Will antibacterial chemotherapy be efficacious for gastritis and peptic ulcer?

Gastric and duodenal ulcers may be precipitated by treatment with non-steroidal anti-inflammatory drugs, and a gastric ulcer may show malignant change; but up to now, for most peptic ulcers gastric acid appears to be the main precipitating cause. Thus gastroenterologists usually treat non-malignant peptic ulceration with drugs that inhibit gastric acid secretion by H₂-receptor antagonism—cimetidine and ranitidine (Legerton, 1984). Acid secretion is also greatly reduced and ulcers are healed by omeprazole which inhibits the proton-pump mechanism (Prichard et al., 1985). Although peptic ulcers are readily healed by anti-acid drugs, after cessation of such therapy the relapse rate may reach 100% in patients followed for two years (Bardhan et al., 1984). Thus the main problem of treatment is the very high relapse rate, for which up to now there has been no satisfactory explanation.

The significance of inflammation in the gastric mucosa—gastritis—in the aetiology of peptic ulcer has been debated. Active chronic gastritis can be one cause of gastric ulcer (Mackay & Hislop, 1966); and gastric ulcers commonly occur in inflamed antral-type mucosa (Schrager, Spink & Mitra, 1967). Antral-type mucosa is often present in the duodenal cap of patients with a duodenal ulcer (James, 1964). Endoscopic studies by Greenlaw et al. (1980) and Stephen, Lesna & Venables (1978) showed that many patients with symptoms of a peptic ulcer have no ulcer crater, but histologically the mucosa of their gastric antrum shows active gastritis with polymorphonuclear neutrophils in the epithelial layer. Symptoms of non-ulcer dyspepsia may not be relieved by reduction of acid output by truncal vagotomy (Christiansen, Aagaard & Koudahl, 1973).

Curved and spiral bacteria with sheathed flagella were first cultured from endoscopic biopsy specimens of inflamed gastric antral mucosa in 1982 in Western Australia (Marshall & Warren, 1984), and were named Campylobacter pyloridis (Marshall et al., 1984). This name has now been validated (Anon, 1985).

The close association between active gastritis and the presence of Camp. pyloridis, and the absence of Camp. pyloridis from normal mucosa has been confirmed by workers in the Netherlands (Langenberg et al., 1984) and in England (Jones, Lessells & Eldridge, 1984). Rathbone et al. (1985) took biopsy samples from both the body and the antrum of the stomach in each of 150 patients, and found that when Camp. pyloridis was seen on normal mucosa the other biopsy sample always showed gastritis. This has also been our experience in Royal Perth Hospital. Marshall et al. (1985b) have shown that Camp. pyloridis can be found in inflamed mucosa adjacent to a duodenal ulcer, and they have presented convincing arguments for the probable causal significance of Camp. pyloridis in gastritis, and probably also in peptic ulceration not due to non-steroidal anti-inflammatory drugs. They list technical errors particularly in endoscopic technique that can result in failure to detect Camp. pyloridis. Histological studies showed that the gastric mucosa reverted to normal after antibacterial treatment.

Jones et al. (1984) detected specific antibody in patients with gastritis, while antibody was uncommon in patients without gastritis, and in blood donors and antenatal patients. When detected in healthy people, the titre of IgG antibody to Camp. pyloridis is lower than the titre in peptic ulcer patients (Kaldor et al., 1985).

In Perth in 1984 a medical volunteer swallowed Camp. pyloridis organisms—about 10⁹ colony-forming units in alkaline peptone water—and eight days later he developed a transient achlorhydric gastritis (Marshall et al., 1985a). Biopsy specimens taken on the tenth day gave histological and cultural evidence of polymorphonuclear cell inflammation in the antrum associated with Camp. pyloridis. Large numbers of curved and spiral organisms were observed on the surface of the antral mucosa, beneath the gastric mucus. Electron microscopy showed that the antral epithelial cells had lost their characteristic pattern of alignment, and had developed irregular bulging surfaces with depletion of microvilli, and a marked reduction in the numbers of cytoplasmic mucus.
secretory granules. Such bacterial-cell interactions point to a possible cytopathogenic basis for a subsequent erosive lesion of the mucosa due to gastric acid (Marshall et al., 1985b). These distinctive ultrastructural changes, and the presence of "adherence pedestals" at bacterial contact sites, have been noted consistently in antral biopsies containing Camp. pyloridis from patients with gastritis, and are not seen normally or in gastritis unassociated with demonstrable Camp. pyloridis (Armstrong, unpublished).

Martin et al. (1984) reported that after treatment with tripotassium dicitrato bismuthate there was a lower relapse rate than after cimetidine, but in another study, one year after cessation of therapy the relapse rate after both drugs was 75% (Kang & Piper, 1982). Bismuth citrate is antibacterial to Camp. pyloridis (Marshall et al., 1985b). Metronidazole, which is active against 80% of isolates of Camp. pyloridis in Perth (Marshall et al., 1985b) has been reported to heal peptic ulcers (Shirokova, Filimonov & Poliakova, 1981), as has furazolidine (Zheng et al., 1985). McLean et al. (1984) have suggested that cimetidine may promote ulcer relapse by raising intragastric pH to provide an ideal growth environment for bacteria; and Camp. pyloridis multiplies between pH 6-9 and pH 8-0 (Collins, Goodwin & Blincow, unpublished). Fortunately Camp. pyloridis is very sensitive to most antibiotics; for isolates in Western Australia the MIC₉₀ of amoxycillin is 0-25 mg/l, of benzyl penicillin is 0-5 mg/l, and erythromycin is 0-25 mg/l (Goodwin, Blake & Blincow, in press).

Although prolonged treatment with cimetidine does not alter the relapse rate (Bardhan et al., 1982) a few ulcers remain healed, and omeprazole gives promise of lower relapse rates. The blood level of cimetidine after standard dosage is 2 mg/l, (Burland et al., 1975), but against Camp. pyloridis the MIC₉₀ is 800 mg/l and the MIC₉₀ of ranitidine is 64 mg/l (Goodwin, Blake & Blincow, 1986). Also omeprazole is without antibacterial action against Camp. pyloridis (Blincow & Goodwin, unpublished). Thus long term healing of some peptic ulcers may be achieved by drugs with little or no activity against Camp. pyloridis.

In conclusion, a fascinating new chapter of clinical bacteriology has been opened by the discovery of Camp. pyloridis. Recent studies of the organism suggest that it differs substantially from other campylobacters in respect of fatty acid composition and ultrastructure, and may ultimately be excluded from that genus (Goodwin et al., 1985). Whether antibacterial therapy aimed at eradication of Camp. pyloridis will assume a vital place in the treatment of peptic ulcer, and if so the precise form and duration of such therapy, are questions that will yet take some time to answer.

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