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ILL NO. : 8641523 TGQ : 674238 **Service type** : Copy **Service Level** : Core

Call no. : held **Expiry Date** : 04/08/2011

Author : Menge, H., 1939-

Title : Helicobacter pylori 1990

Subtitle : proceedings of the Second International Symposium on Helicobacter Pylori, Bad Nauheim, August 25-26th, 1989

Publisher : Springer-Verlag

Place of Publication : Berlin;New York

Date of Publication : c1991.

Pagination : 120-131

Author of Chapter/Article/Paper : Marshall, BJ

Title of Chapter/Article/Paper : Gastritis epidemiology and natural history

Additional : LCN: 90010449

ISBN : 9780387526164;0387526161

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Gastritis Epidemiology and Natural History

B. J. Marshall

Introduction

Gastritis has been studied intensively over the past 20 years. In older studies, *Helicobacter pylori* was overlooked, the terminology used to describe histological findings was unstandardized, and observations were only occasionally backed up with published illustrations. As a result, it is not always possible to relate new findings to earlier observations, and many of the earlier studies are being duplicated.

Normal Histology

Antrum. The normal gastric antrum has an epithelial cell layer of mucus-secreting cells, folded into glandular structures within a loose lamina propria. Seen under the dissecting microscope, antral mucosa appears similar to the surface of the brain, with "gyri" and "sulci." The mucous epithelial cell layer occupies about one-half the depth of the mucosa, the remaining half being taken up by mucus glands, gastrin cells (G cells), and rare parietal cells. There are few mononuclear cells in the lamina propria and virtually no polymorphonuclear leukocytes.

Body (Corpus). The body mucosa has an epithelial cell layer similar to that of the antrum, but the lamina propria is of course quite different. The mucus epithelial cells are not folded into glands but merely dip into depressions called gastric pits. Several acid-secreting glands connect to each pit. The lamina propria is packed with these glands, so that the only space below the epithelial cell layer is the tissue between the gastric pits. In this region, immediately below the surface epithelium, however, a small amount of loose connective tissue contains room for the migration of inflammatory cells. In the normal body mucosa, as in the antrum, there are few mononuclear cells and virtually no polymorphonuclear leukocytes.

Duodenal Bulb Mucosa. The normal appearance of duodenal bulb mucosa and the transition zone between duodenum and stomach has recently been described by Lawson et al. [1]. The mucosal change between the stomach and duodenum usually occurs at the pylorus where the gastric mucus-secreting epithelium has a scalloped junction with the duodenal intestinal-type mucosa. A 10-mm transition zone exists between gastric- and intestinal-type epithelium. In this zone, microscopic islands of gastric-type epithelium commonly occur within the villous intestinal-type epithelium. Such gastric epithelium has been observed in 90% of duodenal ulcer borders, often in

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association with adherent *H. pylori* [2]. It can therefore be assumed that duodenal ulcers are more likely to occur in this junctional zone than elsewhere in the duodenum. Thus the junction between the stomach and duodenum has three zones:
a) antral-type duodenal mucosa,
b) transitional-type duodenal mucosa, and
c) jejunal-type duodenal mucosa.

Gastritis

Clinical Gastritis and Endoscopic Gastritis. Clinical symptoms and endoscopic findings are mentioned here only to state that they are unreliable indicators of the gastric histology. Clinically apparent gastritis (symptoms) and endoscopic gastritis (red stomach) are often accompanied by histological changes [3], but they may also occur when there is no histological evidence of gastritis. They may be the result of superficial erosion of the epithelium with subsequent bleeding (erosive gastritis) or capillary dilatation (red stomach). The endoscopic appearance may be abnormal if the patient heaves excessively during the endoscopic intubation, if bile refluxes into the stomach, or if undigested food is present. Many investigators have tried to correlate endoscopic findings with the presence of histological gastritis, usually without success [3, 4].

Histologic Gastritis. The histological description of gastritis is by quantification of the various normal and abnormal components of the gastric epithelium. In practice this is done by grading these components for degrees of abnormality, as described by several authors [5–9]. The two major grading systems in use prior to the discovery of *H. pylori* were those of Siurala et al. [7] (Table 1) and Whitehead et al. [14] (Table 2).

