cells, indicating intestinal metaplasia. The lamina propria is sparsely cellular. This biopsy specimen came from a patient with pernicious anemia. (HE; original magnification $\times 103$.) (B) Type B or multifocal or environmental chronic atrophic gastritis involving the antrum. In the center of the field is relatively normal mucosa with clusters of antral mucous glands at the base. On either side the glands have been lost, and intestinalized tubules with goblet cells extend from the surface to the base. (HE; original magnification $\times 83$.)

and anti-intrinsic factor antibodies are helpful, as is the presence of the basal endocrine cell nodules.

Finally, as is true for all the other gastritides, there is imperfect correlation between what the endoscopist sees and refers to as atrophic gastritis and what biopsies of such a stomach will yield. In general, endoscopic atrophy is represented by flat mucosa with few or no folds and a prominent vascularity, thought to be submucosal vessels more easily viewed due to an unusually thin mucosa. In truth, this appearance often does correlate with atrophic gastritis, but we have observed a number of cases of diffuse body atrophic gastritis in stomachs with normal folds or even exaggerated folds.

MULTIFOCAL ATROPHIC GASTRITIS

Quite frequently a biopsy specimen, especially one from the antral mucosa, has a small patch of intestinal metaplasia or even a single metaplastic pit. The question arises as to whether or not this is a *forme fruste* of atrophic gastritis. Clearly no one knows the answer with certainty, so the answer becomes a philosophical matter. If we assume that any intestinal metaplasia, no matter how small the focus, is the result of injury and if that patch of intestinal metaplasia is accompanied by diminution in the number of adjacent or underlying glands, then this patch should qualify as a focus of atrophic gastritis. Such patches occur in stomachs that have *H pylori* gastritis in the next microscopic field and others occur in otherwise normal mucosa. It is likely that they are manifestations of the most common gastric inflammation worldwide, other than *H pylori* gastritis. This is a multifocal gastritis that has glandular atrophy and intestinal metaplasia as its histological components and that can involve any part of the stomach, but most commonly the antral and/or transitional mucosae of

the antrum or antral-body junction, especially along the lesser curvature at the incisura region (Fig 2B).⁵⁸ This process has been designated as "multifocal atrophic gastritis" to emphasize its distribution or as "environmental gastritis" to suggest its epidemiological associations or as "type B chronic atrophic gastritis" to separate it from the type A atrophic gastritis that involves the body diffusely and spares the antrum.^{9,14} It is possible that every patch of intestinal metaplasia is a tiny manifestation of this multifocal disease. However, this disease, in spite of its worldwide dominance, is omitted from some chronic gastritis classifications, which appear to bury it in other categories that are likely to include *H pylori* gastritis.¹⁰⁻¹³ This is the type of gastritis that seems to be the most common precursor of tubule-forming adenocarcinomas and its geographic distribution is the same as that of stomach cancer.⁹ In an analysis of precancerous lesions associated with 1,900 cases of early gastric cancer from Japan, atrophic gastritis of this type was found in almost 95% of the cases.⁵⁹ It shares many histological features with Barrett's esophagus and diffuse body gastritis, including glandular atrophy; intestinal metaplasias of all varieties (both complete and incomplete); pyloric gland metaplasia when it involves body mucosa, lymphocytes and plasma cells in the lamina propria, and little, if any, neutrophilic activity.

The causes of this gastritis have not been clearly elucidated. It is almost endemic in some parts of the world, such as in Japan, whereas it is much less prevalent in other places, such as in the United States. Obviously, this suggests that there are distinct environmental influences, such as diet, but the specific information is lacking, although excess salt and lack of certain fresh fruits and vegetables have been implicated.⁹ Recently *H pylori* has been implicated as a potential cause. The evidence for this association is circumstantial, but it is

