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). A cholecystokinin receptor antagonist dezapevde 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 longer hypergastrinemia 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 pancreatic 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 pancreateotropin: enteroglucagou 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 pancreatoecllular diversion; here again cholecystokinin seems to be the key intermediary, and lorglumide prevents the response. 6

R C N WILLIAMSON
Department of Surgery, Hammeater Hospital, Du Cane Road, London P WATANAPA
Department of Surgery, Siriraj Hospital, Bangkok, Thailand


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 gastrojejunoanastomosis than controls, although this did not reach statistical significance. 1

More recently, however, our larger series is probably 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 gastrojejunoanastomosis group, but here they concluded that partial gastrectomy increases plasma cholecystokinin. 2 It is interesting to note that humans with longstanding pancreatic disease show increased concentrations of cholecystokinin postprandially, although their gastrin concentrations are quite normal. 3 Although gastrin concentrations were increased after gastrectomy, 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 gastrojejunoanastomosis and do not lower those seen in their split gastrojejunoanastomosis group.

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 head resection because this study showed 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 the ductal adenocarcinoma, the common tumour type in humans, is controversial. 4,8

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

T E ADRIAN
Cancer Center, Creighton University School of Medicine, Omaha, USA

T GASSLANDER
Department of Surgery, University Hospital, Linköping, Sweden


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 epithelium of Peyer’s patches drawn from patients suffering from acute or chronic appendicitis or in children with recurrent appendicitis. We found the follicles of Peyer’s patches positive. It is 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 demonstrate 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. 5,9 In humans the diffusely scattered intraepithelial lymphocytes are mainly CD8+ T cell* cells 8 of the T cell receptor a/b variety with a small (4–5%) admixture of T cell* cells. 10 It is therefore concluded that only adhesion molecule suggested to be important for their homing to the epithelium is the integrin aE87 (detected by monoclonal antibody HML-1), 10 which apparently binds to the epithelial E-cadherin (ICAM-1). 10,11 This is in contrast to the findings of Fujimura and Kihara. The lymphocytes found in relation to the membrane cells might rather be ascribed to the antigen transporting capacity of these special epithelial cells. In fact, up to 50% of such aggregated lymphocytes consist of B cells—apparently representing topical extensions of the underlying follicles— together with a comparatively high proportion of CD4+ CD45R0+ T cells (memory-helper phenotype), 12 but without admixture of the T cell receptor y6 subset. 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 CD4+ 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 This 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 15 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 structures16 and cathepsin E expression.15 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.17

In view of this immunological 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 we suggest blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

P BRANDTZÆG
T N FARSTAD
Laboratory for Immunohistochernistry
Immunopathology (LIIPAT),
Institute of Pathology,
The National Hospital, Rikshospitalet,
N-0027 Oslo, Norway

6 Kvale D, Brandtzæg P. Constitutive and cytokine-induced expression of HLA molecules, secretory component (SC), and ICAM-1 are modulated by butyrate in the colonic epithelial cell line HT-29. Gut 1995; 37: 465–71.
9 Farstad IN, Halstensen TS, Fausa O, Brandtzæg P. Heterogeneity of M-cell associated B and T cells in human Peyer’s patches. Immunology 1993; 83: 457–64.

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 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 B and T cells in human Peyer’s patches—that is, that the B cells are strikingly heterogeneous with characteristics of both mantle (sIgD sIgM+) and marginal (sIgD sIgM-) zone lymphocytes, and that some lymphocytes in membrane cells populating follicle associated epithelium showed Ki-67 and CD45RO strongly.1 They, therefore, suggested that B lymphocytes can proliferate and concentrate in the mucosal 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 sites of 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.

Y FUJIMURA
T KIHARA
Division of Gastroenterology,
Department of Medicine, Kawasaki Medical School,
577 Matsushita, Kurashiki 701-01, Japan

1 Farstad IN, Halstensen TS, Fausa O, Brandtzæg P. Heterogeneity of M cell associated B and T cells in human Peyer’s patches. Immunology 1993; 83: 457–64.

Ménétrier’s disease

EDITOR.—We read with interest the case report by Bayerdorff et al showing that Helicobacter pylori is a potential cause of Ménétrier’s disease (Gut 1994; 35: 701–4). 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 peptic ulceration and restoration of normal gastric mucosa. We disagree, however, with the authors’ assumption 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 gas- tropathies Ménétrier’s disease and Zollinger–Ellison syndrome enlargement 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 gastric folds, the total 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. In rare cases, Ménétrier’s disease is described in patients with malignant large gastric cell carcinoma. (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 change 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.5

We urge authors and editors not to use the term Ménétrier’s disease as a generic designation for any condition associated with enlarged rugae. The eponym should be limited to those rare cases that fulfill Ménétrier’s original description of massive foveal hyperplasia without gastritis. This approach is essential from nosologic and patient treatment standpoint if the varied aetiologies and resulting treatment implications of hypertrophic gastropathy are to be considered in their true context. We would like Bayerdorff et al we would have preferred to see it termed simply H pylori associated hypertrophic gastritis.