Table 1. Histological classification of gastritis – Siurala et al. [7]

Grade 1: normal gastric mucosa	May include a small number of mononuclear cells in the loose connective tissue beneath the epithelial cell layer; may also include small collections of lymphoid cells above the muscularis	
Grade 2: superficial gastritis	Increased plasma cells and lymphocytes just below the surface epithelium but with normal body mucosa glands	Includes specimens with increased mononuclear cells between relatively normal glands and tubules
Grades 3–5: atrophic gastritis	Loss of body mucosa glands, usually with inflammation affecting both superficial and glandular areas of mucosa: – mild, Grade 3 – Moderate, Grade 4 – Severe, Grade 5	This definition is applied regardless of the occurrence of inflammatory changes and metaplasia; in fact, as metaplasia and atrophy increase, inflammation may decrease.

Table 2. Histological classification of gastritis by Whitehead et al. [14]

Mucosal type	Grade of gastritis	Metaplasia
Pyloric (antrum)	Superficial	Pseudopyloric
Body (corpus)	Quiescent	
Cardiac (fundus)	Active	Intestinal
Transitional	Atrophic	
Indeterminate	Mild	
	Moderate	
	Severe	
	Quiescent	
	Active	

The former had the advantage of simplicity, but the classification fitted a model in which gastritis was age related, and intestinal metaplasia was an aspect of the inflammatory process. When the original paper of Siurala et al. [7] is studied carefully, it can be seen that most of the illustrations of gastritis are in fact pictures of *H. pylori*-associated gastritis, mainly of body mucosa, with varying amounts of intestinal metaplasia present. The classification of Whitehead et al. [14] was descriptive and did not assume any progression from one type to another. It correctly separated intestinal metaplasia as a process not always linked to inflammation. Careful examination of the original illustrations of gastritis presented by Whitehead et al. reveals that most of these are also pictures of *H. pylori*-associated gastritis.

The major disadvantage with both of these classification systems is that they do not lend themselves easily to assessment of gastritis healing. This would not be a problem if gastritis were only an accompaniment of aging since reversal would be unlikely. With the discovery of *H. pylori,* however, reversal of at least some components of gastritis are seen to be possible and must be measured. The second disadvantage is that they can not distinguish late type A (pernicious anemia type) gastritis from type B *(H. pylori* type) gastritis. Both systems ignore damage to gastric epithelial cells. Such damage is more likely to be the result of type B *(H. pylori)* gastritis. An additional problem with the classification of Siurala et al. is that it totally ignors the presence or absence of polymorphonuclear leukocytes. Thus, residual mild chronic inflammation from past *H. pylori* infection would be graded only on the amount of atrophy present (see column 2, Table 1) and would receive the same grading as gastritis with epithelial cell damage, polymorphonuclear leukocyte infiltration, and atrophy due to current *H. pylori* infection.

Since the classification of Whitehead et al. [14] distinguished anatomical changes (mucosal type, atrophy, metaplasia) from inflammation, it is more easily modified into a grading scale for gastritis. Warren and Marshall [10] recognized the limitations of the previous methods and adapted Whitehead et al.'s classification. The second column in Whitehead's classification (Table 2) relates to the amount of inflammation in the mucosa. This component can be accurately assessed only when the specimen contains mainly the gastric type of mucosa, either antral or body type. Once this has been replaced by metaplasia, gastritis may no longer be an appropriate term to use, particularly if inflammatory cells are no longer present.

If polymorphonuclear leukocytes, mononuclear cells, and mucus cell damage are graded separately on a scale of 0–3, a combined score of 0 to 9 can be obtained for all biopsies containing gastric epithelium [10]. When graded in this way, any excess of polymorphonuclear leukocytes is likely to be associated with *H. pylori* infection. After the bacterium has been eradicated, past *H. pylori* infection leaves a slight excess of mononuclear cells [11], which may be referred to as inactive or quiescent chronic gastritis [14]. Thus, a grading of 2, 2, and 1 in terms of mononuclear cells, polymorphonuclear leukocytes, and epithelial cell damage (decline in mucin content), respectively, may be followed after therapy by one of 1, 0, and 0; however anatomical changes such as atrophy and intestinal metaplasia remain.

