LETTERS TO THE EDITOR

Colonic mucus and colitis

Sir,—I found the review on mucus and colitis by J M Rhodes (Gut 1989; 30: 1660–6) most interesting, but I was surprised by the absence of several pertinent references. It must surely be relevant that about 8% of the general population show a constitutional lack of the O acetylated, sialic acid resistant form of sialic acid.1 These people do not appear to show an increased proneness to ulcerative colitis.2 Patchy alteration in sialic acid structure (loss of O acetyl groups) is seen in hyperplastic epithelium in colitic biopsy material. Such mucosal alterations are likely to be secondary to inflammatory injury.1 Thus mucin heterogeneity, whether genetically determined or acquired, appears to be unimportant in the aetiology of ulcerative colitis. Perhaps these observations should be added to the other negative findings catalogued by J M Rhodes. I suggest that they reduce the likelihood of a ‘mucus/bacteria’ hypothesis.

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Reply

Sir,—I am sorry that Professor Jass’s excellent papers were not referred to in my leading article. This was, however, intended as a presentation of hypotheses to act as stimuli for further studies rather than as a comprehensive review of published work. As pointed out in the article a change in the O acetylation of mucin sialic acids is just one of the multifarious alterations in mucin structure that could have an effect on its interaction with bacteria. Others include alterations in sulphation, sialylation, length, and branching of oligosaccharide side chains and changes in the expression of carbohydrate receptors for bacterial adherence lectins.

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Scavenger effect of sulphasalazine (SASP), 5-aminosalicylic acid (5-ASA), and olsalazine (OAZ)

Sir,—We read with interest the paper by Williams and Hallett on the action of SASP and 5-ASA on toxic oxygen metabolite production by neutrophils. The authors conclude by suggesting a scavenger effect is produced by both drugs, as previously reported.2,3

We have recently concluded a similar experiment, evaluating the influence of SASP, its metabolites (sulphapyridine and 5-ASA) and OAZ, on the generation of reactive anions (O2•−) by activated neutrophils and by a cell free xanthine-xanthine oxidase system. Human neutrophils were prepared from heparinised peripheral blood of healthy volunteers by using a combined dextran/Ficoll-Hypaque separation procedure and hypotonic lysis to remove contaminating erythrocytes. The resulting cells (>95% neutrophils) were washed twice in phosphate buffer (pH 7.4) and then activated using 0.1 μg/ml of polystyrene myelocytic acid. The production of O2•− by activated neutrophils was measured either by spectrophotometrically reducing cytochrome c (cyt c) at 550 nm in a cuvette maintained at 37°C, or monitoring the O2•− dependent light emission at 37°C on a Perkin-Elmer luminescence spectrophotometer.

For testing the scavenger effect of SASP and OAZ, we could not use the chemiluminescence method, because of its intense yellow colour in solution, which interferes with the measurement of light emission. We therefore used the reduction of cyt c assay for evaluating the effect of SASP, OAZ and also for sulphapyridine, but we could not use the cyt c assay for 5-ASA. In fact 5-ASA caused a direct chemical reduction of cyt c effect, already reported by Neal et al.1 Therefore, investigating the action of 5-ASA, we adopted the chemiluminescence method. In our study, 5-ASA caused an LDCL, produced a dose dependent inhibition of superoxide anion in both the neutrophils and cell free xanthine-xanthine oxidase system, 5-AWA being the most powerful (50% of inhibition at 10 μM, the lowest concentration used). In contrast, sulphapyridine showed a dose dependent inhibitory effect on the cellular system, not modifying the activity of xanthine oxidase.

As can be seen, our data are only partly in agreement with the findings of Williams and Hallett. In our opinion, this study is not without certain methodological limitations. The authors, in their experiment, did not report the interference of SASP on light emission, because of the yellow colour of the solution, therefore the inhibition on chemiluminescent response determined by SASP in their experiment could be partly attributed to the quenching effect on light emission by this dye. Finally the authors highlight the direct chemical reduction provoked by 5-ASA on cyt c, as already mentioned. This, again, might determine a limitation of their results.

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Reply

Sir,—Gionchetti et al, although providing evidence which supports our conclusion that sulphasalazine and particularly olsalazine (OAZ) are scavengers of a neutrophil derived oxygen metabolite, have questioned two methodological points in our paper.1

The first point raised was that the inhibition of luminal dependent chemiluminescence (LDCL) by sulphasalazine was because of its ‘intense yellow colour’, presumably by absorbing emitted photons, rather than by scavenging a luminal reactive molecule. We do not think the absorbance of sulphasalazine can account for our results for two reasons: (i) at the emission wavelength for lumisol (425 nm) in our luminometer (maximum photon pathlength 0.8 cm) a concentration of sulphasalazine which inhibits peroxidase induced neutrophil LDCL by 50% (16.5 μM) would reduce detection of photons by a maximum of only 8%; (ii) absorbance of photons alone could not account for the differential effect of sulphasalazine. Levine et al2 conclude that sulphasalazine produced no significant reduction of transmission at concentrations which totally inhibit peptide induced LDCL.3

The second point raised concerned the use of cytochrome c reduction as an assay of superoxide production. As cytochrome c readily accepts electrons, only the reduction of cytochrome c which can be inhibited by superoxide dismutase can be defined as due to superoxide.4 At the concentrations of 5-aminosalicylate we used (0.5–50 μM) interference was not a problem. Neal et al4 were unable to use 5-aminosalicylate in this assay but were using considerably higher concentrations of 5-aminosalicylic acid (up to 1000 μM). The widely recognised problems with cytochrome c reduction led us to measure oxygen consumption also and so determine whether regeneration of oxygen as a result of superoxide scavenging had occurred. As we detected no inhibition of oxygen consumption (nor did Neal et al4 in concentrations up to 1000 μM) this confirmed our conclusion that 5-aminosalicylic acid did not scavenge superoxide. We therefore suggested that the inhibition of LDCL by 5-aminosalicylic acid resulted from reaction with another oxygen metabolite which triggers luminal chemiluminescence, namely hypochlorite.5 We have also produced more direct evidence for this. In chemically generating hypochlorite systems (xanthine/xanthine oxidase, plus peroxidase and perhydrogen peroxide) or hypochlorite alone, the accompanying LDCL was inhibited by 5-aminosalicylate.6 Furthermore, the fluores-

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