Variants of intestinal metaplasia in the evolution of chronic atrophic gastritis and gastric ulcer. A follow up study

S Silva, M I Filipe, A Pinho

Abstract
A follow up study with biopsy was initiated in 1982 to define the relations between variants of intestinal metaplasia and the evolution of chronic atrophic gastritis and gastric ulcer. All patients (58 with chronic atrophic gastritis and 66 with gastric ulcer) had intestinal metaplasia at the start of the study. In the six year period to 1988 a total of 241 biopsies were performed on the patients with chronic atrophic gastritis and 243 on the patients with gastric ulcer. Initially, 81% of the patients with chronic atrophic gastritis presented with type I intestinal metaplasia and 14% with type III intestinal metaplasia. During follow up type I was predominant, often associated with grades 2 and 3 active disease (81%) and 45% of these patients reverted to a non-intestinal metaplasia status by the third year of follow up. In contrast, type III metaplasia was more common in the absence of appreciable inflammation (78% of biopsy specimens), being persistent in five of seven patients in the third year of follow up, and was found to be associated with dysplasia in three of these patients. Similarly, the initial biopsy specimen showed type I metaplasia in most patients with gastric ulcer (82%) and type III in only 4%. Type I metaplasia was also predominant in these patients (80%), particularly in active disease (68%), gradually regressing with healing. In contrast, type III was associated with delayed ulcer healing and reactivation (75%; six of eight patients). We conclude that (a) type I is a short term reactive process which regresses with healing; (b) type III is related to prolonged injury and chronicity and may regress or progress to dysplasia; (c) persistent and more immature forms of metaplasia may carry an increased risk of malignancy.

Fundamental to controlling gastric cancer (early detection) and eventual prevention is the knowledge of precursor lesions and their better definition. The majority of gastric carcinomas, particularly the 'intestinal' or 'expansive' type which predominates in high risk populations, are preceded by a prolonged precancerous stage, and there is evidence for progressive change from chronic atrophic gastritis to intestinal metaplasia, dysplasia, and carcinoma as described by Correa et al.1 The early events are inflammation (superficial gastritis) followed by loss of glands (chronic atrophic gastritis) and the replacement of the gastric epithelium by intestinal type epithelium. In routine diagnosis the pathologist recognises different types of chronic gastritis and intestinal metaplasia.

At least three distinct aetiopathological types of chronic gastritis are now recognised: 'autoimmune,' 'hypersecretory,' and 'environmental,' which is relevant to this study. It involves the incisura angularis and the antrum and can progress to intestinal metaplasia and is associated with an increased risk of the 'intestinal' type of gastric carcinoma and peptic ulcer.'

Three variants of intestinal metaplasia have been identified.1 A close relation between the variant characterised by incomplete cell differentiation and sulphomucin secretion (type III intestinal metaplasia or 'colonic' type) and gastric carcinoma of intestinal type has been suggested, while other non-sulphated variants (types I and II or 'small intestinal' type) are predominant where the risk of cancer is low.4-11 If this is so, the presence of atrophic gastritis and sulphomucins in intestinal metaplasia (type III) in a gastric biopsy specimen may indicate increased cancer risk.12

More information is needed on the rate of progression or improvement of chronic gastritis and its association with the evolution of intestinal metaplasia. A change of type of metaplasia may signal an increased risk of subsequent carcinoma. These evolving changes can only be assessed by a series of biopsies over several years.

The aim of this prospective study is to assess the natural history of these changes in patients with peptic ulcer and non-ulcer antral chronic atrophic gastritis.

Retrospective material from an unplanned follow up of 118 patients with chronic gastritis and peptic ulcer is also included to evaluate sampling error and reliability of biopsy interpretation.

Patients and methods

1 PROSPECTIVE STUDY
This covers the period from 1982–8 and includes patients with the diagnosis of gastric ulcer (66) and non-ulcer chronic gastritis (58) confirmed by endoscopy and histology. The criterion for entry to this study was the presence of intestinal metaplasia in the initial biopsy specimen.