Superficial Gastritis. The location of inflammatory changes may be superficial or spread throughout the mucosa, but there is no clinical difference between the two histological types. In body mucosa, because the lamina propria is already tightly packed with glands, inflammation is superficial, immediately below the luminal epithelial cell layer. Another reason for this superficial distribution may be that the mucus-secreting epithelial cells do not fold down into the lamina propria in the case of body mucosa as they do in that of the antrum. As a result, *H. pylori* attach only to the superficial epithelial cell layer, and the inflammation is located nearby. In antral mucosa the mucus-secreting epithelial cells occupy about 50% of the depth of the mucosa, and *H. pylori* often colonize these deeper areas. Since glandular elements are less prominent in antral mucosa, and there is more space between them, widespread inflammation is less likely to appear as atrophy.

Atrophy and Atrophic Gastritis. Atrophy refers to loss of glandular elements from the mucosa. In body mucosa, atrophy occurs when acid-secreting glands are compressed or destroyed by inflammation within the lamina propria. The terms atrophy and atrophic gastritis were developed as means of describing an appearance seen mainly in body-type acid-secreting mucosa [12]. Studies by Kekki et al. [13] indicate that the usual progression is from superficial gastritis to atrophic gastritis. Examination of the grading system and illustrations of their method [7] indicate that lesser degrees of atrophic gastritis resemble extension of superficial gastritis into the glandular elements. In early biopsy studies blind suction instruments were used which sampled mainly the body of the stomach. In this location any inflammation of the glandular elements must be associated with displacement of glands since there is very little space present between glands. This is perhaps why atrophic gastritis was such an impressive entity to the earlier investigators. Atrophy may also be seen when severe chronic gastritis is present in antral mucosa. According to Whitehead et al. [14], atrophy is best appreciated by reticulin stains which show collapse of glandular supporting elements. Atrophic gastritis is variably associated with intestinal metaplasia (see below).

Intestinal Metaplasia. The replacement of normal gastric epithelium with that of intestinal type (brush border and goblet cell) is referred to as intestinal metaplasia. Although it is often associated with gastritis, this may also occur in the absence of gastritis. Studies by Kekki et al. [13] and Siurala et al. [15] suggest that chronic gastritis, as well as being associated with intestinal metaplasia, may actually hasten its

progression. Any process which continually damages normal gastric epithelium may select out an alternate cell type which is resistant to such change. *H. pylori* infection, a disease discriminating against mucus-secreting epithelial cells, may thus favor the growth of intestinal-type epithelium in the stomach.

Confusing Terminology for Gastritis. In some patients intestinal metaplasia of the stomach occurs without apparent inflammation. Intestinal metaplasia may also be present in patchy fashion in patients who have normal histology elsewhere in the stomach, and who also have normal acid secretion (personal observations). In an extreme case, intestinal metaplasia may completely replace the acid-secreting mucosa of the gastric body and thus cause achlorhydria. Such a state is referred to as gastric atrophy. According to Siurala et al. [7], this may also be called severe atrophic gastritis even if inflammation is absent. Such an event is clearly different from the gastric atrophy caused by severe type A (autoimmune) gastritis and from severe long-standing type B *(H. pylori)* gastritis. The term atrophic gastritis should always be further qualified to prevent confusion. In order to assign a probable etiology it is necessary to know the location of the biopsy specimen within the stomach, the proportions of various epithelial cell types present, and the degree of inflammation. If the specimen contains only intestinal epithelium, it may not be possible to determine etiology. In many cases, biopsy specimens from both antrum and body mucosa must be examined to be certain of the type of gastritis.

Type A and Type B Gastritis. Strickland et al. [16] may have been the first to define the two major types of gastritis. They studied 22 patients with histologically established atrophic gastritis and severe hypochlorhydria, 11 of whom had raised serum gastrin and 11 normal serum gastrin. Of those with raised gastrin, nine also had parietal cell antibody. The histological pattern of the hypergastrinemic patients was one of severe body mucosa atrophy in the presence of normal antral histology. In the normogastrinemic patients, the antrum was also abnormal, with at least grade ¾ gastritis. The authors thus postulated two types of gastritis. Both resulted in atrophic gastritis and gastric atrophy of body mucosa, but in the autoimmune hypergastrinemic type (type A) the antrum remained normal, whereas in the normogastrinemic type (type B) the antrum was severely inflamed (now known to be caused by *H. pylori* infection). Walker et al. [17] examined the prevalence of these two types of gastritis in 1970 in an Australian population and concluded the following.

a) The prevalence of atrophic gastritis was around 25%
b) The prevalence of pernicious anemia was around 1% in a population over the age of 50 years.
c) If the lifetime incidence of gastric carcinoma was 10% for both types of gastritis, type B gastritis was 10–28 times more likely (on a population basis) to cause gastric carcinoma than type A gastritis.