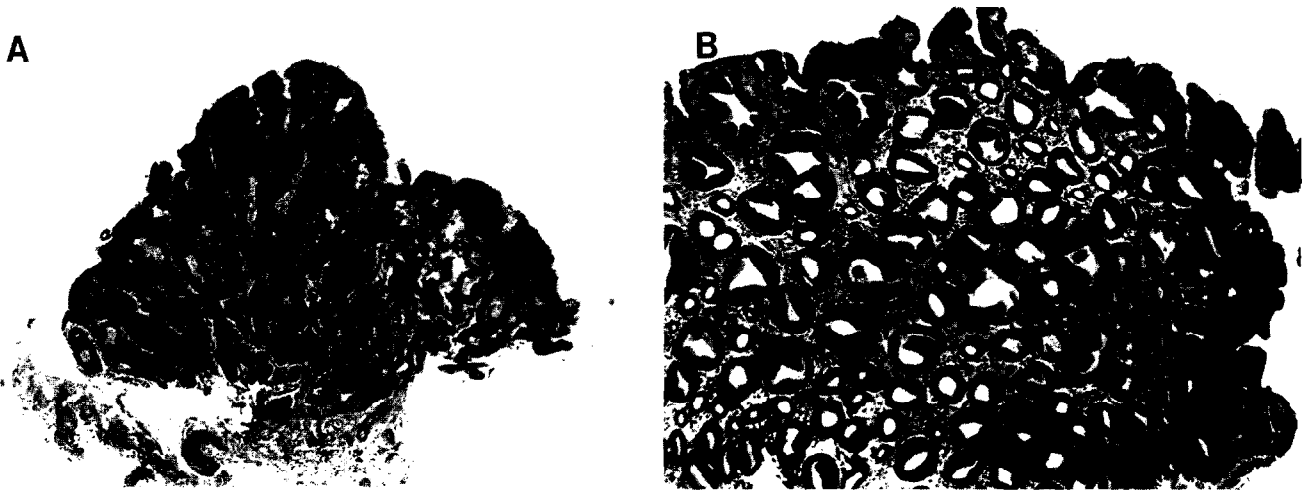


FIGURE 3. Chemical gastropathy. (A) This biopsy specimen came from a gastric antrum that was bathed by bile according to the endoscopist. The pits are lengthened, are tortuous, and have darker than normal epithelium caused by mucous depletion. The lamina propria is expanded, mainly by edema. (B) This is a bias cut of a similar mucosa. The entire biopsy specimen consists of pits in cross and tangential sections. In most of them the epithelium appears darker than normal because of mucous depletion and the presence of enlarged nuclei, both the result of pit hyperplasia. Such a mucosa might be misdiagnosed as low grade dysplasia. The lamina propria is edematous and slightly cellular. (A and B: HE; original magnification $\times 52$.)

compelling nevertheless. In an Italian study the prevalence of antral intestinal metaplasia increased with age and with change in the distribution of *H pylori* from antral alone to antral and body to body alone.⁶⁰ This suggested that *H pylori* first infected the antrum; with time the body became involved and atrophic gastritis developed in the antrum, perhaps secondary to the antral infection.

In spite of its importance as the major gastric cancer precursor worldwide, in most Western societies gastric carcinoma is no longer one of the important cancers numerically. Thus, the finding of this gastritis in a biopsy specimen is no indication for placing any patient on a surveillance program to detect the dysplastic cancer precursors. In contrast, in those societies in which gastric cancer is a numerically important disease, screening programs for early detection are active, but such programs are not based on the finding of this gastritis because it is assumed that this gastritis is endemic in the population being screened.

CHEMICAL GASTROPATHIES, INCLUDING BILE REFLUX

A complex of histological changes in stomachs of patients who had gastroenteric anastomoses that were thought to be the result of reflux of bile into the stomach was described. These patients were likely to have bile reflux because the gastroenterostomy almost always had been performed for peptic ulcer disease and thus was accompanied by a distal gastrectomy, the purpose of which was to remove the antrum and all the gastrin-producing cells. To remove the antrum completely the pylorus with its sphincter also was excised. The gastroenterostomy reattached the stomach to the small intestine, but this attachment had no sphincter, so that bile could easily reflux into the gastric pouch.

