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). As the 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 hypergastrinaemia may be at least as relevant as the more transient hypercholecystokininaemia. That cholecystokinin alone could play a part in the increased 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,[2] an operation that lowers serum gastrin.

Using a different surgical model, massive enterectomy, we found two candidate hormones for the role of pancreatotropin: enteroglucagon and cholecystokinin.[3 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.[5] The strongest stimulus to pancreatic growth and carcinogenesis in our experience has been pancreatobiliary diversion; here again cholecystokinin seems to be the key intermediary, and lorglumide prevents the response.[6 7]

R C N WILLIAMSON
Department of Surgery, Hammersmith Hospital, Du Cane Road, London

P WATANAPA
Department of Surgery, Siriraj Hospital, Bangkok, Thailand

1 Watanapa P, Flaks B, Oztas H, Deprez PH, Calam J, Williamson RCN. Duodenogastric reflux enhances growth and carcinogenesis in the rat pancreas. *Br J Surg* 1992; **79:** 791–4.
2 Watanapa P, Flaks B, Oztas H, Deprez PH, Calam J, Williamson RCN. Enhancing effect of partial gastrectomy on pancreatic carcinogenesis. *Br J Cancer* 1992; **65:** 383–7.
3 Watanapa P, Beardshall K, Calam J, Williamson RCN. Tropic role of enteroglucagon in pancreatic adaptation to subtotal enterectomy. *Br J Surg* 1991; **78:** 917–20.
4 Watanapa P, Egan M, Deprez PH, Calam J, Sarraf CE, Alison MR, *et al*. Role of cholecystokinin in pancreatic adaptation to massive enterectomy. *Gut* 1992; **33:** 959–64.
5 Watanapa P, Williamson RCN. Experimental pancreatic hyperplasia and neoplasia: effects of dietary and surgical manipulation. *Br J Cancer* 1993; **67:** 877–84.
6 Watanapa P, Efa EF, Beardshall K, Calam J, Sarraf CE, Alison MR, *et al*. Inhibitory effect of cholecystokinin antagonist on the proliferative response of the pancreas to pancreatobiliary diversion. *Gut* 1991; **32:** 1049–54.
7 Watanapa P, Flaks B, Oztas H, Deprez PH, Calam J, Williamson RCN. Inhibitory effect of a cholecystokinin antagonist on pancreatic carcinogenesis after pancreatobiliary diversion. *Br J Cancer* 1993; **67:** 663–7.

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 because of data variability.[1] 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.[2] It is interesting to note that humans with longstanding primary duodenogastric reflux have increased concentrations of cholecystokinin postprandially, although their gastrin concentrations are quite normal.[3] 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.

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 gastrectomy, because in this 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 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 pancreatotrophic effect associated with massive 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.[9–11]

