LETTERS TO
THE EDITOR

Oral submucous fibrosis—a chronic disseminated intravascular coagulation syndrome with local coagulopathy

EDITOR,—We have read the leading article in Gut with great interest. (Gut 1992; 33: 4–6).
We were, however, disappointed as the work on oral submucous fibrosis, published in Indian journals1 and the American Journal of Clinical Pathology2 has not been covered by the authors. After working for about 15 years on oral submucous fibrosis, we cannot agree with the views expressed.

According to Jayanthi et al, oral submucous fibrosis has been attributed to local irritation caused by tobacco and chilies used in cooking and that the progression of the disease can be halted by stopping tobacco, pan, etc. but it does not seem to be that simple or straightforward. We have seen young female patients who were not exposed to such irritants and they still developed the disease.

We have seen that oral submucous fibrosis is a chronic disseminated intravascular coagulation syndrome but it is well compensated for in most patients. We have shown that there is a thrombin like substance identified as fibrin producing factor in the saliva of patients suffering from oral submucous fibrosis.1 This is in contrast with the findings in normal saliva. In normal saliva fibrinolytic substances have been shown, however, Morimoto et al have found considerable amounts of proactivator and plaminogen in mixed, parotid, and submaxillary sublingual saliva. Several centres in India have confirmed the presence of fibrin producing factor in oral submucous fibrosis (personal communication).

In 1984, using a haemaggulination inhibition technique (Wellcome Kit HA-14) we showed that fibrinogen/fibrin degradation products—which we prefer to call molecules immunologically similar to fibrinogen (MISFI)—were detected both in the plasma and sera of the patients with oral submucous fibrosis.1 These MISFI were like fibrin monomers, because paracoagulation tests were positive and cryoprecipitation was absent.

In addition to the discovery of MISFI we have done global or first line clotting time tests in oral submucous fibrosis (unpublished data). These screening tests—activated partial thromboplastin time, thrombin time, and fibrinogen time—yield interesting information. The clotting times of oral submucous fibrosis are either prolonged or normal or even shortened. When working on oral submucous fibrosis plasma, it is important to appreciate that there is a strong tendency for the formation of cryofibrinogen so that tests should be performed on fresh plasma and sera. When the plasma is stored at −20°C, cryofibrinogen can develop in a matter of two to six hours.

We find cryofibrinogen in almost all patients with oral submucous fibrosis. The presence of cryofibrinogen suggests that a small quantity of thrombin like material is being added to the circulating plasma.1 Our data suggest that this thrombin like procoagulant is present in the saliva of patients with oral submucous fibrosis. Furthermore, we are tempted to suggest that the varying clotting times, the presence of MISFI (or fibrinogen/fibrin degradation products) and cryofibrinogen should point to hypercoagulation. According to Wintrobe3 hypercoagulation and chronic disseminated intravascular coagulation are superficially different but basically the same phenomena and disseminated intravascular coagulation is virtually always associated with fibrinolysis.

Oral submucous fibrosis seems to have a genetic basis. It is suggested that in oral submucous fibrosis the local fibrinolytic mechanism in the oral cavity is defective and cannot match or matches imperfectly with the hypercoagulation produced by the fibrin producing factor.

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Reply

EDITOR,—We thank Dr Phatak for his interest shown in our paper on oral submucous fibrosis. The article was based on the work done in the Institute, on factors that might be responsible for oral submucous fibrosis and placed in perspective the impact that ‘bettle nut’ and ‘bettle leaf’ (pan) consumption would have among south Asians in the United Kingdom. Oral submucous fibrosis is a multifactorial disease, some factors are initiators, others cofactors, and some promoters. Dr Phatak’s suggestion of a defect in the fibrinolytic mechanism in genetically predisposed subjects is well taken, but their hypothesis does not suggest the group which needs screening for fibrin producing factor. Also the ill effects of ‘bettle nut’ chewing cannot be readily dismissed and legislations to ban their import in the United Kingdom and thereby the Indian subcontinent cannot be over emphasised.