Chronic gastritis group (Table I) A total of 241 biopsies were carried out in 58 patients with histologically proven chronic gastritis.13 The antrum was sampled in all patients and in some cases additional biopsy specimens were taken from the body (n=15) or incisura angularis (n=6). These patients were followed up for two years (n=58), three years (n=41), four years...
### TABLE I  Prospective follow up study 1982-8: summary of clinical data

<table>
<thead>
<tr>
<th>Disease</th>
<th>No</th>
<th>Sex</th>
<th>Age (range) years</th>
<th>No</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic gastritis</td>
<td>58</td>
<td>F22</td>
<td>31-68</td>
<td>241</td>
<td>Antrum (all)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>66</td>
<td>F14</td>
<td>40-72</td>
<td>243</td>
<td>Ulcer border (all)</td>
</tr>
</tbody>
</table>

*Criteria: intestinal metaplasia in first biopsy specimen.

(n=19), five years (n=7), and six years (n=1). The group consisted of 22 women, aged 31-68 years (mean 61 years) and 36 men, aged 31-76 years (mean 56 years).

**Gastric ulcer group** (Table I) A total of 243 biopsies were carried out in 66 patients. The ulcers were sited in the antrum (29), incisura angularis (26), and body (14). Three patients presented with two ulcers. There were 14 women, aged 40-72 years (mean 50 years) and 52 men, aged 34-72 (mean 55 years). Initial biopsy specimens were taken from the ulcer border in all patients and additional samples were obtained from areas distant from the lesion in 11 cases. Follow up biopsies were carried out in these patients over the next two years (n=66), three years (n=28), and four years (n=15). Biopsy specimens were taken from areas of re-epithelialisation or scar identified at endoscopy.

Endoscopy was performed in all patients, by the same endoscopist (ACP), using an Olympus Gifa Fibroscope and the site of each biopsy was recorded in a diagram. The diagram was used as a reference for the subsequent follow up biopsies.

All tissues were fixed in 10% formal saline, routinely processed in paraffin wax, cut at 5 μm and stained with haematoxylin-eosin. Biopsy specimens showing intestinal metaplasia were also stained with Alcian blue (pH 2.5)/periodic acid Schiff and diamine/Alcian blue (pH 2.5) (HID/AB) techniques to characterise types of intestinal metaplasia as described below.

### II RETROSPECTIVE MATERIAL

This includes 388 gastric biopsies performed on 118 patients with gastric ulcer (n=43) and histologically proved non-ulcer chronic gastritis (n=75), during 1981. These were not part of a planned follow up study. Endoscopy was carried out by different endoscopists, and on average two to four biopsy specimens were obtained from each patient. The subsequent biopsy specimens were taken from the same gastric region but no diagram was used for site control.

In the gastric ulcer group there were 31 men and 12 women (M/F 2:5) with a mean age of 50 and 57 years respectively. Biopsy specimens were taken from the ulcer border in the antrum (65%), body (20%), and incisura angularis (15%).

The chronic gastritis patients consisted of 44 men and 31 women (M/F 1:4) with a mean age of 53 and 56 years respectively. Biopsy specimens

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**Figure 1:** Intestinal metaplasia type I (complete) composed of mature absorptive cells (non-mucus) and goblet cells producing acid mucin. (Diamine/Alcian blue. Original magnification ×500.)

**Figure 2:** Extensive intestinal metaplasia type III (incomplete) characterised by columnar mucus cells secreting predominantly sulphomucins (black), and goblet cells producing either sialo-(grey) or sulphomucins (black). (Diamine/Alcian blue. Original magnification ×200.)
**TABLE II**  
Chronic gastritis: correlation between intestinal metaplasia types and inflammatory activity in follow up biopsy specimens from 58 patients

<table>
<thead>
<tr>
<th>Degree of gastritis*</th>
<th>Intestinal metaplasia</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>Total</th>
<th>Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>128</td>
<td>241</td>
</tr>
<tr>
<td>I</td>
<td>25 (50)</td>
<td>86 (67)</td>
<td>26 (41)</td>
<td>121 (57)</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1 (2)</td>
<td>6 (5)</td>
<td>3 (8)</td>
<td>10 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3 (6)</td>
<td>2 (2)</td>
<td>22 (35)</td>
<td>25 (12)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21 (42)</td>
<td>33 (26)</td>
<td>10 (16)</td>
<td>64 (27)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Severity of inflammation.  
Percentage of total number of biopsy specimens in each degree of gastritis in parentheses.

