Gastro-duodenitis: Bits and Bugs

Non-specific inflammatory lesions of the upper gastrointestinal tract mucosa are frequent and their pathophysiology and clinical features remain obscure. Easy accessibility to gut mucosa with fiberoptic endoscopy in recent years has accelerated research in this area. Three articles in the current issue focus our attention on this problem in our country.

In the first article from Bombay, the authors show that one third of their 52 patients with gastritis, one fifth of 38 patients with duodenal ulcer, and none of five with gastric ulcer had Campylobacter pylori (C pylori) infection, diagnosed by a combination of microscopy, culture and specific biochemical tests. The most relevant finding of this preliminary study was an overall lower frequency of C pylori infection in Bombay as compared to Western patients. Blaser recently reviewed experience from four continents in 17 studies in symptomatic patients and three studies in asymptomatic volunteers and observed the presence of gastric C pylori in 75-2% of 778 symptomatic patients with gastritis as compared to only 9-1% of 359 symptomatic patients without gastritis and none of 43 asymptomatic volunteers. Except for the lone study from Australia which shows nearly equal rates in patients with or without gastritis, the relation between histological gastritis and gastric C pylori infection appears highly significant. On the other hand, the relation between symptoms and gastritis is somewhat less established, since 11 (20-4%) of 56 asymptomatic patients (with mean ages of 27-30 years) in three studies had histological gastritis which was associated in a majority with C pylori infection. These observations expose an important lacuna in our knowledge of the relation between symptoms and histology, and call for well-planned studies to answer this question decisively.

Two recent studies have prospectively looked at the question whether C pylori per se causes dyspeptic symptoms and characteristic gastric pathology. This was achieved by infecting volunteers who were themselves co-authors of the studies. In both studies baseline gastric biopsies were shown to be normal. Marshall swallowed 10^9 organisms of C pylori after cimetidine treatment. Morris ingested 4 x 10^7 organisms of the Marshall strain without pre-treatment and developed no clinical or laboratory evidence of disease; a second attempt at infection following cimetidine treatment and ingestion of 3 x 10^9 organisms of the first subculture of a local strain of C pylori was successful. In both the studies a characteristic disease picture consisting of clinical symptoms suggestive of acute gastritis, hypochlorhydria, histological acute antral gastritis and the presence of C pylori infection in the mucosa was produced. This was indeed very close to satisfying Koch's postulates, and there can now be no denying that C pylori causes acute antral gastritis. The controversy now is if chronic antral gastritis, which is considered to be the characteristic lesion, occurs with C pylori infection. Accurate diagnosis of this characteristic lesion is therefore a basic issue and standard histological criteria should be followed in all reports for a fair comparison.

Unfortunately although most authors refer to the work of Whitehead et al., they have modified the original criteria in a significant manner. Whitehead et al reserve the term acute activity in chronic gastritis to migration of "polymorphs into and degenerative changes of the epithelial elements of gastric mucosa." "Quiescent" gastritis has been defined as "mucosa with minimal epithelial degenerative changes and a slight chronic inflammatory infiltrate." In the first communication from the Perkin group on this subject (a letter), Warren classifies the biopsies as those with no inflammation, chronic gastritis, or active chronic gastritis, giving little importance to the epithelial cell layer. The thrust of the paper was entirely microbiological. Later work of the group too fails to take a closer look into the histological criteria. Extremely important observations which relate C pylori infection with gastritis continue to ignore histological aspects, although some studies have stuck faithfully to them. The scoring pattern to diagnose chronic active antral gastritis followed by the Dutch group was as follows: density of inflammatory infiltrate in the lamina propria (0-2), density of polymorphs in the lamina propria (0-3), presence of interepithelial polymorphs (0-3) and superficial erosions (0-2), giving a total maximum score of ten; only five of ten scores thus conform to the original recommendations and superficial erosions are only one of the signs of epithelial degeneration. Although the authors mention their attempts at recording the presence of glandular atrophy, intestinal metaplasia and dysplasia, they do not further describe these features. Metaplastic changes and glandular atrophy have been regarded as signs of advanced chronic gastritis in the original work, another study and by us. The Bombay workers did not include epithelial cell layer changes at all in grades 0-2, but regarded the presence of polymorph cells in glands, epithelial cells and lamina propria as necessary to diagnose grade 3 gastritis. These criteria appear accurate enough for diagnosing active acute antral gastritis, but omission of consideration of metaplastic changes and glandular atrophy might have ignored severe gastritis without polymorphonuclear cell infiltration, which might be an important evidence of recent active inflammation. It may be appropriate to recall that C pylori have been found to be present in the duodenum only in association with gastritis, metaplasia and are not present in antral mucosa with intestinal metaplasia. These findings should stimulate the Bombay group to have a closer look for metaplastic changes in the mucosa of their patients and how they relate to C pylori infection.

