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Gastric mucosal atrophy: interobserver consistency using new criteria for classification and grading

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SUMMARY

Background and aims: Considerable difficulties persist amongst pathologists in agreeing on the presence and severity of gastric atrophy. An international group of pathologists pursued the following aims: (i) to generate an acceptable definition and a simple reproducible classification of gastric atrophy; and (ii) to develop guidelines for the recognition of atrophy useful for increasing agreement among observers.

Methods: After redefining atrophy as the 'loss of appropriate glands' and examining histological samples from different gastric compartments, three categories were identified: (i) negative; (ii) indefinite; (iii) atrophy, with and without intestinalization. Atrophy was graded on a three-level scale. Interobserver reproducibility of the classification was tested by κ statistics (general and weighted) in a series of 48 cases.

Results: The medians of the general agreement and weighted κ values were 0.78 and 0.73, respectively. The weighted κ coefficients, obtained by cross-tabulating the evaluation of each pathologist against all others, were, with only one exception, > 0.4 (moderate to excellent agreement).

Conclusions: By using the definition of atrophy as the loss of appropriate glands and distinguishing the two main morphological entities of metaplastic and non-metaplastic types, a high level of agreement was achieved by a group of gastrointestinal pathologists trained in different cultural contexts.

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This article is dedicated to the memory of Rodger Haggitt, who was actively involved in this international group until his tragic death. He was one of the most prominent gastrointestinal pathologists of our times and an unforgettable friend to many of us.

INTRODUCTION

Chronic gastritis, a condition virtually always caused by *Helicobacter pylori* infection, creates the background on which a sequence of genotypic and phenotypic alterations may occur and lead to neoplasia.[1–3] One pivotal stage in this multistep process is the development of atrophy of the gastric mucosa. Subjects infected with

H. pylori may develop either non-atrophic, antral-predominant gastritis, a condition more common in the industrialized world and associated with duodenal ulcer disease, or a progressive, multifocal, metaplastic, atrophic gastritis.[4–6] The proportion of infected subjects that develop atrophic gastritis is greater in populations residing in developing countries, and is closely related to the incidence of gastric cancer of the intestinal type.[7] The relationship between atrophic gastritis and gastric cancer has been established in numerous epidemiological and pathological studies.[8–10] Therefore, the recognition and quantification of atrophy are perceived as important elements in determining cancer risk and, ultimately, the prevention of gastric cancer.

Atrophy of the gastric mucosa has been traditionally defined as the loss of glands.[4] Despite this deceptively simple definition, histopathologists have experienced considerable difficulties in reaching agreement on the nature,[11, 12] presence and grading of gastric atrophy.[13–16] In an attempt to reduce the interobserver variability in the assessment of the major histopathological features of gastritis, the updated Sydney System proposed the use of a visual analogue scale as a reference standard for grading the density of *H. pylori* infection, acute and chronic inflammation, intestinal metaplasia and atrophy.[6, 17] Whilst this approach has achieved good reproducibility in the evaluation of the former features, pathologists' agreement on the recognition and grading of gastric atrophy has remained elusive.[13–16] One can argue that the variability in pathologists' assessment of gastric atrophy may have only minor consequences for the care of individual patients. However, this lack of uniformity will seriously compromise the validity of studies aimed at elucidating the natural history of *H. pylori* infection, the interactions between *H. pylori*, atrophy and gastric cancer, and the effects of therapeutic and/or preventive intervention.[18]

As part of an ongoing international effort devoted to the standardization of the diagnostic criteria for the histological reporting of inflammatory and pre-neoplastic lesions of the stomach,[19, 20] a group of gastrointestinal pathologists agreed to pursue the following aims: (i) to generate a widely acceptable, evidence-based definition and classification of gastric atrophy; and (ii) to develop guidelines for the recognition and quantification of mucosal atrophy that could be used to increase agreement among trained observers. This article reports on how the group has progressed towards these goals by testing the interobserver consistency of a proposed classification of atrophy in chronic gastritis.

MATERIALS AND METHODS

The consensus conference

The project aimed at reaching an international consensus on the histological criteria for the diagnosis of gastric atrophy stemmed from the perception that the visual analogue scale proposed in the updated Sydney System[6] had inadequately addressed the evaluation of gastric mucosal atrophy and its relationship with intestinal metaplasia. Thus, eight of the participants in the 1996 Updated Sydney System Workshop recruited other gastric pathologists who had made contributions in the area of atrophy and metaplasia, and formed an international group that, with minimal membership fluctuations, remained unchanged from October 1997 to May 2000. During this period, the group met three times: in Houston (February 1998), in Orlando (May 1999) and in New Orleans (May 2000). The first meeting focused on the theoretical and practical problems that emerged after the updated Sydney System had begun to be widely used. The second phase was aimed at identifying the major points of discrepancy that interfered with diagnostic assessment. To this end, a set of 46 slides from gastric biopsy specimens (33 from the antrum and 13 from the corpus), stained with haematoxylin and eosin, was circulated to all participants. Each pathologist independently classified these test cases by applying the terminology currently used in his or her diagnostic practice, and graded each case using the Sydney System numerical scale from 0 to 3. From these results, κ values were calculated separately for the agreement achieved on each case. Values ranged from 0.05 to 0.87; whilst the highest values were achieved for the absence of atrophy in normal specimens from the corpus, the lowest values resulted from haphazard disagreement on the categorization of atrophy in the antral mucosa. The results of this exercise were presented in Orlando in May 1999, where all cases were reviewed in an open discussion. This plenary assessment revealed that considerable problems, both conceptual and interpretative, still persisted. Therefore, after listing a number of propositions on which the majority of participants could agree (see below), it was established that: (i) a list of robust diagnostic guidelines and an easily applied grading system should be devised;

(ii) a new set of slides would be circulated and graded according to the criteria provided; and (iii) the potential use of morphometry in the objective recognition of gastric atrophy would be explored.