**TABLE IV**  
Chronic gastritis: evolution of disease in relation to intestinal metaplasia types and degree of gastritis (58 patients)

<table>
<thead>
<tr>
<th>Evolution of disease</th>
<th>Intestinal metaplasia groups</th>
<th>Degree of gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unchanged</td>
<td>A</td>
<td>5</td>
</tr>
<tr>
<td>(n=41)</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>Worsened</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>(n=10)</td>
<td>B</td>
<td>7</td>
</tr>
<tr>
<td>Improved</td>
<td>A</td>
<td>7</td>
</tr>
<tr>
<td>(n=7)</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

A= None of the follow up biopsy specimens showed type III intestinal metaplasia.  
B= At least one of the follow up specimens showed type III.  
*Patients with dysplasia (*= one patient).  
†Patient later developed ulcer.

were taken from the antrum (54%), body (34%), and incisura angularis (12%).

All tissues were fixed and stained, as in the prospective study above.

**MORPHOLOGICAL CRITERIA FOR CHRONIC GASTRITIS AND INTESTINAL METAPLASIA**  
Chronic gastritis was defined according to Whitehead.19 The criterion for entry to this study was the presence of intestinal metaplasia in the first biopsy specimen, which implied a degree of atrophy of the gastric epithelium. No attempt was made to classify subsequent biopsy material into superficial or atrophic gastritis.19 The severity of inflammation was graded 1–3 as follows: Grade 1 Light mononuclear cellular infiltrate with or without oedema. Grade 2 Inflammatory infiltrate of variable density, composed predominantly of mononuclear cells; a few polymorphonuclear leucocytes found; no active inflammation present. Grade 3 Marked inflammatory infiltrate rich in polymorphonuclear leucocytes, eosinophils, and neutrophils in the lamina propria and in both the glandular and the surface epithelia; active inflammation present.

Intestinal metaplasia was categorised into three types3*: type I (complete) was composed of mature absorptive cells (non-mucus secreting) and goblet cells producing mucus, and occasionally sulphomucins, and occasionally sulphomucins (Fig 1). Type II (incomplete) has few or no absorptive cells, columnar mucous cells containing non-sulphated mucins, and goblet cells as in type I. In type III (incomplete) intestinal metaplasia cell immaturity is more pronounced and characterised by columnar mucous cells secreting pre-
TABLE V  Intestinal metaplasia in biopsy specimens from patients with gastric ulcer (66 patients; 243 biopsy specimens)

<table>
<thead>
<tr>
<th>Intestinal metaplasia type</th>
<th>Gastric ulcer</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute (No. %)</td>
<td>Healing (No. %)</td>
<td>Healed (No. %)</td>
<td>Total (No. %)</td>
</tr>
<tr>
<td>I</td>
<td>86 (68)</td>
<td>20 (59)</td>
<td>32 (41)</td>
<td>138 (56)</td>
</tr>
<tr>
<td>II</td>
<td>12 (9)</td>
<td>4 (11)</td>
<td>6 (7)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>III</td>
<td>5 (4)</td>
<td>5 (14)</td>
<td>1 (1)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>0</td>
<td>24 (19)</td>
<td>9 (16)</td>
<td>39 (51)</td>
<td>72 (31)</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>38</td>
<td>78</td>
<td>243</td>
</tr>
</tbody>
</table>

dominantly sulphomucins. Goblet cells as in types I and II (Fig 2).

In cases where more than one biopsy specimen was taken from the same patient, the biopsy specimen was selected according to the most complete type of intestinal metaplasia present—this is, type III.

Exclusion criteria: biopsy specimens from gastro-oesophageal junction and post-Billroth I and II gastrectomy patients.

Results

I PROSPECTIVE STUDY: CHRONIC GASTRITIS GROUP (58 PATIENTS, 241 BIOPSIES)

Degree of inflammation and types of intestinal metaplasia
The majority of the biopsy specimens (53%) taken from these patients during up to six years of follow up showed a moderate degree of inflammation (grade 2). Severe active inflammation was present in only 21%, the remaining 63 biopsy specimens being grade 1. Intestinal metaplasia, present in the initial biopsy specimen, was also found in 177 of the follow up specimens (73%). Type I intestinal metaplasia was predominant (77%), while type III was seen in 16% of the intestinal metaplasia positive biopsy specimens. Type I was more often associated with severe active and moderate inflammation (81%), whereas type III was more common in the absence of appreciable inflammation (78%) and rarely found in severe active gastritis (11%). The number of specimens showing type II was too small to be conclusive (Table II).

Dysplasia, found in six biopsy specimens from three patients, was associated in all cases with type III intestinal metaplasia, representing 37.5% of the patients in this category during follow up.