Relationship Between Chronic Gastritis and Intestinal Metaplasia

Before the discovery of *H. pylori,* the topography of gastritis was measured by Hebbel in Minnesota (1949) [18]. By studying the gastric mucosa of persons who died from sudden death he was able to determine the background frequency of the disease in normal persons. Hebbel studied all ages and found that below the age of 50 years, 55% of adults had gastritis whereas above the age of 50 years the prevalence was 87%. Hebbel also noted that 5% of young persons showed intestinal metaplasia of the body or greater curve mucosa in the stomach. In persons over the age of 15 years, 23% showed metaplasia. He concluded that metaplasia is more common in persons with gastritis and is probably the result of long-standing inflammation.

Kreuning et al. in 1978 [19] studied the gastric mucosa of 50 healthy volunteers with a mean age of 33 years and found gastritis to be present in 18 (33%). Antral gastritis was usually confirmed when fundic gastritis was present (16/18). These authors found severe atrophic gastritis in one patient but did not state exactly what definition of this term was used; they may have been describing intestinal metaplasia. In this study, as in most others, antral and fundic gastritis were usually found to coexist if the fundus was abnormal.

In Japan, Tatsuta et al. [20] studied the topography of the gastric mucosa with a chromoendoscopic technique. Their method [21] consisted of filling the patient's stomach with 20000 units of pronase administered orally to digest the mucus layer; the patient was then given an anticholinergic subcutaneously. At endoscopy 20 min later, the mucosa was sprayed with methylene blue to indicate intestinal-type mucosa (unstained by the dye); the stomach was then sprayed with bicarbonate and Congo red, and, finally, pentagastrin was given to make the stomach secrete acid. At this stage, intestinal metaplasia appeared white, gastric, antral type mucosa blue, and acid-secreting mucosa black. Biopsies confirmed the method to be an excellent indicator of epithelial cell type.

After an observation period of 1–3 years, Tatsuta et al. repeated the studies and found that progression of the lesion occurred mainly in subjects with gastritis. In 6.8% of patients extension from antral to fundic gastritis occurred. In subjects with gastric ulcer or merely gastritis, 25% worsened during the study period. In healthy subjects without gastritis, there was little intestinal metaplasia in the initial biopsies, and only two of 44 normal subjects developed metaplasia during the observation period. However, in the groups with gastritis or gastric ulcer, 44.5% developed extension of metaplasia during the study period. In addition, of persons with gastric ulcer who did not have metaplasia initially, 35% developed it by the time of the second examination. The authors concluded that intestinal metaplasia was related to gastritis, and that aging was a less important cause.

Relationship Between Chronic Gastritis and Gastric Metaplasia in the Duodenum

In a study directed more at the lower stomach, Shousha et al. [22] looked at 120 patients with the nonulcer dyspepsia syndrome. Most of the patients were males. The mean age was 50 years. Intestinal metaplasia of the antrum was present in 25% of the males and 34% of the females (not statistically significant). Notably, 89% of those with intestinal metaplasia also had gastritis – 100% of 17 males and 83% of 15 females. Paneth's cells (which secrete lysozyme) were present in the intestinal metaplasia tissue of one-third of the patients. Gastric metaplasia of the duodenal mucosa was

present in 54% of males and 21% of the females. If this difference is also present in normal persons, it could explain why duodenal ulcers are more common in males. There was no statistically significant relationship between gastric metaplasia in the duodenum and gastritis or intestinal metaplasia in the stomach. Both types of metaplasia were present in 11 patients, representing 9% of all patients and 16% of those with metaplasia. Thus, a duodenal ulcer type of appearance in the duodenal bulb (gastric metaplasia) was no guarantee that there would not also be a gastric ulcer type of appearance (gastritis and gastric metaplasia) in the stomach. Duodenitis was seen only in patients with gastric metaplasia.

