Abnormal absence of antibodies stimulating H$_2$-receptor mediated cyclic adenosine monophosphate (cAMP) production in peptic ulcer disease

Sr.,—We read with great interest the paper by Burman et al (Gut 1991; 32: 620–3). Using porcine gastric mucosal cells as an in vitro test system, the authors could not find any stimulatory effect on cyclic adenosine monophosphate (cAMP) production by sera or immunoglobulin (Ig) fractions of 57 patients with relapsing ulcer disease. As the authors reported, their results are in contrast with data obtained by De Lazzari et al.1 This group found in duodenal ulcer patients antibodies stimulating cAMP production in enriched guinea pig parietal cell extract. Thus, De Lazzari et al have suggested that duodenal ulcer disease may be caused by exposure to stimulating antibodies to H$_2$-receptors, which therefore are proposed as 'a new addition to the growing list of receptor antibodies in human diseases'. By using another in vitro test system, we have also investigated the possible role of cAMP stimulatory antibodies in peptic ulcer disease. We tested the effects of Ig preparations on cAMP production in cultured human gastric tumour cells (HGT-1; kindly provided by Dr C. Emami, INSERM U 55, Paris). These cells have H$_2$-receptors and are considered to be a useful tool for studies of cAMP mediated gastric acid secretion.2 Igs were derived from sera of 36 peptic ulcer patients. The patients were classified as adequate (AK; n=16) and inadequate responders to ranitidine (IR; n=20) by intragastric pH monitoring.3 Sera were not tested directly because of several undefined conditions which decreased cell viability from 91 to 52% after four hour incubation of the cells with 20% serum. IgG was isolated by column chromatography on protein G- sepharose and concentrated by micro-ultrafiltration. Other proteins were removed by precipitation with ammonium sulfate (1:6 mol/l). The Igs were tested at concentrations of 4 (IgG) and 1 (non-IgG) mg protein/ml medium. HGT-1 cells were grown as monolayers and incubated for 10, 30, 60, 180, and 360 minutes with Igs in the presence of 1 mmol/l phosphodiesterase inhibitor (IBMX). Standard IgG (Behringwerke) was used as control. The total amount of cAMP was measured by radioimmunoassay (Amer sham Buchler).

The basal value of cAMP production in HGT-1 cells was mean (SD) 10.7 (7.1) pmol/mg protein and was stimulated after 10 minutes incubation (10 IgG) to 80.4 (15.0) pmol/mg protein in all experiments (n=36). The stimulation could be blocked by the H$_2$-receptor antagonists cimetidine and ranitidine with IC$_{50}$ values of 0.400 and 0.034 µmol/l, respectively, confirming the presence and specificity of H$_2$-receptors on this cell type.4 No statistically significant stimulation of cAMP production could be obtained after incubation of HGT-1 cells with any Ig preparation tested (see Table).

Our results agree with those of Burman et al. In neither in vitro test systems were there evidence for cAMP stimulating antibodies in peptic ulcer patients. In addition, we conclude that antibodies to H$_2$-receptors do not cause an inadequate response to H$_2$-antagonists as has been assumed.5 However, despite these results, it can not be totally ruled out that auto-immunological processes have a role in specific subpopulations of patients with peptic ulcer disease. Moreover, the differing results of Burman et al and our group on one hand and De Lazzari et al on the other may be caused by the different in vitro test systems used. In particular, De Lazzari et al failed to detect any cAMP stimulatory effects on antibodies, unless the parietal cell content in cell suspensions was at least 50%.

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Non-colonic symptomatology and the irritable bowel: is it really of diagnostic value?

Sr.,—We read the paper by Maxton and colleagues on the diagnostic value of ‘non-colonic’ symptoms in the irritable bowel syndrome with interest.1 We have some major concerns about their study, however, which we hope they can clarify.

Our first concern relates to the study design. No healthy controls were included for comparison; this makes it difficult to determine the clinical significance of ‘non-colonic’ systems, which are known to be common in otherwise healthy people.2 The measurement of symptoms is also of concern because the reliability and validity of the symptom assessment was not documented. If the authors did not define and measure each of the symptoms carefully, these might have been interpreted in different ways by the interviewee and the patients, and thus the discriminatory ability of

Cyclic adenosine monophosphate (cAMP) production (pmol/mg protein) in human gastric tumour cells HGT-1 after incubation with Ig preparations derived from sera of ulcer patients with adequate and inadequate responses to ranitidine. (Values, mean (SD))
these symptoms inaccurately determined. The investigation also included patients with various organic diseases as controls. It is unclear, however, what symptoms led these patients to present, and it is likely that some of these patients also had irritable bowel syndrome. The gall stone group (who may have had incidental gall stones discovered during their evaluation). Such misclassification could have diluted the discriminant value of symptoms between patients with irritable bowel syndrome and organic disease.

Our second concern relates to the statistical analyses. The authors seem to have relied largely on univariate analyses (χ² tests). As 78 tests of association were performed (13 symptoms times six comparison groups), however, several spurious significant results could have been obtained just by chance alone. One way to adjust for the number of tests undertaken would be to multiply each p value by the number of comparisons. When evaluated in this way, only p values less than 0.0006 would be significant at the 5% level. While the authors did use a multiple logistic regression analysis, it appears that the same symptoms could distinguish irritable bowel syndrome from each of the control groups using logistic regression analysis; instead all the organic disease patients were lumped together (a criticism that the authors justifiably levy at past studies). In addition, their analysis is likely to have seriously overestimated the discriminant value of the symptoms identified; it is well recognised that estimates based on a single data set are typically biased towards giving a good fit of the data. The authors have not estimated a model of the symptoms to identify any symptoms that might be minimising possible differences of interpretation. Irritable bowel syndrome is a common disorder and, as Dr Prather suggests, could easily coexist with other organic diseases. In the absence of a diagnostic test for irritable bowel syndrome, there is no easy way of preventing or excluding this possibility. As Dr Prather rightly points out, however, this would reduce rather than increase the discriminant value of the symptoms in separating organic from functional bowel disease thus making our findings more reliable. The gall stone patients included in the study had symptoms suggestive of this disorder at first clinic attendance which improved after cholecystectomy. None had gall bladder disease as an incidental finding.

The statistical problem of multiple comparisons is well known but remains a potential flaw in statistical testing (without proper adjustment) to establish definitive relationships in inflammatory bowel disease thus making our findings more reliable. The gall stone patients included in the study had symptoms suggestive of irritable bowel syndrome at first clinic attendance which improved after cholecystectomy. None had gall bladder disease as an incidental finding.

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