The observations of complete absence of active
gastritis in Bombay patients raise a new issue as to why these patients differ from Western patients. In a group of 67 patients with duodenal ulcer from Hong Kong, using the criteria of Whitehead et al., chronic active inflammation was found in 71.1%, 100% and 25-5% of cases within the duodenum, antrum and fundus respectively. This study also made some important observations which may contradict findings of other studies. These workers could culture C. pylori from the duodenum in 25% antrum in 76.7%, and fundus in 63.3% of cases. The rates of isolation of C. pylori from the duodenum and fundus were higher possibly because of the sensitive culture techniques they used. The Bombay study reports negative cultures from the gastric body mucosa in their first nine patients. Other workers have however shown evidence that even normal fundal mucosa has C. pylori in symptomatic and asymptomatic patients. This evidence has prompted a hypothesis that C. pylori are normal residents of healthy fundic mucosa and colonize antral mucosa when gastritis develops. This hypothesis however is yet unproved. C. pylori therefore occur in the fundic mucosa of Orientals with symptoms and in healthy Peruvians from the tropical zone, contrary to the observations from Bombay where, after the negative culture for C. pylori from the mucosa of the gastric body in the first nine patients, further search was given up. The most important message of the Hong Kong study was that C. pylori persisted in almost the same numbers even after the duodenal ulcers had healed and inflammation had partially subsided.

I have thus identified problems in interpreting the clinical, histopathological and microbiological investigations in the story of C. pylori and chronic gastritis. The explanation that these patients might have more quiescent gastritis does not appear adequate. The theory of causal association of C. pylori with chronic gastritis and duodenitis has been enveloped in fresh clouds of uncertainty and mystery, particularly after the Hong Kong study. The nature of the hour is a fresh look at the problem, employing comprehensive, multipronged protocols. We must ask clear questions and seek their answers. In our country, the following basic questions must be answered: (i) how often do the healthy subjects have histological gastritis and duodenitis and how often do they have C. pylori in the mucosa, and (ii) how often do our dyspeptic patients with or without ulcers have the above changes and what is the influence of specific anti-C. pylori therapy on symptoms and histology.

Let us now shift to a more familiar but equally confusing track, presently beaten by the Delhi group of workers who report in patients with non-ulcer dyspepsia an excellent overall correlation between grades of severity in mucosal abnormalities as judged by endoscopy and histology. They also observe that, in spite of this excellent correlation, specific features like nodularity and atrophy diagnosed by the two methods were not correlated. Since we had previously concluded from a detailed study of 25 dyspepsias from Chandigarh that histology was more sensitive than endoscopy, I re-evaluated our data to make it comparable with this study (Table) and found that our conclusions remained essentially unchanged. The different conclusions in the two studies may be ascribed to the differences in histological criteria and in the methodology. We believe that lamina propria infiltrates are not specific nor objectively evaluable and therefore insisted on the stringent criterion of epithelial cell layer abnormalities.