The changes that were blamed on bile reflux in-

cluded the following: (1) foveolar hyperplasia, (2) decreased mucin in the foveolar cells, (3) superficial edema, (4) increased smooth muscle fibers in the lamina propria, and (5) little inflammation (Fig 3).⁶¹ In other words, this was not really a gastritis but a gastropathy, unless we regard the edema as an inflammatory exudate. All or any subset of these changes occur with regularity in stomachs that are anastomosed to the small bowel, but the most common are the pit hyperplasia, the mucin depletion, and the absence of intense inflammation. Such changes occur not only in the gastric pouch but at the anastomotic site where they are often accompanied by prolapse changes that include pit distortion and even more smooth muscle in the lamina propria. In the stump one additional alteration is usually present, namely, glandular atrophy. This is independent of the reflux gastropathy and is the result of the antrectomy that removed the gastrin-producing cells, resulting in hypogastrinemia and subsequent atrophy of the body glands, especially the parietal cells that are dependent on normal gastrin secretion for their maintenance.

Bile reflux is best diagnosed either by the endoscopic finding of bile bathing the gastric mucosa or by a low luminal pH in the intact stomach that has proven normal acid secretion. Although the same histological changes occur in intact stomachs without gastroenterostomies, in such cases it appears that they are rarely caused by bile reflux but instead by other surface-damaging agents, such as NSAIDs.⁶² In fact, NSAIDs-related changes in the stomach have been described, consisting of the bile reflux complex plus a deep inflammation in the lamina propria that includes an infiltrate of eosinophils.⁶³ Thus, the changes of pit hyperplasia and mucin depletion with little superficial inflammation form the basis for a group of gastric reactions to superficial injuries. The causes of many such injuries are considered to be chemical agents and the basic group of histological

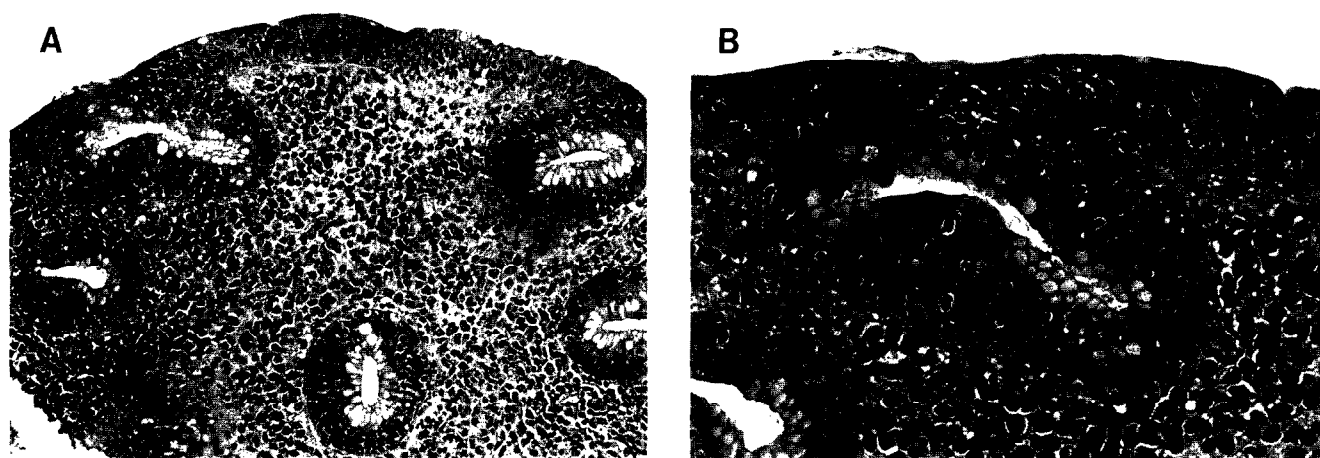


FIGURE 4. Lymphocytic gastritis involving antral mucosa. (A) Low magnification: plasma cells fill the lamina propria, and the surface and pit epithelium contain many extra nuclei. (HE; original magnification $\times 165$.) (B) High magnification: the surface epithelium and that of the pit are disorganized and infiltrated by lymphocytes. In fact, it is difficult to determine which nuclei are lymphocytes and which are epithelial cells. (HE; original magnification $\times 330$.)