Evolution of intestinal metaplasia in biopsy specimens during follow up (Table III)
The majority of the 58 patients with chronic gastritis presented with type I intestinal metaplasia in the initial biopsy (81%), types II and III being found in 5% and 14% respectively. Patients with type I remained unchanged (61%) or reverted to a 'no intestinal metaplasia' status (34%) in the second year, and by the third year 21 patients showed no metaplasia (45%). None of the patients in this group developed type III metaplasia during the follow up period.

In contrast, in the type III group, this lesion persisted in five out of seven patients during the third year of follow up, and was found to be associated with dysplasia in three. One of these patients has now been followed up for six years, with biopsy specimens showing type III metaplasia and dysplasia, and another developed a small ulcer. In this group an additional patient, who refused follow up, developed carcinoma five years after the initial biopsy (Table III).

Intestinal metaplasia and the pattern of evolution of gastritis (Table IV)
Analysis of the follow up biopsy material suggests three broad patterns of evolution of severity and activity of inflammation: unchanged (n=41), worse (n=10), or improved (n=7). In

TABLE VI  Gastric ulcer: intestinal metaplasia in the follow up biopsy specimens from 66 patients

Follow up (No of patients) | Intestinal metaplasia group
---------------------------|---------------------------
1st (66)                   | I                         | II                       | III                      |
|                           | 54                        | 0                        | 3                        |
| 2nd (66)                  | 30                        | 2                        | 21                       |
|                           | 16                        | 11                       |
| 3rd (31)                  | 9                         | 3                        | 1                         |
|                           | 7                         | 1                        | 3                         |
| 4th (15)                  | 2                         | 2                        | 1                         |

* Inactive ulcer. †Re-epithelialisation. ‡Re-epithelialisation and erosion. §Scarred areas. ¶Followed up with surgery. Specimen showed extensive intestinal metaplasia; no malignancy.
each of these categories two subgroups were identified: group A with no type III metaplasia in any of the follow up biopsy specimens, and group B with type III metaplasia in at least one of the follow up biopsy specimens.

The data in Table IV suggest differing patterns of evolution of types I and III metaplasia in patients. Type III occurred in patients with a persistent unchanged gastritis (group B), which in all but one showed only a mild/moderate degree of inflammation, a variable degree of glandular atrophy, and slight fibrosis in two. The one patient in this group presenting with severe gastritis later developed an ulcerative lesion and has since been lost to follow up. As mentioned above, all three patients with dysplasia are in this group.

Fewer patients with an unchanged pattern of gastritis and type I metaplasia (group A) seem to regress to a 'no intestinal metaplasia' status when compared with the overall pattern of the type I group as shown in Table III (9% and 34% respectively for the second year follow up).

Three patients in the 'worse' category later developed peptic ulcer (one) and erosions (two), but neither these nor four others showed metaplasia in the follow up biopsy specimens.

Five of the six patients with initial type I metaplasia reverted to a 'no intestinal metaplasia' status as the inflammatory process 'improved' during the follow up period.

**Biopsy site and pathology**

In 58 patients samples were taken from the antrum in both the first and subsequent biopsies. The gastric pathology described above refers largely to the antrum. In 20 patients additional biopsy material was taken from the body (n = 14) and incisura angularis (n = 6). The body mucosa was rarely involved (3/14) irrespective of the degree of changes in the antrum, while the changes in the incisura angularis matched those in the antrum.

**I PROSPECTIVE STUDY: GASTRIC ULCER GROUP (66 PATIENTS, 243 BIOPSIES)**

A total of 243 biopsy specimens were obtained from 66 patients with gastric ulcer during a four year period, of which 171 (70%) showed intestinal metaplasia. Intestinal metaplasia was present in the initial biopsy specimen in each patient as the criterion for entry to the study.

**Intestinal metaplasia in active and healed gastric ulcer (243 biopsies)**

The incidence of intestinal metaplasia was higher in biopsy specimens from the border of active ulcers (80%), decreasing during healing (76%) to 50% in healed gastric ulcers. Overall, type I metaplasia was the prevalent type (80%), with types II and III showing a low prevalence (13% and 6% respectively). Type I continued to be predominant in active disease (68%), gradually declining during healing (59%) to 41% in healed ulcers. No such trend was noted for types II and III, but the numbers are too small for statistical analysis (Table V).