Overview

From the available literature it can be concluded that there are two types of gastritis (Fig. 1), which together account for at least 90% of the abnormalities seen in the gastric mucosa. Type A gastritis is uncommon, affects the body (acid-secreting) mucosa, and is associated with antibodies to parietal cells. This type spares the antrum but may lead to atrophy and metaplasia in the body mucosa. The endpoint of type A gastritis may be gastric atrophy with either intestinal-type mucosa or antral-type

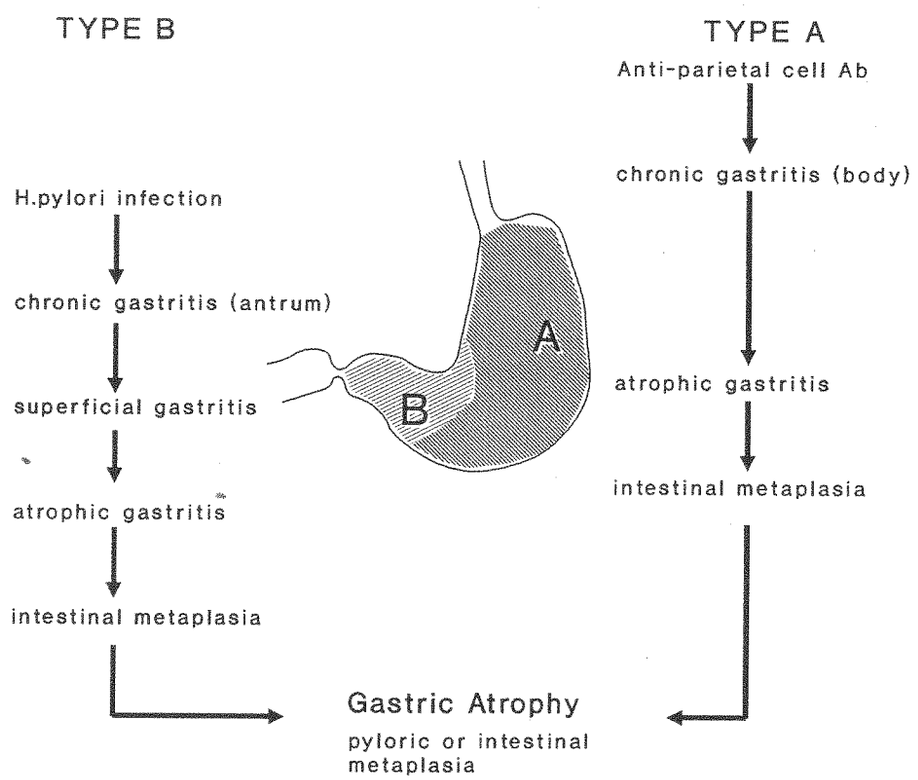

Fig. 1. Natural history of gastritis

mucosa (pyloric metaplasia). Type A gastritis is underrepresented in patients attending gastroenterologists because acid secretion is very low or absent and dyspeptic symptoms are uncommon. The endstage of type A gastritis is gastric atrophy. When gastric atrophy is present, it can be assumed to be type A gastritis when the antrum is relatively uninflamed, parietal cell antibody is present, and serum gastrin is raised.

Type B gastritis is caused by *H. pylori* or in rare cases by other spiral bacteria [23]. Type B gastritis commences as a pangastritis with achlorhydria. At some time, probably 3–12 months after initial infection, acid secretion returns, and gastritis becomes milder and very superficial in the fundus, but remains more extensive in the antrum. The lower density of *H. pylori* in the fundus may result from mucus-secreting epithelial cells being less numerous in the fundus or differing in their ability to attract the organism [24]. With time, type B gastritis extends to involve deeper layers of the antral mucosa and more of the body mucosa. As this occurs, glandular elements are replaced with inflammatory cells. In many cases, mucus-secreting epithelium is replaced by epithelium of the intestinal type. These changes result in the appearance of atrophic gastritis or atrophic gastritis with intestinal metaplasia. Severe, widespread replacement with intestinal epithelium may cause hypochlorhydria and a decreased tendency to form peptic ulcers. The endstage of type B gastritis in body mucosa is very similar to that of type A gastritis, with an appearance of gastric atrophy both endoscopically and histologically.

Type B gastritis is 10–20 times more common than type A gastritis. Both types may predispose to gastric carcinoma. Other types of gastritis are far less common and have not been discussed here. Types A and B gastritis make up 80%–90% of all histological abnormalities seen in gastric mucosa.

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Discussion

Tytgat: Dr. Sipponen, could you clarify the slide on the evolution of gastritis in duodenal ulcer disease? The gastritis score in duodenal ulcer disease was very low. Was that the overall gastritis score or only the score for the body mucosa?

Sipponen: It was the mean score of gastritis in the body mucosa. Duodenal ulcer patients nearly always have gastritis in antrum, but not so often in the gastric body. That is the reason why the mean score was so low.