alterations has been called "chemical gastropathies."^{14,62}

Non-steroidal anti-inflammatory drugs are emerging as the dominant cause of this reaction, although as with everything else in gastritis the data are conflicting. In one study there was no difference in the histological findings of chemical gastropathy among patients with either rheumatoid or osteoarthritis taking NSAIDs compared with a control group that did not take the drugs.⁵⁰ In contrast, in another study histological chemical gastropathy occurred about four times as often in NSAIDs users compared with those not taking the drugs.⁵¹

The recognition of this family of chemically induced abnormalities has greatly helped to simplify the classification of gastritis, although they are not always inflammations. The changes of pit expansion, mucous depletion, and superficial edema are common to several diseases, including the gastritis of *H pylori*, some phases of the atrophic gastritides, the overhanging edges of peptic ulcers, the tips of hyperplastic polyps, and the tops of the folds in some of the giant fold diseases. Finding them in isolation, unassociated with bacteria, atrophy, metaplasias, ulcers, polyps, or big folds, should raise the possibility of chemical injuries as potential instigators.

LYMPHOCYTIC GASTRITIS

We now recognize a chronic gastritis with intense lymphocyte infiltration of the surface epithelium and the superficial pits, accompanied by lymphocytosis and plasmacytosis of the lamina propria (Fig 4). This has been given the name of "lymphocytic gastritis."^{64,65} We can assume that this gastritis existed before it was named less than a decade ago. We probably placed it in some other category, such as "superficial gastritis." The lymphocytes are small, mature T cells. The infiltrated epithelium is disorganized, it has diminished mucin content, and the nuclei are stratified. These changes are virtually identical to those observed in the surface epithelium in the primary intestinal malabsorption syn-

dromes or sprues. In fact, some cases occur in patients with the sprues, both gluten-sensitive and -resistant.⁶⁶ At times the deeper pit epithelium also may be full of lymphocytes and there may be an accompanying pit hyperplasia. In one of the early reports it was thought that this peculiar inflammation was a response to a local antigen, possibly *H pylori*, but this has never been proven.⁶⁷ When it accompanies one of the sprues we suspect that the gastric epithelium is being damaged by the same mechanisms that damage the surface epithelium in the small intestine. However, other than this association with malabsorption we have no idea of its cause or causes.

Endoscopically, lymphocytic gastritis tends to produce a complex of abnormal patterns that have been grouped into the category of "varioliform gastritis." This includes thickened folds, often topped by small bumps or nodules with central depressions that may look like tiny erosions. However, there are no histological erosions, so this is still another example of poor endoscopic-histological correlation. We have observed lymphocytic gastritis produce small endoscopic polyps, sometimes single, but other times as one of several polyps, the others usually being hyperplastic polyps. In fact, we have even observed gastric hyperplastic polyps in which the surface and superficial pit epithelia were infiltrated by lymphocytes in a pattern identical to lymphocytic gastritis.

Lymphocytic gastritis usually does not produce symptoms. However, one type of giant fold disease, or hypertrophic gastropathy, is a diffuse form of lymphocytic gastritis associated with pit hyperplasia and accompanied by many of the clinical features of Ménétrier's disease, including protein loss in about a third of the patients as well as nausea, vomiting, and abdominal pain.⁶⁸

MISCELLANEOUS CHRONIC GASTRITIDES

There are many gastritides that do not differ significantly from similar inflammations elsewhere, includ-

