The important difference between these two studies is that Gaslander et al found a raised plasma cholecystokinin concentration in rats with duodenogastric reflux (at two weeks and six weeks), whereas we found a normal plasma cholecystokinin concentration (at six months). Although cholecystokinin receptor antagonist devazepide did not completely inhibit the tropic effect of the operation, they suggest that gastrin may also be important as an intermediary, our own data clearly support this interpretation. In the context of promoting neoplasia, the longterm hypergastrinemia may be at least as relevant as the more transient hypercholecystokininemia. That cholecystokinin alone could play a part in the induction of pancreatic cancer in patients with previous gastrrectomy is confirmed by another study (again not cited) showing enhanced pancreatic carcinogenesis in rats with distal gastrectomy, an operation that lowers serum gastrin. Using a different surgical model, massive entercetomy, we found two candidate hormones for the role of pancreatoctropin: enteroglucagon and cholecystokinin. Cholecystokinin may be more important because the cholecystokinin receptor antagonist longlumide completely abolished the effect of this operation on pancreatic growth. We have previously speculated on the relation between these two hormones. The strongest stimulus to pancreatic growth and carcinogenesis in our experience has been pancreatoctropic biversion; here again cholecystokinin seems to be the key intermediary, and longlumide prevents the response.

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Reply

EDITOR,—We appreciate the interest that Professors Williamson and Watanapa have shown in our paper and apologise for failing to reference the important contributions they have made in the field of pancreatic growth and carcinogenesis.

These authors suggest that an important difference between their study and ours is that we saw an increase in circulating cholecystokinin concentrations and they did not. In fact mean basal cholecystokinin concentrations in their study were 59% higher in animals with split gastrojejunostomy than controls, although this did not reach statistical significance (Gut 1984; 35: 46–50). The title of this paper was exciting because our laboratory has without success tried to show expression of intercellular adhesion molecule-1 (ICAM-1) on autologous human intestinal adenomas or adenomas of the cecum in the 50% of individuals with diabetes, or healthy gut (unpublished findings). This is also in accordance with other reports.1–4 We were able to upregulate ICAM-1 expression in the human adenocarcinoma cell line HCT-116; however, by using a monoclonal antibody, particularly the combinations interferon γ/IFN α/γ tumour necrosis factor α and IFN γ/interleukin 1 in the presence of butyrate.5 It was therefore quite intriguing when the title of the article by Fujimura and Kihara suggested that the follicle associated epithelium of Peyer’s patches expresses ICAM-1. Unfortunately, the study had been performed in rats rather than humans and the title was further misleading because the localisation described for ICAM-1 was restricted to a subepithelial layer of fibroblasts. Contrasting this finding, which was claimed to be related to the unique immunobiology of follicle associated epithelium, the authors were unable to show expression of ICAM-1 beneath the villus epithelium. They therefore speculated that the massive lymphocyte traffic between follicle associated epithelium and the lymphoid follicles of Peyer’s patches might be explained by the topical ICAM-1 expression. In our opinion this hypothesis is not plausible. Lymphocytes in follicle associated epithelium are unevenly distributed, being particularly concentrated in small aggregates related to the ‘membrane’ cells; outside these foci the intraepithelial occurrence of lymphocytes is more similar to that seen in the villus epithelium in terms of numerical as well as phenotypic distribution.3–4 In humans the diffusely scattered intraepithelial lymphocytes are mainly CD8 + T cells8 of the T cell receptor αβ variety with a small (4–5%) population of γδ T cells9 present. It follows that only adhesion molecule suggested to be important for their homing to the epithelium is the integrin αEβ7 (detected by monoclonal antibody HML-1),10 which apparently binds to the epithelial E-cadherin.11 Intraepithelial lymphocytes found in relation to the membrane cells might rather be ascribed to the antigen transporting capacity of these specializations. In contrast, membrane cells in the 50% of such aggregated lymphocytes consist of B cells—apparently representing topical extensions of the underlying follicles— together with a comparatively high proportion of CD19+ and CD20+ B cells,12 but without admixture of the T cell receptor αβ subset.9 It is indeed difficult
to accept that the rather even distribution of ICAM-1 below the follicle associated epithelium, as reported by Fujimura and Kihara, should have anything to do with the numerically and phenotypically heterogeneous distribution of lymphocytes in this epithelium.

The authors further discuss extensively the nature of membrane cells; without reservation it is claimed that these cells express MHC class II molecules and therefore may be present in luminal antigens to T cells. This area is quite controversial, however, and the first study on class II expression in rat Peyer’s patches reported that the complete follicle associated epithelium is negative.13 The antigen presenting capacity of membrane cells is therefore questionable although they are probably some extent able to degrade foreign material as suggested by their lysosome like structures16 and cadhepin E expression.17 We have recently proposed that membrane cells might provide an opportunity for intraparadosed B cells to present partially processed luminal antigens to CD4+ memory T cells, thereby promoting diversification of mucosal immune responses.