Proposed classification

Most participants subscribed to the following statements.

(a) Two main types of atrophy can be recognized: one characterized by the loss of glands, accompanied by fibrosis or fibromuscular proliferation in the lamina propria, and one characterized by the replacement of the normal (native) glands with metaplastic glands (i.e. glands not normally belonging to that area).
(b) By modifying the definition of atrophy from the 'loss of glands' to the 'loss of *appropriate* glands', both metaplastic and non-metaplastic atrophy would be included.
(c) Both metaplastic and non-metaplastic atrophy can be allocated to one of three grades of severity, using grading criteria modelled on those suggested by the original and the updated Sydney System.[6, 21]

In the presence of a marked inflammatory cell response in the lamina propria (frequently co-existing with lymphoid aggregates or follicles), it may be impossible to determine whether glands that 'appear to be lost' have actually disappeared or are obscured or displaced by the inflammatory infiltrate. To categorize such cases as atrophic may subject the patient to unnecessary follow-up, whilst a 'false negative' opinion could result in possible under-surveillance. In either event, the patient would be allocated to an inappropriate group in clinical studies. In such cases, a preliminary diagnosis of 'indefinite for atrophy' ought to be made, and the diagnostic judgement should be deferred until the inflammation is resolved (in most cases, after the cure of *H. pylori* infection).[11, 18, 22]

These concepts were incorporated into a formalized classification (Figure 1). In the months following the Orlando meeting, a new series of 48 cases was circulated, together with a diagram of the classification represented in Figure 1. The following requirements, deemed to be indispensable for the correct evaluation of a biopsy specimen, were satisfied: (i) the specimen needs to be a full-thickness sample of the gastric mucosa and must be properly fixed, accurately orientated and

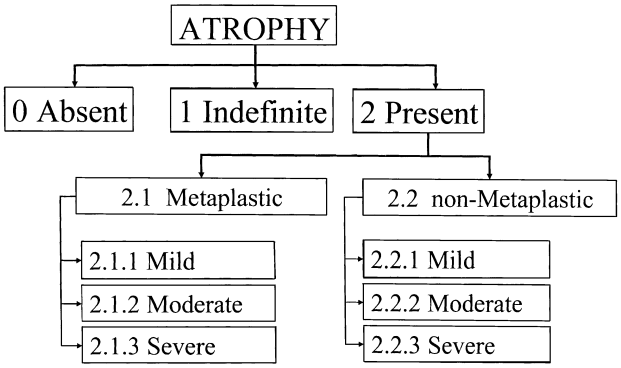

Figure 1. Gastric atrophy: the morphological spectrum.

appropriately sectioned;[23] (ii) at least three levels should be obtained from the same paraffin block; (iii) haematoxylin and eosin staining is adequate for distinguishing between atrophic and non-atrophic samples, but special stains (Alcian blue–periodic acid–Schiff) may be helpful in detecting minimal foci of glandular intestinalization; (iv) the site from which the biopsy sample is obtained should always be indicated.[6, 21, 24–26] Furthermore, the group agreed to the following description of the phenotype of each diagnostic category.

0 *Negative for atrophy.* Gastric glands appropriate for the compartment from which the specimen originates are present in adequate numbers. There is neither appearance nor evidence of gland loss. Examples of non-atrophic antrum and corpus are depicted in Figures 2 and 3, respectively. Minimal foci of intestinal metaplasia, limited to scattered goblet cells, may be present if the overall density of the appropriate gastric glands is not affected. Foveolar-restricted (or partial) metaplasia in the antrum without atrophy is represented in Figure 4.

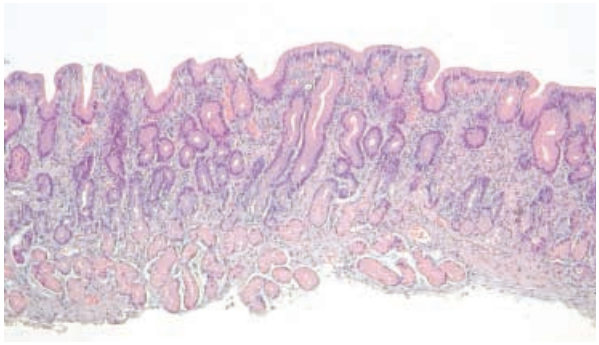

Figure 2. Non-atrophic antrum.