| Table: Comparison of data on non-ulcer dyspepsia | Atmakuri et al. | Naik et al. |
| Endoscopy | Histology | I | II | III | Total | Endoscopy | Histology | I | II | III | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 17 | 4 | 0 | 21 | 0 | 3 | 1 | 5 | 0 | 3 | 1 | 5 |
| 1 | 9 | 6 | 1 | 16 | 1 | 4 | 7 | 12 | 1 | 4 | 7 | 12 |
| 2 | 0 | 2 | 3 | 5 | 2 | 0 | 3 | 5 | 2 | 0 | 3 | 5 |
| Total | 26 | 12 | 4 | 42 | Total | 7 | 12 | 6 | 25 |

$\chi^2 = 21.3, \text{ df } = 4, \text{ p < 0.0001}$

<p>| Table: Comparison of data on non-ulcer dyspepsia | Naik et al. |</p>
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$\chi^2 = 5.67, \text{ df } = 6, \text{ p > 0.4}$

In another recent study of 15 non-ulcer dyspeptics from Bombay, we showed that high dose liquid antacids administered over a 4-week period led to definite and impressive benefit in symptoms and gastro-duodenal histology. The protocol of this study was much the same as in our previous study but symptoms were analysed in greater detail and histology was supplemented by staining with alcian blue-periodic acid Schiff technique to bring out metaplastic changes more definitively. In this study too, we observed that endoscopy was a very poor technique to diagnose gastro-duodenal inflammation. The recent (unpublished) data we have completed comparing high dose liquid antacids, milk and placebo over a 2-week study. Whereas antacids, milk and placebo all relieved symptoms in these patients, only antacids relieved night pain as well as reduced modified sham food stimulated and peak histamine stimulated acid secretion. In the 2-week period, no change in histology could be shown. Both studies were blind and have shown a consistent superiority of histology over endoscopy. Moreover most dyspeptics showed a definite histological change. The lack of correlation between endoscopy and histology together with the diffuse nature of inflammation may even make it convenient to omit endoscopic criteria altogether from objective evaluation in future studies; but surely such a step must await more careful observations.
The last in the series of these studies in this issue is from Chandigarh and describes endoscopic and histological features of upper gut mucosa in 30 patients with and stage renal disease. Two thirds of the patients showed endoscopic abnormalities. Of the 30 evaluated histologically, over three fourths showed abnormalities, which included duodenitis, gastritis and esophagitis, in that order of frequency. The criteria followed for histological grading were those described by Whitehead et al. The mucosal abnormalities were essentially of mild and moderate grades and similar to those observed by other workers quoted by the author, histologically.

1. Jaffe and Luing first described in 1934 either “diphtheritic” ulcers or “pseudomembranous lesions in one fifth of 136 patients who died due to end stage renal disease; with the advent of hemodialysis gross mucosal lesions have become uncommon and milder grades of lesions are seen. It is believed that these mucosal inflammatory lesions sometimes cause upper gastrointestinal hemorrhage. Important conclusion in one of the recent studies is that renal transplantation is associated with increased chances of bleeding, which contribute significantly to mortality in these cases. Unfortunately most recent studies do not answer the questions as to whether patients with chronic renal disease have higher chances of mucosal abnormalities and symptoms ascribable to them than in the normal population. There are also no studies with adequate sample size of patients who have been studied before hemodialysis is started and thus we do not know how the mucosal lesions get modified after hemodialysis and renal transplantation.

Histological gastritis, its relation with symptoms and its causes are as yet widely open for research and there are numerous unresolved questions. There is an urgent need for further endoscopic, histopathological and microbial studies to agree to work using standardized protocols and techniques. Short of a multicentric approach, controversies in this area will continue only to reinforce our dogmas and ignorance.

Department of Gastroenterology,
Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 001

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INdian J Gastroenterol Vol 7 No 2 July 1988

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