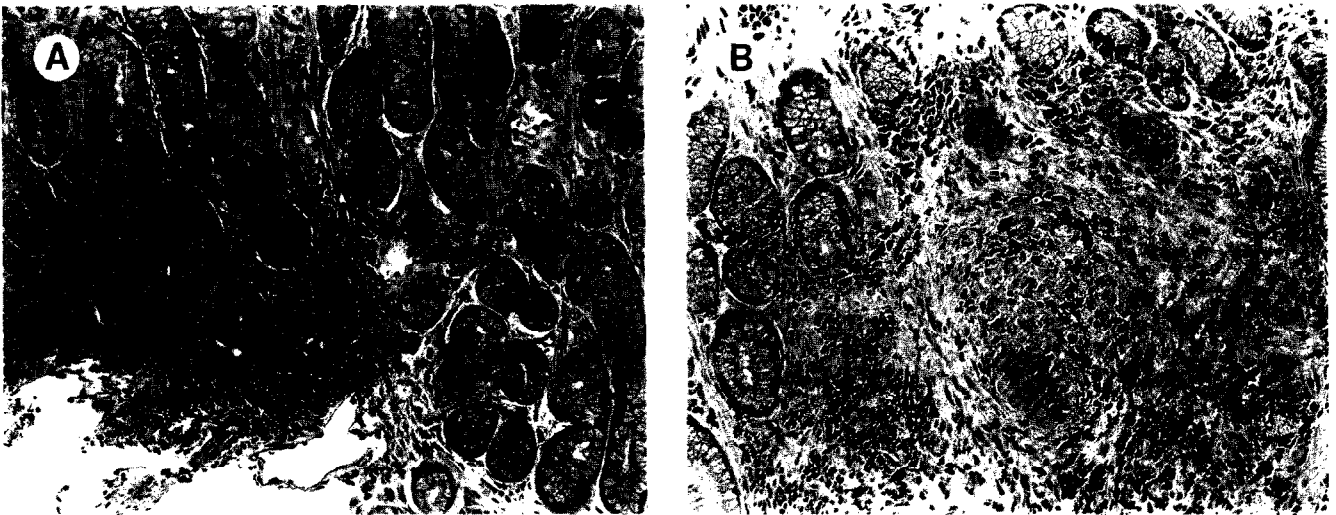


FIGURE 5. Two examples of the broad group of miscellaneous gastritides. (A) Focal inflammation (focal gastritis) in which the cluster of glands in the center is surrounded by a dense mantle of inflammatory cells, mostly lymphocytes in this case, and one of the glands is invaded by the same cells and is damaged. This biopsy specimen might have come from a patient with Crohn's disease, in which case it is a helpful diagnostic hint, or it may be an isolated finding, in which case it is an unexplained annoyance. (B) Granulomas like the tight non-necrotizing one in the center might be part of any disease that has granulomas, from sarcoidosis to Crohn's disease to granulomatous infections to the isolated granulomatous disease that only involves the stomach. In this case the patient had Crohn's disease. (A and B: HE; original magnification $\times 165$.)

ing those that occur in syphilis, mycobacterial and cytomegalovirus infections, histoplasmosis, candidiasis, and other opportunistic fungi. Even cryptosporidiosis in the immunosuppressed patient, such as in those infected by the human immunodeficiency virus, involves the stomach.¹⁴ These are not unique gastric inflammations and will not be covered in this article because of space limitations.

In any surgical pathology practice affiliated with a busy endoscopy service, there are likely to be a few annoying gastric biopsy specimens containing inflammations that do not fit neatly into any established category. Such processes justify the inclusion in the gastritis classification system of a category that recognizes unusual inflammations and outliers, that is, inflammations that partly satisfy the diagnostic criteria for one of the established gastritides but that lack one or more criteria or have unusual or unique features (Table 2). Included in this category are the focal gastritides, often characterized by patches of intense inflammation in an otherwise normal mucosa (Fig 5A). Usually these are foci of lymphocytosis and/or plasmacytosis associated with lymphocytic or neutrophilic infiltration of pits, glands, or necks. Most of these have no names and they may be viewed as comparable to the focal inflammatory lesions, or pimples, that dermatologists often biopsy and that challenge classification by dermatopathologists. In general, except for Crohn's disease, microscopic focal inflammations anywhere in the gastrointestinal tract lack diagnostic specificity, but as we see more of them we will gradually begin to name them.