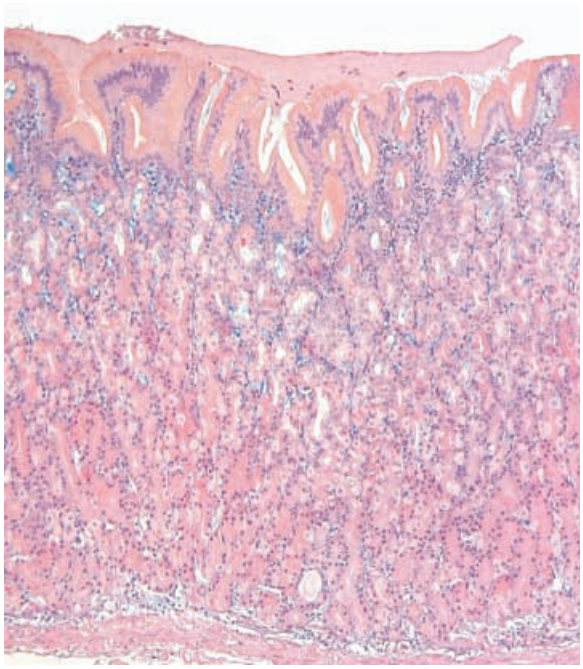

Figure 3. Non-atrophic corpus.

1 *Indefinite for atrophy*. Inflammation of the gastric mucosa is mostly related to *H. pylori* infection. In some cases, inflammation may consist of a dense infiltrate of mononuclear cells throughout the lamina propria, often accompanied by lymphoid aggregates or follicles (Figure 5). In such cases, both the mucin-secreting antral glands and the oxyntic glands may be obscured or displaced by the inflammatory infiltrates. Whenever inflammation prevents a clear distinction from being made between the non-atrophic and atrophic phenotype, a preliminary categorization as 'indefinite for atrophy' should be used. This category, inspired by the classification for non-invasive neoplasia, i.e. dysplasia in the gastrointestinal tract, is not intended to represent a biological entity.[20] Rather, it reflects the absence of reasonable certainty in the evaluation of a histopathological change. 'Indefinite for atrophy' is a temporary categorization; in *H. pylori*-positive cases, successful eradication treatment will induce a substantial reduction or resolution of inflammation within a few months; after such a period, it becomes possible to make a more informed evaluation of atrophy. An example of this situation occurring in the oxyntic mucosa is depicted in Figure 6. The diagnostic category 'indefinite for atrophy' should not be used in the presence of intestinalization of the entire glandular unit (even when there is marked inflammation in metaplastic areas). Any metaplastic transformation of a whole glandular structure is objective evidence of atrophy.
2 *Atrophy.* Atrophy of the gastric mucosa is defined as the loss of appropriate glands. By adding the adjective 'appropriate' (i.e. native to the specific area) to the original definition, metaplasia is incorporated in the definition of atrophy. Thus, two types

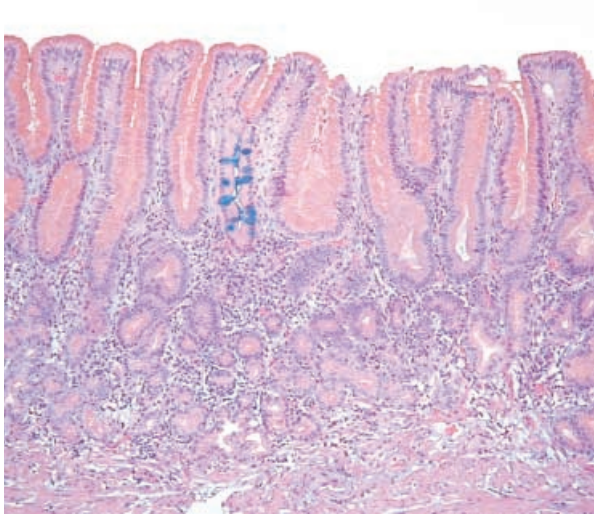

Figure 4. Corpus: foveolar-restricted intestinal metaplasia. A few goblet cells are confined to the foveolar region of the glands. Because of the preservation of the appropriate glands, the case is categorized as non-atrophic gastritis (category 0).

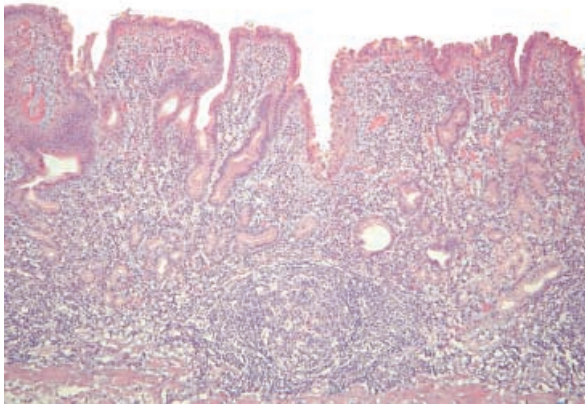

Figure 5. Antrum: indefinite for atrophy (category 1). A small follicle, co-existing with high-grade, full-thickness infiltration of inflammatory cells, makes it impossible to distinguish between 'true loss of appropriate glands' or disappearance of glands due to high-grade inflammation.