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Reply

EDITOR,—We agree with Chassade and Sogni that the influence of the washout on our results remains a difficult problem. We emphasise that we used the washout only to facilitate the endoscopy and not to mimic a condition similar to a colonic transit.

We agree that because of the mechanical removal of the intraluminal contents, an impairment in the splitting of the azo bond can be expected for Dipentum and Salazopyrin. The comparison of mucosal concentrations with and without lavage, however, can exclude this effect as the sole explanation for the very low concentrations after Salazopyrin. The influence on Dipentum seems more important. This suggests that in a clinical setting, diarrhoea mainly changes the results expected after treatment with Dipentum and to a lesser extent of Salazopyrin and the release modified drugs.

We did not study the influence of the washout on the mucosal concentrations after Asacol and Claversal 500 because we did not expect absorbance of an abdominal x-ray done 48 hours after the ingestion of radiopaque markers showed that patients with acute ulcerative colitis had proximal colonic stasis whereas resectosigmoid transit in a clinical rapid. It is possible that the ingestion of laxatives three days before the study will decrease the time for the colonic bacteria to split the azo bond of Dipentum and Salazopyrin. The very low mucosal concentrations of these drugs seen in this study, could be partly because of the decreased colonic transit time.

Secondly, there is only some information in this paper about the effect of the oral bolus lavage on mucosal concentrations of the 5-ASA and Asc-5-ASA in human rectosigmoid biopsy homogenates after ingestion of Salazopyrin, Dipentum, and Claversal 250. The data presented on table V show that colonic lavage is associated with an important decrease of 5-ASA concentration for Dipentum and Asacol 250 but not for Salazopyrin and we have no information for Asacol 500 and Claversal, which gave the highest concentration. Therefore, we believe that in vivo dialysis of faeces is perhaps a more physiological way to measure concentrations of 5-ASA and Asc-5-ASA after oral 5-ASA preparations as proposed Lauritsen et al.1

Thirdly, in their study, Vos et al measure the concentration of 5-ASA in human ileocolonic biopsy homogenates that are considered the active drug of all these compounds. This is true for coated 5-ASA compounds and Dipentum but it is not true for Salazopyrin, which is not only a prodruk but also has direct effect on the inflammatory process seen in ulcerative colitis.1 Therefore the colonic mucosal concentration of 5-ASA is not sufficient to assess the effects of this drug in inflammatory bowel disease.

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Concentrations of 5-ASA and Asc-5-ASA in human ileocolonic biopsy homogenates

EDITOR,—I read with interest the paper by (Gut 1992; 33: 1338–42) Vos et al. This is a new approach to the study 5-ASA compounds in humans but further studies are necessary to correlate these concentrations with clinical benefit in inflammatory bowel diseases.

Firstly, I would like to comment about the experimental protocol. In their study, Vos et al have their patients to discontinue colonic lavage and to obtain similar conditions to those found in ulcerative colitis. It has been shown previously, however, by Rao et al from Sheffield that total colonic transit time is not decreased in patients with acute ulcerative colitis. Segmental distribution of markers

the appreciable differences seen in the results.

The studies of Lauritsen et al., with faecal dialsytes reflect only the intraluminal concentrations but provide no information about the intramucosal concentrations. We are not unhappy to learn that our patient is the second rather than the third. We are well used to coming second!

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Riedel's thyroiditis, retroperitoneal fibrosis, and sclerosing cholangitis: diseases with one pathogenesis?

EDITOR.—We have read the case report on multifocal fibrosis by Laitt et al. (Gut 1992; 33: 1430–2) and agree that the combination of Riedel's thyroiditis with retroperitoneal fibrosis as well as sclerosing cholangitis is very rare. We have recently collected from world-wide studies 14 reports on the 14 patients with both Riedel's thyroiditis and retroperitoneal fibrosis and suggested a common pathogenetic mechanism.