Graham: Dr. Sipponen, I loved your talk. I am pleased actually to see you present after reading your data all these years. I have one question, or maybe a comment relating to your slide about what happens when each kind of mucosa is compared. I think this still needs modification because a certain percentage of the patients with normal mucosa, say 1% per year will move into the next group and so that group does not remain zero with respect to the development of gastritis. Over 10 years, 10% of these patients will then get the next type of gastritis. This makes the concept a bit more dynamic and the numbers will change only slightly.

Sipponen: We have to remember that gastritis is an age-related disease. The data I showed are from cross-section analysis of an adult population. When a patient gets older he moves from one box to the next.

Talley: I enjoyed your talk. I do have a comment and a question. The comment concerns the Minnesota data. We have recently looked in a small study at the epidemiology of *H. pylori* in asymptomatic volunteers. In contrast to Hebbel in 1949, we found that the prevalence of *H. pylori* gastritis was actually very low even in older persons. Overall only 11% were infected. This is really quite different to some of the other epidemiology studies reported from different parts of the United States. The question I have relates to eosinophils. You did not mention eosinophils in your discussion of gastritis classifications. I am wondering if you think that eosinophils play any role in gastritis.

Marshall: There is evidence in the literature. I believe, that eosinophils were prominent in acute infection and I think in Dr. Graham's description of an acute infection there was a prominent eosinophil infiltration. But I am not sure that there is any new information on it.

Talley: The reason I ask is the following: we have an immunofluorescent technique that measures antibody to eosinophilic major basic protein, which is one of the cationic proteins. We observed that in *H. pylori* gastritis there was a significant increase in eosinophilic infiltration and degranulation compared with all other types of gastritis including specific gastritis and what appears to be the rare *H. pylori*-negative non-specific gastritis.

Veldhuyzen van Zanten: I would like to ask Dr. Sipponen whether he has stratified his data for aspirin, nonsteroidals and smoking, and if so, whether he found any differences.

Sipponen: Unfortunately, we have no data concerning smoking and dietary habits in relation to gastritis, but as far as I have understood from the literature, smoking is not related to gastritis. It is related to peptic ulcer disease and is a very heavy risk factor in this connection, but it is unrelated to gastritis.

Stadelmann: Dr. Sipponen, in your material, patients with AB gastritis had a high degree of atrophy. We examined by stepwise biopsies more than 50 patients with gastric carcinoma of the intestinal type related to the definition of *Lauren* and found in more than 50% AB gastritis, mostly with a low degree of atrophy. Only one patient presented the pernicious type of gastritis. Can you give any comment on this?

Sipponen: In our grading and in our classification, we call gastritis AB type if there is at least a moderate degree of it in both antrum and body.

Stadelmann: I think that in the 1960s and 1970s atrophic gastritis was overdiagnosed because we mostly grouped together all degrees of atrophy.

Tytgat: Dr. Sipponen, did you have a chance to restudy all that material looking for the prevalence of *Helicobacter* organisms according to the various stages of gastritis and atrophy.

Sipponen: Yes, we did do this. The data were published in "Gut" last year. We analyzed the frequency of *Helicobacter* as stained by the Giemsa method. The frequency of *Helicobacter pylori* in our population was very, very high and it went hand by hand with gastritis.

Marshall: Dr. Sipponen, in your recent paper published in "Gut", you found that when there was atrophic gastritis in the body, not as much *H. pylori* was seen. But from reading the paper, I could not tell whether the atrophic gastritis patients had intestinal metaplasia. If you sampled intestinal I-type mucosa in the biopsy, the sensitivity of your biopsy for *H. pylori* would be decreased.

Sipponen: Yes, you are right. Usually the patients also have intestinal metaplasia. And you are also right about the sensitivity.

Petersen: Tomorrow I am going to show you my slides which suggest not only that acute gastritis may heal but also that chronic gastritis may heal. A question to both speakers: Do you consider healing possible?

Marshall: I have observed that chronic gastritis can virtually heal but atrophic gastritis does not heal.

Sipponen: Yes, I agree. We have performed studies with bismuth compounds where we have morphometrically counted the cells in the mucosa. The acute gastritis component disappears immediately when the bacteria have been eradicated. There seems to be also some effect on chronic gastritis, but the effect is very small as Prof. Tytgat has shown.