Crohn's disease affects the stomach, although duodenal involvement is more common and more important clinically. The prevalence of gastric involvement probably depends on whether patients with newly diagnosed Crohn's disease of the small bowel and/or the colon have careful upper endoscopic examina-

tions.^{69,70} Possibly as many as a third of patients with small intestinal and colonic Crohn's disease have upper gastrointestinal involvement, but the changes are more likely to be microscopic with no associated endoscopic findings. The typical histological appearances of gastric Crohn's disease are comparable with those of Crohn's disease in other sites, namely, patchy or focal inflammation, including such diverse changes as lymphoid aggregation, pititis or glanditis mediated either by neutrophils or lymphocytes, plasmacytosis, tiny ulcers, and granulomas. Unfortunately, these are the changes described above in the unnamed focal lesions, which are found periodically in random gastric biopsy specimens in individuals without Crohn's disease. Nevertheless, a set of biopsy specimens that contains multiple focal lesions as described above should raise the possibility of Crohn's disease.

There is a family of granulomatous reactions or granulomatous gastritides (Fig 5B). Some of these are part of a systemic granulomatous disease, such as sarcoidosis, and some have been described as part of a systemic vasculitic syndrome or as an accompaniment of Whipple's disease. Others are the gastric manifestations of focal gut diseases (usually Crohn's disease), and in such cases the granulomas are almost always small and solitary.^{71,72} Still others are not associated with any other disease and such cases have been designated as "isolated granulomatous gastritis." Finally, occasional granulomas occur next to ruptured pits, apparently reactions to extravasated mucin comparable with the ruptured crypt granulomas that are found in the colon in many inflammatory diseases.

Allergic gastritis is usually part of a more extensive allergic gastroenteritis.⁷³ It mainly affects children, especially young children, who present with vomiting, diarrhea, weight loss, peripheral blood eosinophilia, elevated serum immunoglobulin E, and a history of allergy

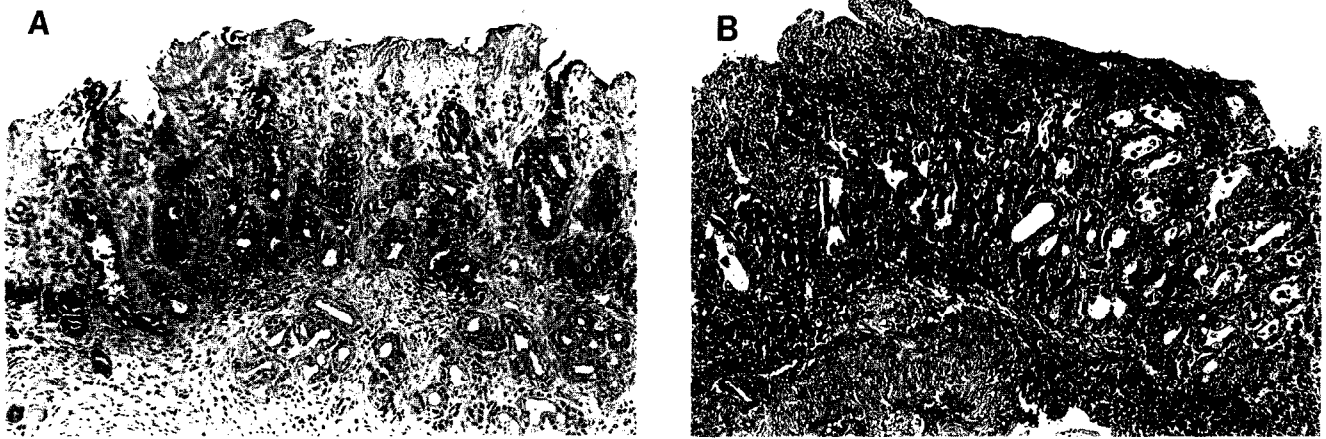


FIGURE 6. Two examples of acute gastritides. (A) In this acute erosion the superficial mucosa is necrotic and sparsely cellular, whereas the underlying pits are regenerative with dark epithelium. Very little inflammation is present considering the intensity of the destruction. (B) Acute hemorrhagic gastritis. The entire superficial mucosa is necrotic with extension into the mid-mucosa on the left. The dark, granular appearance in the necrotic areas is caused by large numbers of extravasated erythrocytes. (A and B: HE; original magnification $\times 103$.)

