Letters

...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 Peyser'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 pre- sent 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 it is too speculative when Fujimura and Kihara on the basis of their findings in rat Peyser's patches of blocking of ICAM-1 as a potential treatment for inflammatory bowel disease in the future.

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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; 36: 424-32.
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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 nodular lesions 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 gas- tropathies' Ménétrier's disease and Zollinger-Ellison syndrome, the development 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 associ- ated with large gastric folds, increased 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 and based on different diagnostic criteria for this gastropathy. (3) The cases described in 1888 by Ménétrier as 'polyydarme 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'.1 2 3 Furthermore, Ménétrier's description and illustrations do not suggest that chronic gastritis, the hallmark of $H$ pylori gastritis, is present in this entity. We have found no evidence in the literature of malignant degeneration, which is an additional condition associated with sarcoïdosis, allergic (eosinophilic) gastritis, and Cronkhite-Canada syndrome. (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 accompany- ing change in distribution and activity of transforming growth factor $\alpha$ in the gastric mucosa in Ménétrier's disease. In addition, the experimental induction of an excess of gastric transforming growth factor $\alpha$ in transgenic mice results in similar mucosal cell hyperplasia.4 (5) It is highly probable that 'hypertrophic hypersecretory gastropathy' (Schindler's disease), another distinctive entity that is sometimes mistakenly design- ated as Ménétrier's disease, is a malad- istation of $H$ pylori gastritis with large folds.5 We urge authors and editors not to use the term Ménétrier's disease as a generic designa- tor for membrane T cell and all 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.

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1 Farstad IN, Halsensten TS, Faursa O, Brandtzæg P. Heterogeneity of M cell associated $B$ and $T$ cells in human Peyer's patches. Immunology 1994; 83: 457-64.
of present day 'hyperplastic' polyps, which the drawing of the macroscopic findings in Ménetrier'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—Ménetrier described an inflammatory infiltrate ('infiltré de cellules migratrices'). And also in the case of the 'polynédomes en nappes', Ménetrier noted 'des phénomènes de gastrixis 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 'polynédomes en nappes' changes in the corpus and fundus are typical of lymphocytic gastritis, doubts that Ménetrier had ever really described an individual entity or that the cases of Ménetrier'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 Ménetrier's disease, we should in future give more consideration to the possibility that the condition peculiar to 'polynédomes pylorici' induced gastric, which can then be cured by eradicating the H pylori.

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Reply

EDITOR,—We agree with Hendrix and Yardley that Helicobacter pylori infection with hypertrophic gastric folds or 'polynédomes pylorici' and not Ménetrier'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 Ménetrier's disease. In particular, most publications failed to evaluate inflammatory infiltration as an exclusion criterion for Ménetrier's disease. Thus, for example, Schindler described Ménetrier's disease in his article on 'hypertrophic glandular gastritis', and Scharschmidt 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 Ménetrier's disease.

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

The description 'polynédomes polypeux' given by Ménetrier himself, did not indicate macroscopically evident hypertrophic gastric folds, and his histological description fits that 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. Peeters et al expressed their results as CrEDTA/PEG 400 ratios and found that the permeation of both markers was significa-

644-52.


1 Schindler O. On hypertrophic glandular gastritis, hypoproteinemia, and parietal cell mass. Gastronterology 1963; 45: 77-82.

Polyethylene glycol (PEG) (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 recovery of CrEDTA 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 studies, 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. Peeters et al expressed their results as CrEDTA/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 secreted in vivo at rates greater than those of other probes of similar molecular weight such as lactulose (MW 342) and the absorption of PEG is reduced in conditions associated with flat mucosa whereas that of lactulose is increased. 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 other probes 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 the other molecules of comparable size because of its shape. However, this theory has not stood up to experimental analysis. 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 that PEG is lipid soluble, it interacts with the phospholipid bilayer of the cell wall. In a recent in vitro study comparing PEG with lactulose and mannitol we were able to show that PEG (in contrast with the other molecules) could traverse lipid barriers with comparative ease. Another problem with the use of PEG as a marker of intestinal permeability is the wide variability in the recovery of PEG across a range of small intestinal permeabilities 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. 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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Ménétrier's disease.

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