**II RETROSPECTIVE MATERIAL (GASTRIC ULCER 43, CHRONIC GASTRITIS 75)**

As different types of intestinal metaplasia often coexist in the same patient, sampling error may play a part in the changing patterns of metaplasia found in the follow up biopsy specimens. To assess this we looked at retrospective material from unplanned follow up where several biopsy specimens were taken from each patient, by different endoscopists, within one year of the initial diagnostic biopsy. Thirty four of 75 patients with chronic gastritis did not show intestinal metaplasia in any of the biopsy specimens. In 28, the pattern of change alternated between negative for metaplasia and type I (26), type II (one), or type III (one) on subsequent specimens. Only 13 patients consistently presented with intestinal metaplasia in all biopsy specimens taken. In nine of this group the same
type of metaplasia seemed to persist - type I in eight and type III in one - while the remaining cases alternated between types II and I (two) or types III and I (two).

Biopsy specimens from 18 of the 43 gastric ulcer patients failed to show intestinal metaplasia, while in 14 the biopsy pattern alternated between type I and metaplasia negative; and in 11 patients intestinal metaplasia was present in all biopsy specimens - persistent type I (eight) or alternating types I and III (two), or types I and II (one).

**Discussion**

To our knowledge this is the first prospective follow up study of the relation between intestinal metaplasia types and the evolution of chronic atrophic gastritis. Cross sectional data have shown the relative risk of gastric carcinoma in patients with severe antral atrophic gastritis to be 18-fold higher than in control subjects, and the cumulative risk within 10 years of diagnosis has been calculated as 8-7% for patients in the age group 50-54 years. The time interval between the diagnosis of atrophic gastritis and the development of malignancy can be as long as 20 years (generally 10-15 years). In addition, there is evidence that sulphomucin-secreting incomplete intestinal metaplasia (colonic or intestinal metaplasia type III), is more selectively related to gastric carcinoma than the non-sulphated types I and II, but the natural history of type III is not known and its precancerous nature has not yet been confirmed in longterm follow up studies.

This uncertainty concerning the prognostic importance of gastritis and metaplasia raises a number of questions which are, as yet, unanswered. (1) Is the risk factor in severe atrophic gastritis, as measured by the degree of glandular atrophy, independent of the presence of intestinal metaplasia or the type of metaplasia, or both? (2) Is the risk factor related to a particular pattern of evolution of the disease? (3) Do types I and III metaplasia reflect different stages in the evolution of chronic atrophic gastritis?

The first question prompts the need for standardised morphological criteria for the classification of chronic atrophic gastritis. Our criteria were based on the presence of intestinal metaplasia and the degree and activity of inflammation. It is broadly similar to Whitehead's classification but differs from that proposed by the Finnish group. The latter used the degree of glandular atrophy independent of both intestinal metaplasia and inflammation. The argument for a single criterion is easy classification and application to mathematical models and that atrophy can occur in the absence of metaplasia. It excludes, however, morphological features which provide information on the evolution of the disease and the host response to stimuli, which together play a part in the outcome of the process. We do not know why in some cases the gastric epithelium reacts to injury by simple loss of gastric glands, while in others aberrant regeneration occurs, leading to intestinal epithelium in all its variants. Different pathways of response may be involved. Furthermore, glandular atrophy is easy to identify in its more advanced forms, but mild atrophy (and Cheli’s pre-atrophic gastritis) is subjective and thus not applicable for multicentre or comparative studies. Though its importance is not clear, we believe that intestinal metaplasia is an important feature and should be included in the classification of chronic gastritis, together with inflammation and epithelial and glandular changes.

Another aspect to consider in follow up studies is the reliability of biopsy material in assessing the evolution of disease, in terms of endoscopic interpretation and topographical variations. This difficulty has been minimised in the present

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**TABLE VII** Intestinal metaplasia types, impaired healing, and recurrence in the follow up of patients with gastric ulcer (n=33)

<table>
<thead>
<tr>
<th>Follow up (No of patients)</th>
<th>Intestinal metaplasia groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 27</td>
</tr>
<tr>
<td></td>
<td>II 10</td>
</tr>
<tr>
<td></td>
<td>III 0</td>
</tr>
<tr>
<td>2nd (33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 10</td>
</tr>
<tr>
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<td>II 6</td>
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<td></td>
<td>III 0</td>
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<tr>
<td>3rd (18)</td>
<td></td>
</tr>
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<td></td>
<td>I 6</td>
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<td></td>
<td>II 0</td>
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<td></td>
<td>III 1</td>
</tr>
<tr>
<td></td>
<td>1+</td>
</tr>
<tr>
<td></td>
<td>1+</td>
</tr>
<tr>
<td>4th (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I 2</td>
</tr>
<tr>
<td></td>
<td>II 1</td>
</tr>
<tr>
<td></td>
<td>III 1</td>
</tr>
</tbody>
</table>