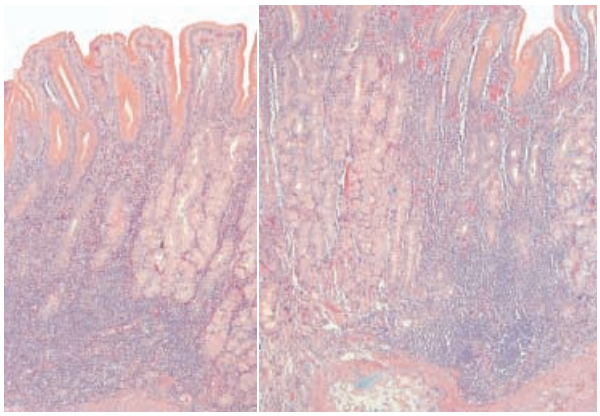

Figure 6. Corpus: indefinite for atrophy (category 1). Normal appearing oxyntic glands are separated and displaced by a dense inflammatory infiltrate. Once inflammation is resolved, it may be possible to determine whether there is a true loss of glands.

of atrophic lesions may be distinguished: one (metaplastic) is characterized by the metaplastic replacement of native glands, whilst the other (non-metaplastic) consists of a decreased density of native gland units with a corresponding increase in the interglandular extracellular matrix. Metaplastic and non-metaplastic patterns are not mutually exclusive and they may co-exist in the same patient and also in the same biopsy sample. In such a case, because of the increased cancer risk associated with intestinalization,[8, 27–30] the biopsy should be assigned to metaplastic atrophy (atrophy associated with metaplasia: category 2.1).

Category 2.1: atrophy associated with metaplasia

This represents the most easily recognizable phenotype of atrophic transformation of the gastric mucosa in both the antral and the oxyntic mucosa. By definition, intestinalized glands represent atrophy when the metaplastic change involves the entire length of the original glandular unit. Metaplastic changes restricted to the foveolar segment of the gastric glands are not considered as atrophy, because they do not completely replace a native gastric gland. Scattered foci of superficially located goblet cells are not uncommon in the gastric mucosa of subjects with and without *H. pylori* gastritis, and should be reported as 'foveolar-restricted (i.e. partial) intestinal metaplasia' (Figure 4).

When it is more extensive, intestinal metaplasia is associated with an irregular profile of the glandular

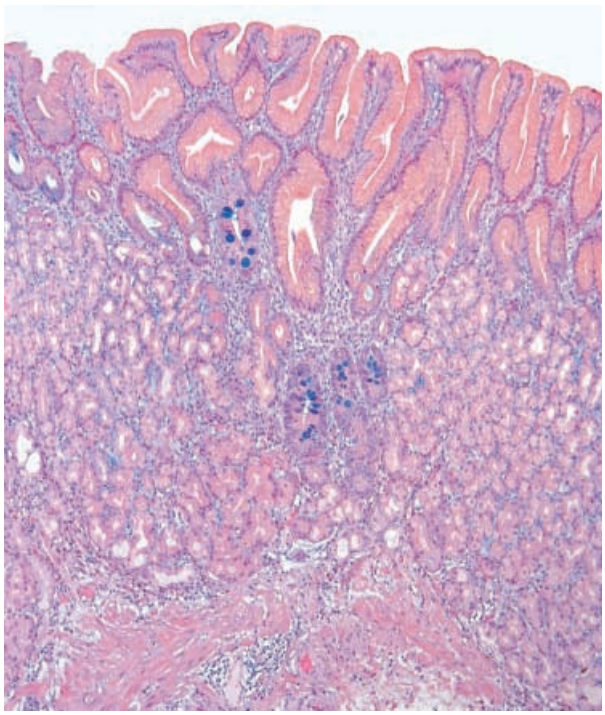

Figure 7. Corpus: mild atrophy with intestinal metaplasia (category 2.1.1). A few native oxyntic glands are replaced by intestinalized glands. In the metaplastic area, there is an increased amount of interglandular connective tissue.

structures. Frequently, there is also an increased amount of extracellular matrix (Figure 7, mild corpus atrophy, category 2.1.1; Figure 8, moderate antral atrophy, category 2.1.2), but, in some cases, metaplastic glands may be closely packed with a minimal amount of interglandular connective tissue. This is exemplified in Figure 9 (severe metaplastic atrophy of the antrum, category 2.1.3) and Figure 10 (severe metaplastic atrophy of the corpus, category 2.1.3). In grading metaplastic atrophy, three levels can be distinguished following the scheme suggested by the visual analogue scales of the updated Sydney system:[6, 11] mild atrophic lesions (category 2.1.1, Figure 7) are characterized by the sporadic intestinalization of a gland; extensive intestinalization equates to severe atrophy (category 2.1.3; Figures 9 and 10); and an intermediate grade of metaplastic transformation is considered as moderate (category 2.1.2, Figure 8).

In the oxyntic compartment, native glands may be replaced either by a downward extension of mucus neck cells or by mucus-secreting glands similar to those found in the distal antro-pyloric region (so-called 'pseudo-pyloric metaplasia')[30, 31] (Figure 11). These

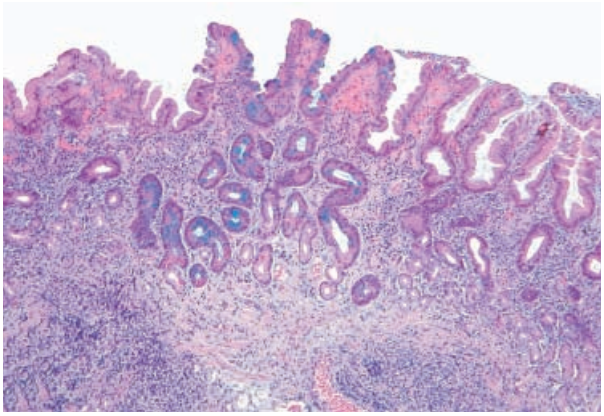

Figure 8. Antrum: moderate metaplastic atrophy (category 2.1.2). Several atrophic glands are seen at each side of the metaplastic area.

