The important difference between these two studies is that Gasslander 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) in rats with 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 longstanding pathologic gastrin may also be important as a candidate hormone for the increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal.

Using a different surgical model, massive enterectomy, we found two candidate hormones for the role of pancreatic tropic: enteroglucagon and cholecystokinin. Cholecystokinin may be the 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 pancratotrophic biliary diversion; here again cholecystokinin seems to be the key intermediary, and longlumide prevents the response.

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Letters

We have appreciated 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.15 Statistical variability.2 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 and lower than those seen in their split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal.

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 previous 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 human Peyer’s patches. Therefore, we were particularly interested in the findings of Arai and Ichikawa that the ICAM-1 expression was upregulated in human Peyer’s patches compared to control rat intestine.13–16 It was therefore quite intriguing when the title of the article by Fujimura and Kihara suggested that the ICAM-1 expression might be upregulated in human Peyer’s patches. 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 able to show expression of ICAM-1 in 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 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.2,3 In humans the diversely scattered intraepithelial lymphocytes are mainly CD8+ T cells8 where the majority of lymphocytes, particularly in small bowel, are CD8+. They result in the fact that the 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 peripheral E-cadherin.6 However, the lymphocytes found in relation to the membrane cells might rather be ascribed to the antigen transporting capacity of these special lymphocytes. In fact, only 50% of such aggregated lymphocytes consist of B cells—apparently representing topical extensions of the underlying follicles—whereas 50% of the T cells (membrane helper phenotype),12 but without adhesion of the T cell receptor y6 subset.13 It is indeed difficult

References

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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.15 Statistical variability.2 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 and lower than those seen in their split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal. Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the tropic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. It is interesting to note that humans with longstanding pathologic duodenogastric reflux have increased concentrations of cholecystokinin postoperatively, although their gastrin concentrations are quite normal.
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 Peyrer's patches reported that the complete follicle associated epithelium is negative.13 This has been contested 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 some extent able to degrade foreign material as suggested by their lysosome like structures16 and cathepsin 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 Peyrer's patches of blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

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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, high endothelial venules, and migrating cells in rat Peyrer’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 Peyrer’s patches, suggested blocking of ICAM-1 as potential treatment for inflammatory bowel disease in the future.

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

We also agree that it is still controversial whether membrane cells at all sites of the gut associated lymphoid tissue express HLA-DR. Further investigations are also required to find the mechanism regulating lymphocytes migration into the follicle associated epithelium of human gut associated lymphoid tissue.
Expression of adhesion molecules in human Peyer's patches.

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