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

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

1 Watanapa P, Flaks B, Oztas H, Deprez PH, Calam J, Williamson RCN. Duodenogastric reflux enhances growth and carcinogenesis in the rat pancreas. *Br J Surg* 1992; **79:** 791–4.
2 Watanapa P, Flaks B, Oztas H, Deprez PH, Calam J, Williamson RCN. Enhancing effect of partial gastrectomy on pancreatic carcinogenesis. *Br J Cancer* 1992; **65:** 383–7.
3 Wilson P, Welch NT, Hinder RA, Anselmino M, DeMeester TR, Adrian TE. Abnormal plasma gut hormones in pathologic duodenogastric reflux and their response to surgery. *Am J Surg* 1993; **165:** 169–77.
4 Herrington MK, Adrian TE. On the role of cholecystokinin in pancreatic cancer. *Int J Pancreatol* (in press).
5 Adrian TE, Permert J, Wang Q, Herrington MK, Takahashi T, Larsson J, *et al*. Is CCK involved in pancreatic ductal cell cancer? *Dig Dis Sci* 1994; **39:** 1814.
6 Herrington MK, Permert J, Kazakoff K, Pour PM, Zucker KA, Bilchik AJ, *et al*. Effect of high fat diet and cholecystokinin receptor blockade on pancreatic growth and tumor initiation in the hamster. *Carcinogenesis* 1993; **14:** 1021–6.
7 Herrington MK, Permert J, Kazakoff K, Pour PM, Adrian TE. Effect of CCK receptor blockade on pancreatic tumor initiation and promotion in hamsters fed high fat diet. *Clin Res* 1993; **41:** 708A.
8 Herrington MK, Permert J, Kazakoff K, Pour PM, Zucker KA, Bilchik AJ, *et al*. Effects of a raw soya diet and cholecystokinin receptor blockade on pancreatic growth and tumor initiation in the hamster. *Cancer Lett* 1994; **82:** 7–16.
9 Gornacz GE, Ghatei MA, Al-Mukhtar MYT, Yeats JC, Adrian TE, Wright NA, *et al*. Plasma enteroglucagon and CCK levels and cell proliferation in defunctioned small bowel in the rat. *Dig Dis Sci* 1984; **29:** 1041–9.
10 Miazza BM, Ghatei MA, Adrian TE, Bloom SR, Dowling RH. Are hormonal factors responsible for the intestinal and pancreatic hyperplasia of pancreatico-biliary diversion (PBD)? *Regul Pept* 1982; **3:** 77.
11 Gasslander J, Axelsson J, Hakansson R, Ihse I, Lilja I, Rehfeld J. Cholecystokinin is responsible for growth of the pancreas after PBD in rats. *Scand J Gastroenterol* 1990; **25:** 1060–5.

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) by human intestinal epithelium in the normal 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 certain cytokines,[5] particularly the combinations interferon γ (IFN γ)/tumour necrosis factor α, and IFN γ/interleukin 1 in the presence of butyrate.[6] 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 detect 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.[7–9] In humans the diffusely scattered intraepithelial lymphocytes are mainly $CD8^+$ T cells[7 8] of the T cell receptor α/β^+ variety with a small (4–5%) admixture of T cell receptor γ/δ^+ cells[9]; 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 epithelial E-cadherin.[11] The high density of lymphocytes found in relation to the membrane cells might rather be ascribed to the antigen transporting capacity of these specialised epithelial cells. In fact, about 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 γ/δ^+ 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 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 $CD4^+$ 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] 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 structures[16] 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.[12]

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 suggest blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

P BRANDTZAEG
I N FARSTAD
Laboratory for Immunohistochemistry and Immunopathology (LIIPAT), Institute of Pathology, The National Hospital, Rikshospitalet, N-0027 Oslo, Norway