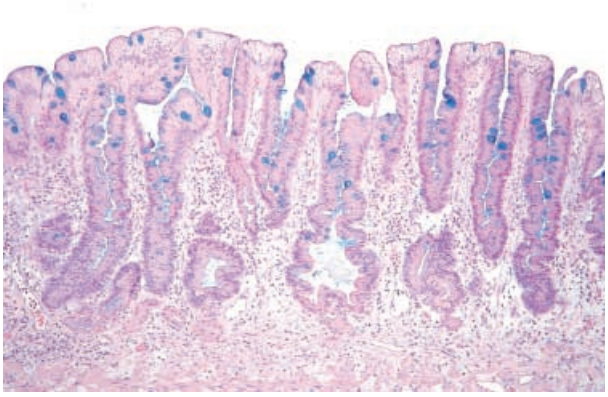

Figure 9. Antrum: severe metaplastic atrophy (category 2.1.3). Native glands are completely substituted by intestinalized glandular units; the original architecture of the antrum is not recognizable.

changes are most frequently seen in the advanced stage of autoimmune gastritis and are often associated with endocrine-like cell (ECL) cell hyperplasia.[6, 32–35] Because oxyntic glands are replaced by other, inappropriate glands, the definition of atrophy applies to this change, which is classified as 'metaplastic (pseudo-pyloric) atrophy', and graded depending on its severity. For example, the mucosa depicted in Figure 11 is graded as category 2.1.3 (severe metaplastic atrophy).

In the antral body transitional zone, particularly in the region of the incisura angularis, it may be difficult to distinguish between non-atrophic antral gastritis and atrophic gastritis of the oxyntic mucosa associated with pseudo-pyloric metaplasia. The proximal extension of

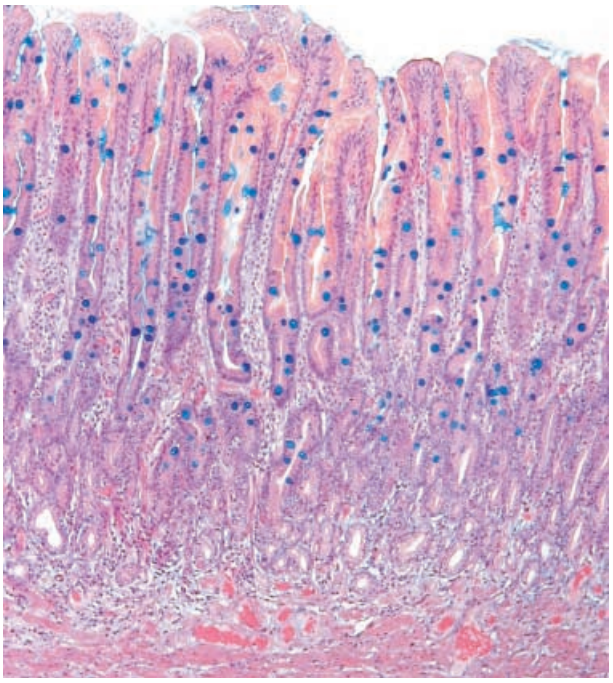

Figure 10. Corpus: severe metaplastic atrophy (category 2.1.3). No oxyntic glands are present. The mucosa has been replaced by a tall intestinalized epithelium.

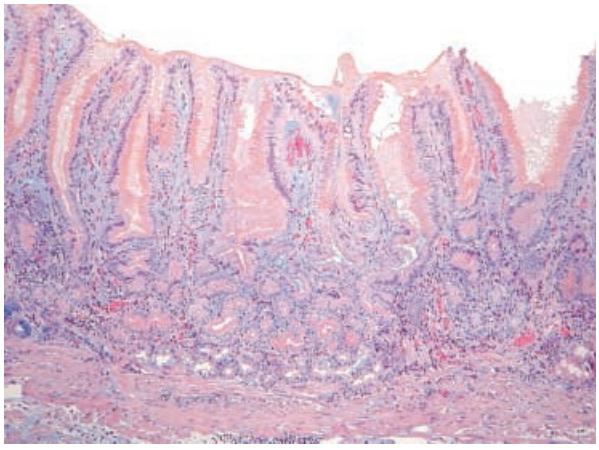

Figure 11. Corpus: pseudo-pyloric metaplasia. Mucin-secreting glandular structures have replaced the original acid-producing oxyntic glands.

the antral phenotype with increasing age (known as 'antral expansion' or 'atrophic border') may hamper the recognition of non-intestinalized atrophy in this transitional mucosa.[26, 36] In biopsy samples taken from this area, only the detection of intestinal metaplasia is considered as a suitable marker of gastric atrophy.

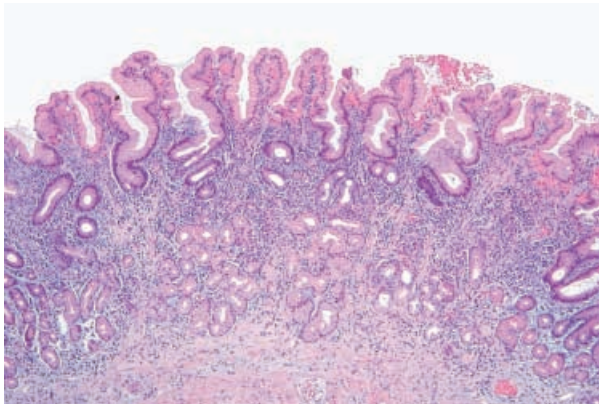

Figure 12. Antrum: mild non-metaplastic atrophy (category 2.2.1).

