

## 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 journals<sup>1</sup> and the *American Journal of Clinical Pathology*<sup>2</sup> has not been covered by the authors. After working for about 15 years on oral submucous fibrosis, we cannot agree with the views expressed by the authors.

According to Jayanthi *et al.*, oral submucous fibrosis has been attributed to local irritation caused by tobacco and chillies 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.<sup>2</sup> This is in contrast with the findings in normal saliva. In normal saliva fibrinolytic substances have been shown. Nitta *et al.*<sup>3</sup> have found considerable amounts of proactivator and plasminogen 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 haemagglutination 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.<sup>2</sup> These MISFI were like fibrin monomers, because paracoagulation tests were positive and cryofibrinogen was present.

In addition to the discovery of MISFI we have done global or first line clotting time tests in oral submucous fibrosis (unpublished data).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, prothrombin time, and thrombin 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.<sup>4</sup> 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 pro-

ducts) and cryofibrinogen should point to hypercoagulation. According to Wintrobe's 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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- 1 Phatak AG. Fibrin producing factor in oral submucous fibrosis. *Indian J Otolaryngol* 1979; 31: 103–4.
- 2 Phatak AG. Hypercoagulation and fibrinolysis in oral submucous fibrosis. *Am J Clin Pathol* 1984; 81: 623–8.
- 3 Nitta H, Sugie I, Morimoto S, Sato S. Studies on physicochemical properties of fibrinolytic substances in human saliva. *Nagoya Med J* 1967; 13: 151–63.
- 4 Henrich RA, Vonder Acide EC, Clinic RW. Cryofibrinogen formation and inhibition in heparinized plasma. *Am J Physiol* 1963; 204: 419–22.
- 5 Wintrobe HM, *et al.* *Clinical haematology*. Philadelphia: Lea and Febiger. 1981:1251.

### 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 Indian subcontinent on factors that might be responsible for oral submucous fibrosis and placed in perspective the impact that 'betel nut' and 'betel 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 'betel nut' chewing cannot be readily dismissed and legislations to ban their import in the United Kingdom and their use in the Indian subcontinent cannot be over emphasised.

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### Concentrations of 5-ASA and AC-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.* gave their patients a laxative to facilitate colonic washout and to obtain similar conditions to those found in ulcerative colitis. It has been shown previously, however, by Rao *et al.*<sup>1</sup> from Sheffield that total colonic transit time is not decreased in patients with acute ulcerative colitis. Segmental distribution of markers

assessed by 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 rectosigmoid transit time was 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 colonic lavage on mucosal concentration of the 5-ASA and Ac-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 Ac-5-ASA after oral 5-ASA preparations as proposed Lauritsen *et al.*<sup>2</sup>

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 prodrug but also has direct effect on the inflammatory process seen in ulcerative colitis.<sup>3</sup> Therefore the colonic mucosal concentration of 5-ASA is not sufficient to assess the efficiency of this drug in inflammatory bowel disease.

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- 2 Lauritsen K, Hansen J, Bytzer P, Bukhave K, Rask-Madsen J. Effects of sulphalazine and disodium azodisalicylate on colonic PGE2 concentrations determined by equilibrium in vivo dialysis of faeces in patients with ulcerative colitis and healthy controls. *Gut* 1984; 25: 1271–8.
- 3 Editorial. Sulphasalazine: drug or prodrug? (Anonymous) *Lancet* 1987; i: 1299–300.

### Reply

EDITOR.—We agree with Chaussade 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 ulcerative colitis.

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