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 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.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.

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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They pointed out that ICAM-1 could not be shown in human epithelium of the normal or diseased human gut (unpublished findings), but could in human adenocarcinoma cell line HT-29.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 heterogeneous 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.

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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.

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Reply

EDITOR,—We agree with Hendrix and Yardley that *Helicobacter pylori* infection with hypertrophic gastric folds and a protein loss syndrome should in future be termed merely 'Helicobacter pylori induced hypertrophic gastritis' and not Ménétrier's disease; and further, that on detection of hypertrophic gastric folds a search should be carried out for other possible infectious causes or underlying diseases with hypertrophic folds, or both. In the past, this has not been done, either in case reports or reviews of large numbers of cases of Ménétrier's disease. In particular, most publications failed to evaluate inflammatory infiltration as an exclusion criterion for Ménétrier's disease. Thus, for example, Schindler¹ described Ménétrier's disease in his article on 'hypertrophic glandular gastritis', and Scharschmidt² in his review, expressly emphasised that 'round cell infiltration of the lamina propria was also frequently noted and was very prominent in some cases' of Ménétrier's disease.

The suggestion that only massive foveolar hyperplasia in the absence of gastritis should be termed Ménétrier's disease, was made comparatively late by Appelman,³ but was often ignored. The cases of Ménétrier's disease reported from the Mayo Clinic were, for example, accepted as being Ménétrier's disease when 'a hypertrophic gastropathy with hypoproteinaemia' presented. Indeed, in the first synopsis of 43 patients, a 'systematic histological study of the gastric mucosa' was even deliberately not undertaken.⁴ In the latest review of the Mayo Clinic cases, it was then shown that a comparatively large percentage of these patients had a 'lymphocytic gastritis', also with loss of protein.⁵ If we recall that the former 'gastritis en nappe'⁶ has more recently been shown to be a special form of lymphocytic gastritis,⁷ and that this gastritis can also include appreciable foveolar hyperplasia, and if we also take into account the fact that Ménétrier made reference to 'polyadénomes gastriques', which he further subdivided into 'polyadénomes polypeux' and 'polyadénomes en nappes', there are justifiable doubts as to whether Ménétrier's disease as such ever was an individual entity in the first place.

The description 'polyadénomes polypeux' given by Ménétrier himself, did not include macroscopically evident hypertrophic gastric folds, and his histological description fits that

of present day 'hyperplastic' polyps, which the drawing of the macroscopic findings in Ménétrier's publication also seems to confirm, as it shows multiple polyps in the antrum and corpus, but no hypertrophic folds.

Also, in these polyps – in contrast with the interpretation of Hendrix and Yardley – Ménétrier described an inflammatory infiltrate ('infiltré de cellules migratrices'). And also in the case of the 'polyadénomes en nappes', Ménétrier noted 'des phénomènes de gastritis chronique'.

When it is further considered that the histological technology of 1888 was, of necessity, inferior to that of the present day, that the descriptions were based on necropsy findings, and that we now know that 'polyadénomes en nappes' changes in the corpus and fundus are typical of lymphocytic gastritis, doubts that Ménétrier had ever really described an individual entity or that the cases of Ménétrier's disease published over the past decades really represented an individual entity, are considerably strengthened.

Our case history was intended merely to draw attention to the fact that when the clinical and endoscopic pictures suggest Ménétrier's disease, we should in future give more consideration to the possibility that the condition presenting is really *H. pylori* induced gastritis, which can then be cured by eradicating the *H. pylori*.

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Polyethylene glycol (PEG) as a marker of small intestinal permeability

EDITOR,—We were very interested to read the paper by Peeters *et al* who, in an attempt to standardise intestinal permeability test conditions, have studied the effects of probe solution composition and osmolality on the permeation of ⁵¹CrEDTA and PEG 400 (MW 280-634) across the small intestine (*Gut* 1994; 35: 1404-8). We endorse the need for standardisation in the conduct of small intestinal permeability tests and in a recent investigation of the effects of hydration status on urinary probe recovery in normal subjects

we found that fluid hydration had a considerable effect on the recovery of PEG (MW range 280 to 1100). In contrast, mannitol and lactulose recovery were not affected.¹ Peeters *et al* expressed their results as ⁵¹CrEDTA/PEG 400 ratios and found that the permeation of both markers was significantly reduced in the presence of lactulose and mannitol. We wonder whether differences in the hydration status of their subjects might explain their results.

The dependence of PEG permeation on the state of subjects' hydration at the time of the test is just one problem facing those determined to use PEG as a marker of small intestinal permeability. PEG 400 is absorbed and excreted in vivo in much greater amounts than other probes of similar molecular weight such as lactulose (MW 342)² and the absorption of PEG is reduced in conditions associated with flat mucosa whereas that of lactulose is increased.² These anomalies have never been fully explained by the proponents of PEG as a passive permeability marker. In their recent paper, Peeters *et al* attempt to explain the unusually avid permeation of PEG 400 in comparison with sugar molecules of similar size on the basis of theoretical considerations regarding the long, thin shape of PEG. It has been proposed that PEG has access to absorptive areas inaccessible to other molecules of comparative molecular size because of its shape.³ However, this theory has not stood up to experimental analysis.⁴ Furthermore the concept of PEG as a long, thin molecule does not take into account the fact that the effective size of PEG may in fact be much larger because of hydrogen bonding by the available ether oxygen atoms along the backbone of the molecule. Another possible explanation for the avid permeation of PEG across cell walls is, because PEG is lipid soluble, it interacts with the phospholipid bilayer of the cell wall.^{2,5} In a recent in vitro study comparing PEG with lactulose and mannitol we were able to show that PEG 400 (in contrast with the other molecules) could traverse lipid barriers with comparative ease.⁶ Another problem with the use of PEG as a marker of intestinal permeability is the wide variability in the recovery of the lowest molecular weight polymers of PEG 500.⁷ This variability suggests that the smallest polymers may have a larger volume of distribution in the body, a suggestion that was supported by our recent finding that the urinary recovery of the smallest molecules in a range of PEGs is comparatively delayed in normal subjects, suggesting a slow wash out of these molecules from the extravascular space into the circulation.¹

Given all these problems with regard to the permeation of PEG across the intestine and its subsequent urinary recovery we suggest that the time has probably come for this molecule to finally be abandoned as a marker of passive small intestinal permeability in vivo.

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