Category 2.2: atrophy without metaplasia

Despite its documented epidemiological and clinical relevance,[28, 29, 35–37] the existence of gastric antral atrophy in the absence of intestinal metaplasia has been questioned. A recent morphometric study by members of our group has validated both the definition and the grading of atrophic gastritis, even in the absence of metaplastic changes.[38] The number of glandular cross-sections detected at intermediate magnification (× 40) was identified as the most sensitive and easily identifiable morphological alteration in recognizing this variant of gastric atrophy. The updated Sydney System three-tiered visual analogue scales can also be used to grade the severity of non-metaplastic atrophy, which is categorized as mild (category 2.2.1; Figure 12 in the antrum and Figure 13 in the corpus), moderate (category 2.2.2; Figure 14 in the antrum and Figure 15 in the corpus) and severe (category 2.2.3; Figure 16 in the antrum and Figure 17 in the corpus).[6, 11] In the antral mucosa, the coils resulting from the branching of each foveolar channel are decreased in number, with a concomitant expansion of the interglandular connective tissue. In the mucosa of the corpus, the native oxyntic tubules become shortened and the interglandular spaces are widened. In severe cases, the mucosa of the corpus may lose any resemblance to its original architecture and may take an appearance identical to that of normal antrum. In such cases, only the accurate topographical information provided by the endoscopist will make a diagnosis of atrophy possible.

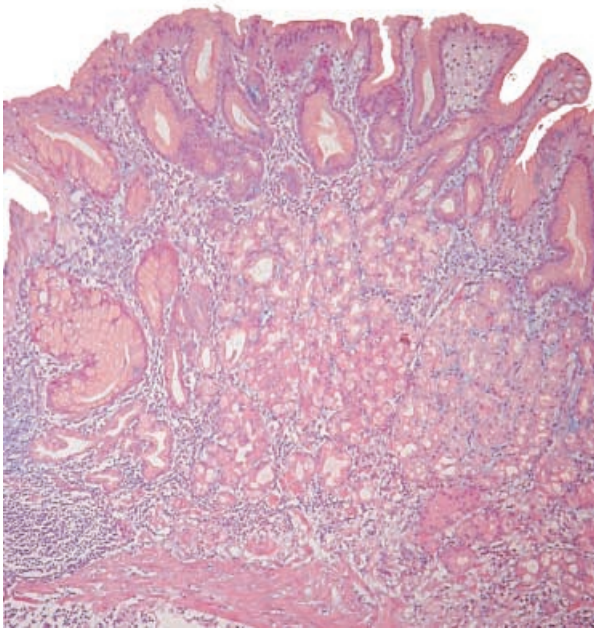

Figure 13. Corpus: mild non-metaplastic atrophy (category 2.2.1). Only a small number of oxyntic glands seem to be missing, replaced by a fibrous matrix and a dilated foveola.

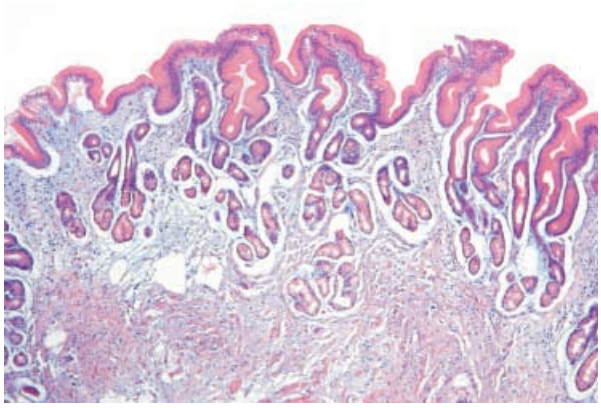

Figure 14. Antrum: moderate non-metaplastic atrophy (category 2.2.2).

Validation of the classification

Cases selected for the validation of the classification (New Orleans, 2000). The set used for the New Orleans Workshop consisted of 48 biopsy samples: 29 from the antrum, nine from the incisura angularis and 10 from the oxyntic mucosa. To ensure that all participants graded the same samples, only two serial sections from each biopsy were obtained from each paraffin block.

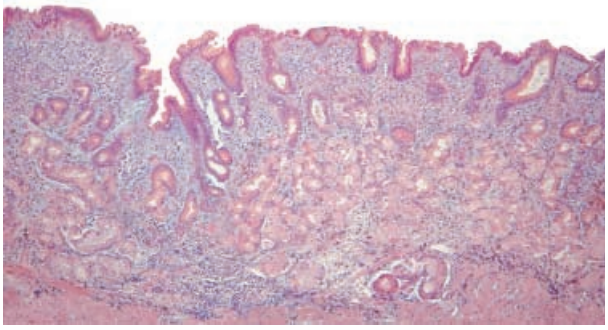

Figure 15. Corpus: moderate non-metaplastic atrophy (category 2.2.2).