*Active ulcer. †Re-epithelialisation. ‡Scar. §Followed up with surgery. Specimen showed extensive intestinal metaplasia; no malignancy.
series where site controlled biopsies were performed by the same endoscopist. The sampling problem is shown in the retrospective group of patients where variable biopsies results were observed in biopsy specimens taken from the same patient within a short period of time.

At the start of this study the prevalence of metaplasia types in the non-ulcer chronic atrophic gastritis patients was 81%, 5%, and 14% for types I, II, and III respectively. These values show a much higher prevalence of type III metaplasia than in previous data from Portugal (2%), the United Kingdom, and France (7%) and may be related to patient selection in the present study.

Intestinal metaplasia, in general, was more common in mild/quiet gastritis (84%) than in active disease (58%) (p<0.01, χ² test). The prevalence of types I and III, however, differed in relation to the inflammatory process and the pattern of evolution of the disease. Type I appeared to be related to severity and activity of gastritis with a tendency to regress on healing. Overall, only three patients in this group changed to type II, in the second and fifth year of follow up, but none changed to type III (Table III). Furthermore, it is interesting that the return to non-metaplasia status was less common in patients presenting with unchanged persistent gastritis (6/31) compared with those in whom the condition "worsened" or "improved" (13/17). In contrast type III is often associated with an non-active, moderate, or quiescent gastritis and atrophy, and all eight patients presented an unchanged pattern of gastritis during follow up.

These observations suggest that type I is perhaps an early event in response to an irritant. On the other hand, type III seems to be related to chronicity. The persistent action of mucosal irritants can lead to progression of changes: from well differentiated type I to more immature or aberrant phenotypes characterised by sulphomucin secretion, expression of fetal intestinal type antigens, and a high proliferative index and new variants of intestinal metaplasia including type III and dysplasia.

Similarly, in patients with gastric ulcer a relation between type I and active disease was apparent, while type III seemed to be independent of the course and more common in delayed ulcer healing or reactivation (75%, 6/8 patients).

The importance of the more immature phenotype of intestinal metaplasia in association with gastric ulcer is not yet known, and one can only speculate. The precise risk of malignancy in gastric ulcer is poorly evaluated but it is reported to be less than 1%.

Type I metaplasia seen in the border of 80% of active gastric ulcers can be interpreted as a reactive process to gastritis, whereas type III metaplasia seems to be related to a long process of injury with repeated episodes of inflammation, regeneration, and repair, higher proliferative activity, and greater numbers of immature cells. These patients may be at an increased risk of malignancy. In our series of 26 early gastric carcinomas 23 presented as peptic ulcers, and in 18 type III metaplasia was seen in the preceding biopsy specimens or in the resected specimens, or both. Of interest, a recent British survey of early gastric carcinoma has shown that symptoms in patients found to have early gastric cancer closely resemble peptic ulceration: 32% were treated with antacids and 10% with H2 blockers and indeed benign gastric ulcer was present in 24 of 47 of these patients with early gastric carcinoma.

Undoubtedly uncertainties remain, but on the basis of our analysis we can say that some morphological features and patterns of evolution of disease may be identified as risk factors for gastric carcinoma though the magnitude of the risk is still unknown. These observations could form the basis for guidelines for follow up surveillance.

(i) Guided and site controlled multiple sample biopsies (six specimens) from the regions more likely to be involved in the process, antrum (3 cm from the pylorus), incisura angularis, and body, should be taken.

(ii) Standardised reporting to include the degree and activity of inflammation, glandular atrophy, and intestinal metaplasia types, dysplasia, and other possibly relevant features.

(iii) Surveillance: the frequency of screening cannot, at present, be suggested with any precision, though the evolution of metaplasia seems to be a long process and an interval of three to five years for follow up may be acceptable. If our hypothesis is correct, surveillance could focus more closely on patients with persistent quiescent chronic atrophic gastritis and type III intestinal metaplasia, and those with gastric ulcers which fail to heal.

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