In view of this immunobiological complexity of gut associated lymphoid tissue we feel that it is too speculative when Fujimura and Kihara on the basis of their findings in rat Peyer’s patches of blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

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5 Kvale D, Kračji P, Brandtzæg P. Expression and regulation of adhesion molecules ICAM-1 (CD54) and LFA-1 on HLA-DR+ cells in human intestinal epithelial cell lines. Scand J Immunol 1992; 35: 659–70.

6 Kvale D, Brandtzæg P. Constitutive and cytokine-induced expression of HLA molecules, secretory components (SC), and ICAM-1 are modulated by butyrate in the colonic epithelial cell line HT-29. Gut 1995; 36: 42.


Reply

EDITOR,—We are grateful to Drs Brandtzæg and Farstad for drawing attention to our paper. They pointed out that ICAM-1 could not be shown in human epithelium of the normal or diseased human gut (unpublished findings), but could in human adenocarcinoma cell line HT-29. Recently, we confirmed ICAM-1 expression on subepithelial fibroblasts, normal epithelial gonules, and migrating cells in rat Peyer’s patches, but not in humans. We do not know how to explain this discrepancy and suppose that the difference in findings may be related to different species or the properties of the monoclonal antibodies. We agreed that it was too speculative when we, on the basis of our findings in rat Peyer’s patches, suggested blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

We also found very interesting their description of the heterogeneity of membrane cell characteristics of human Peyer’s patches—that is, that the B cells are strikingly heterogeneous with characteristics of both mantle (slgD+ slgM+) and marginal (slgD– slgM+) zone lymphocytes, and that some lymphocytes in membrane cell pockets among follicle associated epithelium showed Ki-67 and CD45RO weakly.1 They were therefore suggested that B lymphocytes can proliferate and differentiate more freely in the membrane cell pockets. These findings and suggestions are very impressive and we agree with their conclusions.

We agree also that it is still controversial whether membrane M cells or any other follicle associated lymphoid tissue express ICAM-1. Further investigations are also required to find the mechanism regulating lymphocytes migration into the folically associated epithelium of human gut associated lymphoid tissue.

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Ménétrier’s disease

EDITOR,—We read with interest the case report by Bayerdorffer et al showing Helicobacter pylori is a potential cause of Ménétrier’s disease (Gut 1994; 35: 701). The findings in their patient showed clearly that H pylori gastritis can present as hypertrophic gastritis combined with protein loss and that eradication of the H pylori infection can lead to rapid disappearance of the Ménétrier-like lesion and restoration of normal gastric mucosa. We disagree, however, with the authors’ presumption that Ménétrier’s disease and hypertrophic gastropathy are synonymous. There are many reasons for believing that equating the two terms is ill advised. (1) A variety of conditions can cause enlarged gastric folds. In addition to the true ‘hypertrophic gastropathies’ Ménétrier’s disease and Zollinger-Ellison syndrome, the hypertrophy of gastric folds are seen in hypertrophic gastritis associated with various infections, including H pylori, cytomegalovirus, histoplasmosis, and syphilis, and in miscellaneous other diseases such as sarcoidosis, allergic (eosinophilic) gastritis, and Cronkhite-Canada syndrome. (2) While increased gastric protein loss can be found occasionally in many disorders that are associated with large gastric folds, increased protein loss is not a universal feature of any of these disorders. It is typically lacking in Zollinger-Ellison syndrome, and its reported occurrence in Ménétrier’s disease is variable. (3) We believe that the conditions associated with enlarged gastric folds, in particular Ménétrier’s disease and hypertrophic gastropathy are quite distinct disorders that require different diagnostic criteria for this gastropathy. (4) The concept that massive foveal hyperplasia is a definitive feature of true Ménétrier’s disease is greatly strengthened by studies showing that there is an accompanying increase in the distribution and activity of transforming growth factor α in the gastric mucosa in Ménétrier’s disease. In addition, the experimental induction of an excess of gastric transforming growth factor α in transgenic mice results in similar mucosal cell hyperplasia.4 It is highly probable that ‘hypertrophic hypersecretory gastropathy’ (Schindler’s disease), another distinctive entity that is sometimes mistakenly designated as Ménétrier’s disease, is probably a manifestation of H pylori gastritis with large folds.

We urge authors and editors not to use the term Ménétrier’s disease as a generic designation when describing any condition associated with enlarged rugae. The eponym should be limited to those rare cases that fulfil Ménétrier’s original description of massive foveal hyperplasia without gastritis. This approach is essential from nosologic and patient treatment standpoint if the varied aetologies and resulting treatment implications of hypertrophic gastropathy are to remain clear cut. As researchers Bayerdorffer et al we would have preferred to see it termed simply H pylori associated hypertrophic gastritis.
Expression of adhesion molecules in human Peyer's patches.

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Gut 1995 36: 944-945
doi: 10.1136/gut.36.6.944-a

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