1 Sturgess RP, MaCartney JC, Makgoba MW, Hung C-H, Haskard DO, Ciclitira PJ. Differential upregulation of intercellular adhesion molecule-1 in coeliac disease. *Clin Exp Immunol* 1990; **82:** 489–92.
2 Smart CJ, Calabrese A, Oakes DJ, Howdle PD, Trejdosiewicz LK. Expression of the LFA-1 β2 integrin (CD11a/CD18) and ICAM-1 (CD54) in normal and coeliac small bowel mucosa. *Scand J Immunol* 1991; **34:** 299–305.
3 Scheynius A, Engstrand L. Gastric epithelial cells in Helicobacter pylori-associated gastritis express HLA-DR but not ICAM-1. *Scand J Immunol* 1991; **33:** 237–41.
4 Malizia G, Calabrese A, Cottone M, Raimondo M, Trejdosiewicz LK, Smart CJ, *et al.* Expression of leukocyte adhesion molecules by mucosal mononuclear phagocytes in inflammatory bowel disease. *Gastroenterology* 1991; **100:** 150–9.
5 Kvale D, Krajči P, Brandtzaeg P. Expression and regulation of adhesion molecules ICAM-1 (CD54) and LFA-3 (CD58) in human intestinal epithelial cell lines. *Scand J Immunol* 1992; **35:** 669–76.
6 Kvale D, Brandtzaeg 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; **36:** 737–42.
7 Bjerke K, Brandtzaeg P, Fausa O. T cell distribution is different in follicle-associated epithelium of human Peyer's patches and villous epithelium. *Clin Exp Immunol* 1988; **74:** 270–5.
8 Brandtzaeg P, Bjerke K. Immunomorphological characteristics of human Peyer's patches. *Digestion* 1990; **46** (suppl 2): 262–73.
9 Farstad IN, Halstensen TS, Fausa O, Brandtzaeg P. Do human Peyer's patches contribute to the intestinal γ/δ T-cell population? *Scand J Immunol* 1993; **38:** 451–8.
10 Cepek KL, Parker CM, Madara JL, Brenner MB. Integrin $\alpha^E\beta7$ mediates adhesion of T lymphocytes to epithelial cells. *J Immunol* 1993; **150:** 3459–70.
11 Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL, *et al.* Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the $\alpha^E\beta7$ integrin. *Nature* 1994; **372:** 190–3.
12 Farstad IN, Halstensen TS, Fausa O, Brandtzaeg P. Heterogeneity of M-cell-associated B and T cells in human Peyer's patches. *Immunology* 1994; **83:** 457–64.
13 Mayrhofer G, Pugh CW, Barclay AN. The distribution, ontogeny and origin in the rat of Ia-positive cells with dendritic morphology and of Ia antigen in epithelia, with special reference to the intestine. *Eur J Immunol* 1983; **13:** 112–22.
14 Brandtzaeg P, Baklien K, Bjerke K, Rognum TO, Scott H, Valnes K. Nature and properties of the human gastrointestinal immune system. In: Miller K, Nicklin S, eds. *Immunology of the gastrointestinal tract.* Vol I. Boca Raton, Florida: CRC Press, 1987: 1–86.
15 Bjerke K, Brandtzaeg P. Lack of relation between expression of HLA-DR and secretory component (SC) in follicle-associated epithelium of human Peyer's patches. *Clin Exp Immunol* 1988; **71:** 502–7.
16 Allan CH, Mendrick DL, Trier JS. Rat intestinal M cells contain acidic endosomal-lysosomal compartments and express class II major histocompatibility complex determinants. *Gastroenterology* 1993; **104:** 698–708.
17 Finzi G, Cornaggia M, Capella C, Fiocca R, Bosi F, Solcia E, *et al.* Cathepsin E in follicle associated epithelium of intestine and tonsils: localization to M cells and possible role in antigen processing. *Histochemistry* 1993; **99:** 201–11.

Reply

EDITOR,—We are grateful to Drs Brandtzaeg 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 property 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 heterogenous with characteristics of both mantle ($sIgD^+$ $sIgM^+$) and marginal ($sIgD^-$ $sIgM^+$) 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 topically 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 cells in various 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.

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

1 Farstad IN, Halstensen TS, Fausa O, Brandtzaeg P. Heterogeneity of M cell associated B and T cells in human Peyer's patches. *Immunology* 1994; **83:** 457–64.

Ménétrier's disease

EDITOR,—We read with interest the case report by Bayerdorffer *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 symptoms 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 'hyperplastic gastropathies' – Ménétrier's disease and Zollinger-Ellison syndrome,[1] similar 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 lymphocytic gastritis, 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, excessive 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 'polyadenome 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 descriptions and illustrations do not suggest that chronic gastritis, the hallmark of *H pylori* associated gastritis, was present in his cases. (4) The concept that massive foveolar 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 mucous cell hyperplasia.[4] (5) It is highly probable that 'hypertrophic hypersecretory gastropathy' (Schindler's disease), another distinctive entity that is sometimes mistakenly designated 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 and all conditions associated with enlarged rugae. The eponym should be limited to those rare cases that fulfil Ménétrier's original description of massive foveolar hyperplasia without gastritis. This approach is essential from nosologic and patient treatment standpoints if the varied aetiologies and resulting treatment implications of hypertrophic gastropathy are to remain clear cut. As for the case described by Bayerdorffer *et al* we would have preferred to see it termed simply *H pylori* associated hypertrophic gastritis.