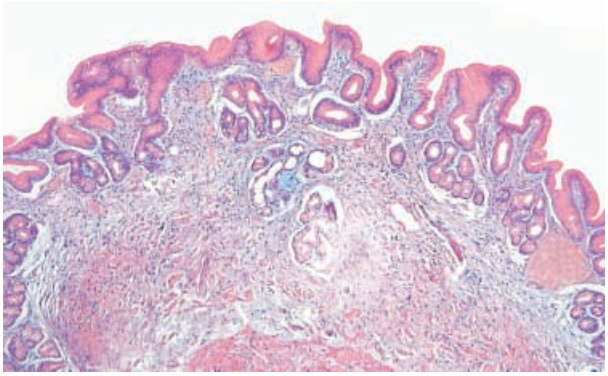

Figure 16. Antrum: severe non-metaplastic atrophy (category 2.2.3). Only the foveolar zone of the original glandular profiles is preserved; the glandular coils have been completely replaced by fibrous tissue associated with minimal inflammation.

Each section was placed on a separate glass slide: the first section was stained with haematoxylin and eosin and the second with Alcian blue–periodic acid–Schiff. Both slides were sent to each participant, who recorded his or her histological evaluation on a standardized reporting sheet sent along with the slides. The only information provided was the gastric compartment from which each mucosal sample had been obtained.

Statistical calculations.

Diagnostic agreement was tested by calculating the general agreement and the weighted κ statistics coefficient. General agreement was defined as the proportion of the cases assigned to the same diagnostic category divided by the total number of cases.[39]

The weighted κ coefficient was calculated for each pair of observers and interpreted in accordance with the benchmarks of Landis & Koch.[40] κ coefficients below 0.4 indicate 'poor agreement', values between 0.4 and 0.8

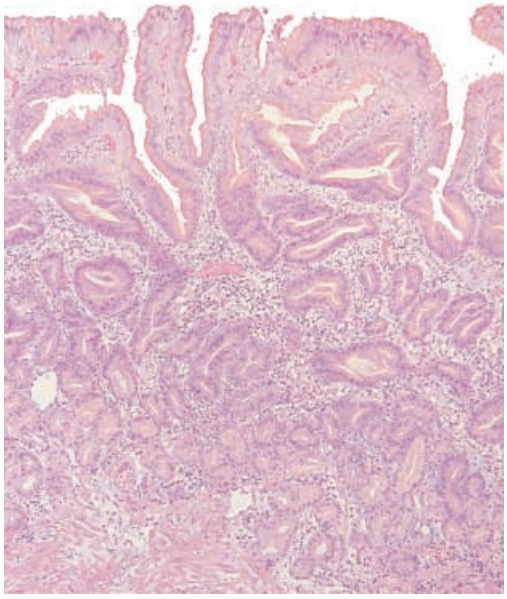

Figure 17. Corpus: severe non-metaplastic atrophy (category 2.2.3). No feature characteristic of the oxyntic mucosa is recognizable: antral-type glands have replaced it completely. In such cases, the only clue to the diagnosis is the topographical information provided by the endoscopist who obtained the biopsy specimen.

represent 'moderate to good agreement' and values greater than 0.8 indicate 'excellent agreement'.[41–43] The median value of the weighted κ coefficient associated with each observer was also calculated, together with the median of the general weighted κ coefficient. The difference between this value and the median value of the weighted κ coefficient calculated for each observer was considered as an expression of the diagnostic variability.

RESULTS

The median values of the general agreement and weighted κ coefficients, calculated by distinguishing the distribution of the cases in the major categories (0, 1, 2.1 and 2.2), were 0.78 (standard error, ±0.018) and 0.73 (standard error, ±0.016), respectively. The matrix shown in Figure 18 illustrates the values of the general agreement (first number) and the weighted (second number) κ coefficients obtained by cross-tabulating the histological evaluation of each pathologist against all the others. With only one exception, all κ values were consistently greater than 0.4, representing moderate to excellent diagnostic agreement.

1											
2	0,809 0,717										
3	0,894 0,853	0,854 0,758									
4	0,553 0,402	0,604 0,515	0,604 0,441								
5	0,787 0,703	0,771 0,715	0,750 0,672	0,500 0,440							
6	0,894 0,822	0,813 0,714	0,854 0,774	0,520 0,370	0,750 0,696						
7	0,894 0,876	0,854 0,780	0,896 0,842	0,583 0,438	0,750 0,700	0,854 0,830					
8	0,787 0,758	0,792 0,784	0,646 0,625	0,542 0,499	0,646 0,632	0,813 0,733	0,771 0,733				
9	0,723 0,593	0,709 0,627	0,688 0,568	0,562 0,504	0,604 0,516	0,708 0,643	0,730 0,615	0,813 0,760			
10	0,851 0,793	0,813 0,753	0,833 0,779	0,583 0,454	0,750 0,735	0,854 0,770	0,813 0,768	0,792 0,779	0,646 0,553		
11	0,915 0,865	0,833 0,729	0,896 0,828	0,583 0,400	0,812 0,748	0,875 0,818	0,900 0,530	0,750 0,684	0,667 0,512	0,854 0,785	
12	0,872 0,873	0,792 0,708	0,854 0,839	0,542 0,429	0,771 0,758	0,854 0,826	0,900 0,885	0,771 0,727	0,667 0,548	0,833 0,799	0,896 0,867
	1	2	3	4	5	6	7	8	9	10	11	12

Figure 18. The matrix illustrates the values of the general agreement (first number) and the weighted (second number) κ coefficients obtained by cross-tabulating the histological evaluation of each pathologist against all the others.