either in the patient, the family, or both. Biopsy specimens of the gastric antrum have a high yield of findings that include eosinophilia of the lamina propria that may be diffuse and intense as well as eosinophilic infiltration of the superficial and pit epithelium with accompanying epithelial damage and concurrent regeneration.

Weird, one-of-a-kind gastritides also occur, some of which even have published names. Thus, there is a single case report of "collagenous gastritis," characterized by a thick subepithelial band of collagen and a mild underlying inflammation.⁷⁴ It is only fitting that we now have collagenous gastritis because collagenous colitis and collagenous sprue in the small bowel already exist. Collagenous esophagitis cannot be far behind!

ACUTE GASTRITIS

Although this article has concentrated on the chronic gastritides because they are by far the most common diagnostic problems and the processes that are currently studied most intensely, there are few truly acute inflammations of the gastric mucosa that deserve recognition. When biopsies are performed on gastric mucosa they add to the diagnostic problems of the surgical pathologist. Some of them may even be superimposed on the chronic gastritides and, as best as we can tell, they do not result in chronic sequellae, except for occasional chronic ulcers. Thus, they are not precursors of the chronic gastritides as far as we know. Acute *H pylori* gastritis was mentioned earlier, but this is not a biopsy issue because biopsies virtually never are performed on acute infectious gastritides, and there is very little published information about them or experience with them.

Many of the important, noninfectious acute inflammatory lesions of the stomach are small superficial erosions in which the epithelium of the surface and superficial pits and the superficial lamina propria are necrotic (Fig 6A). This results in a superficial mucosal

defect with no surface epithelium and a cell-poor granular lamina propria that may have a few extravasated erythrocytes in it. Considering the intensity of the necrosis there is remarkably little inflammation, usually no more than a few neutrophils at the junction between the viable and necrotic tissues. Intense epithelial regeneration usually is present at the same time with regenerating tubules often extending to the base of the mucosa as if the regenerative zone became so active that it encroached on the glandular compartment. The total picture is a reaction to injury that looks much like acute ischemia or other surface necroses, such as occurs in the colon in the acute colitis of verotoxin-producing *Escherichia coli*. These days most such acute erosions are caused by ingestion of one of the NSAIDs, including aspirin. These erosive lesions develop as a result of deficient mucosal protective capabilities and may result from lowered prostaglandin synthesis by the gastric mucosa caused by the drugs.

Alcohol in actively drinking alcoholics has been historically implicated as another cause of such erosions, but although tiny superficial microscopic erosions may occur, alcohol seems to induce mainly a histological chemical gastropathy with reactive surface and pit epithelium. However, in some alcoholics there are subepithelial hemorrhages in an edematous mucosa, both without much necrosis or inflammation.^{12,75,76}

Occasional debilitated patients develop a diffusely necrotizing and hemorrhagic injury involving the superficial mucosa (Fig 6B). This is possibly caused by ischemia in some cases, but the cause is often not known.^{12,77} On occasion this can be life threatening, leading to uncontrollable hemorrhage requiring gastrectomy.