In their article Laitt et al state that 'Bartholomew noted an association of Riedel's thyroiditis, sclerosing cholangitis and retroperitoneal fibrosis in the same patient.' This is not correct. In the article by Bartholomew et al not one but two patients were described; one with sclerosing cholangitis and retroperitoneal fibrosis and the other with Riedel's thyroiditis and sclerosing cholangitis. This last patient, by the way, is the same patient as described by Woolner et al (reference 7 in the article by Laitt).

The patient described by Laitt et al is therefore not the third, but the second reported in published works with this triad of organ involvement. The only other patient was described twice, not only by Gleeson et al (reference 2 in the article by Laitt) but once again with a longer follow up in an article by Katsikas from the same hospital in 1976.

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Microvascular abnormalities in the mucosal prolapse syndrome

EDITOR.—The paper by Dr Lonsdale (Gut 1993; 34: 106–9) presents an intriguing and new theory of ulceration in mucosal prolapse syndrome, and highlighting a previously neglected aspect of its histopathology omits some diagnostic features. Diamond shaped crypts and intramucosal elastin are features of all the conditions that fall within the bounds of the unifying concept of mucosal prolapse.

Also the relation between metaplastic polyps and mucosal prolapse is unclear. While we would agree that most metaplastic polyps are too small to induce mucosal prolapse changes in the immediately adjacent mucosa, histological features of mucosal prolapse are usually seen within the polyps themselves. Meta-

plastic change is seen overlying 30% of cases of mucosal prolapse in most series. The theories of Cripps' and ourselves' relating metaplastic polyps to mucosal prolapse, because of their similar features, may have to be reconsidered now that Dr Lonsdale's paper has uncovered a difference between the vasculature of meta-

plastic polyps and mucosal prolapse.

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5 Franzini G, Scarpa A, Dina R, Novelli P. Transi-

tional and hyperplastic: metaplastic mucosal ulceration in solitary ulcer of the rectum. Histopa-


Inflammatory bowel disease in Asians

EDITOR.—The studies by Probert et al. have provided important information on the incidence of inflammatory bowel disease in South Asians. Furthermore, the results have highlighted the fact that this is not a homogenous group of patients, with significant differences between Hindus, Moslems, and Sikhs. The heterogeneity is perhaps not surprising because of the vast size of the Indian subcontinent, from which these patients originated.

Diet is known to play a part in the cause and subsequent course of inflammatory bowel disease. In addition to the obvious differences between European and Indian diets, there are also important differences in the diet within India. Epidemiological studies have shown that a low fibre diet is a risk factor for inflammatory bowel disease. Areas in the south of India have a lower intake of unrefined fibre when compared with the northern regions.

Other dietary factors, such as antioxidants, may also be of importance. Recently, there is evidence implicating oxygen derived free radi-

cals in inflammatory bowel disease. Healthy subjects in Madras, in south India, have been shown to have lower plasma values of ascorbic acid and β carotene than healthy subjects in England.

Thus, some of the differences seen in the incidence of inflammatory bowel disease from people from the Indian subcontinent may be related to dietary differences. The Indians from the Indian subcontinent, as well as dietary differences between the various groups from within the Indian subcontinent. It would be interesting to know if the findings of Probert et al. were mirrored in Hindus, Moslems, and Sikhs within India.

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7 Chafner C, Schodl F, Kay PM, Mohan V, Schwarzl CA, Brugna MA. Xenobiotic detoxi-

fication and antioxidant profiles in healthy con-


Reply

EDITOR.—I am grateful to Dr Warren and Dr Davies for their comments on my paper. As this was mainly an histopathological examination of vascular changes in prolapsing mucosa, detailed description of all the microscopic features of this condition was not attempted. Diamond shaped crypts and intramucosal elastin, however, were present in some of the specimens. I would agree that metaplastic polyps and mucosal prolapse share some common histological features, and on occasion, especially in a small or distorted biopsy speci-

men, can be a problematical differential diag-

nosis. The lack of observable vascular changes and the rarity of ulceration in metaplastic polyps may be related to differing predisposing factors or initiating stimuli, and is not inconsistent with them being a manifestation of local mucosal prolapse.

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Letters