The deviances of the median weighted κ coefficient of each observer from the median of the general weighted κ coefficient are shown in Figure 19.

CONCLUSIONS

The report of the 1994 Houston Gastritis Working Party concluded that '…no classifications are right or wrong; they can only be useful or useless'.[6] Here, we expand this principle to state that no morphological classification is acceptable if its reproducibility has not been validated.[44]

When applying the recommendations of both the original[21] and the updated Sydney System,[6] important discrepancies in the categorization of atrophic gastritis have become apparent.[11–16] Visual analogue scales were proposed as a reference standard in the assessment of gastric atrophy. However, in spite of well-illustrated guidelines, no significant improvement could be documented in the consistency of the histological assessment of gastric atrophy. Such diagnostic disagreements result in unacceptable consequences both for the management of individual patients and for the acquisition of evidence-based information for therapeutic protocols.[45]

This international group of gastrointestinal pathologists is committed to a project designed to standardize the histological reporting of atrophic gastritis. As part of this effort, the theoretical bases of the classification were discussed, practical tests were performed to better identify the major points of discrepancy, and a classification accompanied by agreed-upon definitions was proposed. The final step was represented by the

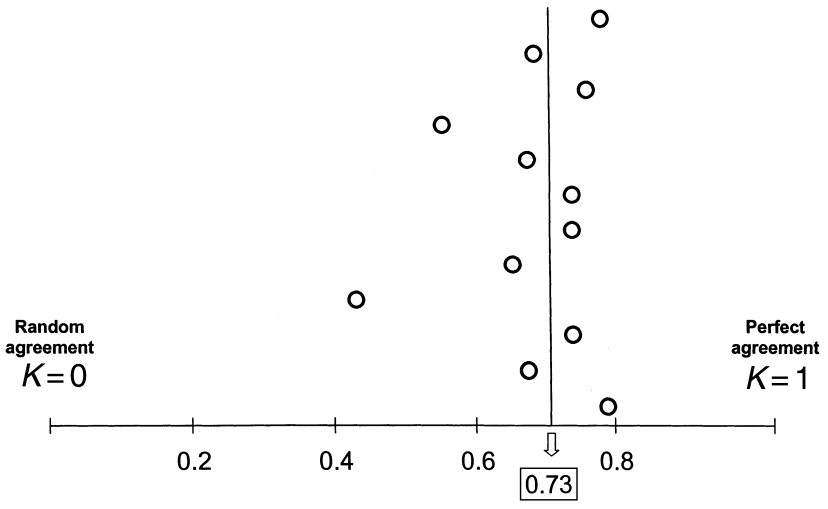

Figure 19. Deviances of the median weighted κ coefficient of each observer from the median of the general weighted κ coefficient (0.73).

validation of the classification, reached by testing its interobserver reproducibility amongst the members of the group. A high level of interobserver agreement was achieved by defining atrophy as the loss of appropriate glands and by distinguishing, within the spectrum of gastric atrophy, two main morphological entities: non-metaplastic and metaplastic types. By applying the visual analogue scales, both phenotypes may be graded on a three-tier scale of severity.

In conclusion, the proposed classification fulfils three main requirements: (i) it is founded on solid and widely accepted peer-reviewed literature; (ii) it is simple, and should be acceptable to both gastrointestinal and general pathologists, in that it employs the three-tiered scoring system currently used in most protocols for clinical studies on gastric pathology; (iii) it has been demonstrated that, following minimal instruction, it can be well reproduced amongst gastrointestinal pathologists who have been trained in different cultural contexts within populations widely different in terms of gastric pathology.

Although the results of this work are encouraging, it seems appropriate to briefly discuss the possible limitations and biases of the approach, particularly in the light of an emerging trend to use more rigorously established methodologies to form expert groups and develop guidelines. A useful example of such methodology has been issued by the Scottish Intercollegiate Guidelines Network.[46] Its three key principles are: (i) development is carried out by multidisciplinary, nationally representative groups; (ii) a systematic review is conducted to identify and critically appraise the evidence; and (iii) recommendations are explicitly linked to the supporting evidence. Our group consisted of gastric pathologists who, because of their interests and published contributions in the area of gastric atrophy and intestinal metaplasia, could be considered to be representative of their respective national academic spheres. The group, however, like many other panels of experts, was self-selected. Thus, it is possible that individuals who might have disagreed with our approach or conclusions were not included. During the proceedings, statements were written on a blackboard and modified until a version acceptable to all (consensus) was reached. Members who were not present at some particular session could exert their veto when preliminary documents were circulated for approval. A more detailed analysis of group dynamics that fostered or hindered consensus are beyond the scope of this paper.

A thorough review of the pertinent literature in several languages was carried out by participants in preparation for each meeting. Participants' views were often based on the literature they cited, but perhaps even more often on their own personal experience. A systematic review of the literature on gastric atrophy would be a challenging and perhaps impossible task, because most published articles express opinions rather than objective measures. A rare exception is represented by an article that resulted from the third atrophy meeting.[38]

The group is well aware that the classification and the recommendations presented here, based on the work conducted at the workshops, represent a preliminary construction. To gain widespread acceptance among pathologists, this classification and scoring system will have to be tested further and validated in studies involving wider groups of both gastrointestinal and general pathologists. The final test, however, will be the demonstration of its clinical usefulness. This can only be achieved through carefully designed clinico-pathological studies.

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