MULTIPLE COEXISTENT GASTRITIDES

If each of these types of gastritis is accepted as a separate entity and because many of them are common, it should not be surprising when more than one of

them is found in a given stomach at the same time, so that a biopsy specimen contains multiple gastritides. As examples, we have observed antral biopsy specimens in which there was *H pylori* gastritis as well as patches of atrophic gastritis with intestinal metaplasia and loss of glands. We have even observed this combination complicated by an acute erosion in a patient treated with long-term NSAIDs. Sometimes patients with diffuse atrophic gastritis of the body, the type associated with pernicious anemia, also have antral biopsy specimens with multifocal atrophic gastritis. Thus, even the two types of atrophic gastritis exist in the same stomachs from time to time. As mentioned earlier, it is unusual for *H pylori* gastritis to be found in the antrum when autoimmune gastritis is present in the body.

CONCLUSION

Is there a preferable, functional, completely useful, intellectually satisfying classification of gastritis, especially chronic gastritis? Of course there is, but it is probably different for different practitioners who work in different countries and in different practice settings. Any useful classification system probably depends on the types of stomachs from which biopsy specimens are obtained, and this is likely to be population-based. Any useful classification system also depends on the needs of the clinicians with whom we work because they are on the receiving end of our diagnoses. We pathologists must not work in a vacuum. The best approach to the classification of gastritis, especially that for the gamut of chronic gastritis, must consider what it is our clinical colleagues want us to tell them.

Furthermore, it is critical that we pathologists know whether it is even necessary and important to ever make a histological diagnosis of any kind of gastritis, because if it is not then the next issue becomes whether it is necessary or important ever to perform a biopsy on the stomach except to detect neoplasms or specific infections. There are facts about the different forms of gastritis, most of which have been presented earlier in this article, that may make most pathological diagnoses of gastritis obsolete in the coming years:

- (1) Virtually every duodenal peptic ulcer is accompanied by *H pylori* antral gastritis. The only reason to perform a biopsy of the antrum in such cases is to determine if it is normal or if it has chemical gastropathy, so that the clinician can be notified that the patient may be an NSAIDs user and the ulcer may be drug-rather than bacterial-induced.
- (2) It is a toss-up whether a given patient with non-ulcer dyspepsia will have *H pylori* gastritis, and some studies indicate that it does not matter if they do because approximately two thirds of all patients with this set of symptoms respond to antibacterial treatment.
- (3) Every patient with pernicious anemia has type A diffuse chronic atrophic gastritis of the body or corpus, so what is the point of biopsy except perhaps to chop out a few tiny carcinoid tu-

mors or screen for dysplasia; however, in neither situation is the biopsy for the gastritis.

- (4) Virtually every patient with tubule-forming gastric adenocarcinoma has multifocal type B chronic atrophic gastritis and except for intellectual gratification or for purposes of epidemiological analysis we are not interested in the nontumorous mucosa.
- (5) If we perform biopsies on enough patients with sprue we shall find that some of them have lymphocytic gastritis, but the real disease is in the proximal small bowel and not in the stomach.
- (6) Perhaps every patient who is a long-term NSAIDs user will have microscopic gastric changes. However, their dyspeptic symptoms will tell us that they have drug toxicity and whether or not we find chemical gastropathy in the biopsy specimen will not matter.
- (7) In patients with known Crohn's disease involving various parts of the small intestine or colon, careful examination of the stomach with many biopsy specimens will pick up focal inflammations in some patients, so why even perform a biopsy? The Crohn's disease that is the target of treatment is the large symptomatic segment, not the incidental focus that is only detected by screening.

All of these statements are true and each is supported by extensive literature. If what we know is applied to the way we practice and if we accept that there are very few indications for histological diagnoses in the nontumorous stomachs, eventually we may put histological chronic gastritis to rest. In the meantime we pathologists shall continue to face the intellectual and professional challenges that require that we make only accurate diagnoses, and we shall continue the search for some satisfying classification scheme for the collection of pits, necks, glands, plasma cells, lymphoid nodules, neutrophils, eosinophils, distortion, atrophy, metaplasias, and epithelial damage that will allow us to place each histological gastritis into a predetermined niche.

APPENDIX

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; HE, hematoxylin-eosin; TNF, tumor necrosis factor; MALT, mucosa-associated lymphoid tissue; ECL, enterochromaffinlike.

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