The important difference between these two studies is that Gaslander et al found a raised plasma cholecystokinin concentration in rats with duodenogastric reflex (at two weeks and six weeks), whereas we found a normal plasma cholecystokinin concentration (at six months). A raised cholecystokinin receptor antagonist devazepide did not completely inhibit the trophic 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 hypergastrinaemia may be at least as relevant as the more transient hypercholecystokininemia. That cholecystokinin alone could play a part in the incidence of pancreatic cancer in patients with previous gastrectomy is confirmed by another study (again not cited) showing enhanced carcinogenic carcinogenesis in rats with distal gastrectomy, an operation that lowers serum gastrin.

Using a different surgical model, massive enteroctectomy, we found two candidate hormones for the role of pancreaticotropin: enteroglucagon and cholecystokinin.1,4 Cholecystokinin may be the more important because the cholecystokinin receptor antagonist lorglumide completely abolished the effect of this operation on pancreatic growth. We have previously speculated on the relation between these two hormones.2 The strongest stimulus to pancreatic growth and carcinogenesis in our experience has been pancreatico bile diversion; here again cholecystokinin seems to be the key intermediary, and lorglumide prevents the response.5

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Letters

EFFECT—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 gastrojejunoanastomosis than controls, although this did not reach statistical significance (for another study in the 50% of cases).11 It is probable that in a larger series it is probable that this would have reached statistical significance. Furthermore, in their study of partial gastrectomy, basal cholecystokinin concentrations were only 46% above control levels and were well below those seen in their split gastrojejunoanastomosis group, but here they concluded that partial gastrectomy increases plasma cholecystokinin.12 It is interesting to note that humans with longstanding pancreatic duodenogastric reflex have increased concentrations of cholecystokinin postprandially, although their gastrin concentrations are quite normal.13 Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the trophic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy.14

We do not fully agree with the conclusion drawn that the study of distal gastrectomy in rats confirms that cholecystokinin may play a part in the increased incidence of pancreatic cancer after this operation, because in their study no trophic effect on the pancreas was seen. Furthermore, while we agree that these hormones are of importance for pancreatic growth and neoplasia in the rat, their role in human neoplasia, the common tumor type in humans, is controversial.14-18

The authors go on to state that they found two candidate hormones, enteroglucagon and cholecystokinin, for the pancreaticotrophic effect associated with the small bowel resection and pancreaticobiliary diversion. However, the increase of cholecystokinin and enteroglucagon and pancreatic growth associated with these surgical procedures had been described earlier.5-7

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Expression of adhesion molecules in human Peyer's patches

EDITOR—We became aware of a publication in Gut by Fujimura and Kihara on human Peyer's patches while reviewing published works (Gut 1994; 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 murine Peyer's patches or diseased 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 HT-29; however, by Fujimura and Kihara particularly the combinations interferon γ (IFN-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 ICAM-1 beneath the villus epithelium. Therefore they 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 concentrated, 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.5-9 In humans the diffuse scattered intraepithelial lymphocytes are mainly CD8+ T cells8;9 of the T cell receptor αβ variety with a small (4-5%) admixture of T cell receptor γδ expressing cells.10 The finding 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 the αE-integrin of epithelial cell membrane.11 Probably such aggregated lymphocytes consist of B cells — apparently representing topical extensions of the underlying follicles — together with a comparatively high proportion of CD4+ T cells (memory-helper cell phenotype),12 but without admixture of the T cell receptor γδ subset.13 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 furthermore discuss extensively the nature of membrane cells; without reservation it is claimed that these cells express MHC class II molecules and therefore may be able to present 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 It has been contradicted subsequently but we found human membrane cells to be negative for HLA-DR compared with the strongly positive remaining follicle associated epithelium. 14 The antigen presenting capacity of membrane cells is therefore questionable although they are probably to some extent able to degrade foreign material as suggested by their lysosome like structures 16 and cathepin E expression. 17 We have recently proposed that membrane cells might provide an opportunity for juxtaposed 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 blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

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16 Allan CH, Mendlack DL, Trier JS. Rat intestinal M cells contain acidic endosomal-lysosomal compartments and express class II major histocompatibility complex determinants. Gastroenterology 1989; 96: 806-10.

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 in human subepithelial fibroblasts, high endothelial venules, 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 agree 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 associated ICAM expression in human Peyer's patches - that is, that the B cells are strikingly heterogeneous with characteristics of both manti (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, therefore, suggested that B lymphocytes can proliferate and differentiate on topically in the membrane cell pockets. Their findings and suggestions are very impressive and we agree with their conclusions.

We agree also that it is still controversial whether membrane cells and all the gut associated lymphoid tissue express HLA-DR. Further investigations are also required to find the mechanism regulating lymphocyte migration into the follicle 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 as 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 hyperplasia and restoration of normal gastric mucosa. We disagree, however, with the authors' presumption that Ménétrier's disease and hypertrophic gastritis 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 'hyperplastic gasropathies' Ménétrier's disease and Zollinger-Ellison syndrome are examples of conditions in which 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, 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 depending on different authors' diagnostic criteria for this gastropathy. (3) The cases described in 1888 by Ménétrier as 'polyaedrone en nappe' had as their cardinal feature exuberant proliferation of gastric mucous cells. This is a distinct entity that has been appropriately termed 'massive foveolar hyperplasia'.2 3 Furthermore, Ménétrier's description and illustrations do not suggest that chronic gastritis, the hallmark of H pylori gastritis, is a feature of Ménétrier's disease, is probably a manifestation of H pylori gastritis with large folds.4 We urge authors and editors not to use the term Ménétrier's disease as a generic designation for all conditions associated with enlarged rugae. The eponym should be limited to those rare cases that fulfill Ménétrier's original description of massive foveolar hyperplasia without gastritis. This approach is essential from nosologic and patient care points of view if the varied aetiologies and resulting treatment implications of hypertrophic gastropathy are to be recognized. Drs Bayerdorffer et al 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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