

## LETTER TO THE EDITOR

### Free radicals in colitis

SIR,—I read with interest the recent article by Keshavarzian and coworkers.<sup>1</sup> They clearly show that reactive oxygen species play a part in their model of experimental colitis.

I disagree, however, with certain of their statements and conclusions. Firstly, superoxide anion is generated extracellularly by neutrophils and macrophages by an NADPH dependent oxidase enzyme present within the cell surface membrane<sup>2</sup> and not intracellularly as the authors stated. Secondly, I would disagree that superoxide anions cannot cause appreciable tissue injury in vivo as they are known to inactivate enzymes, lyse red blood cells, kill cells in tissue culture, kill bacteria, degrade DNA, and depolymerise hyaluronic acid.<sup>3</sup>

Superoxide anion can also result in the formation of other toxic species such as hydrogen peroxide, and the hydroxyl radical as a consequence of dismutation, and the Haber-Weiss and Fenton reactions.<sup>4</sup>

Thirdly, the hydroxyl radical is a highly reactive species with a rate constant of  $10^{10} \text{m}^{-1} \text{s}^{-1}$ . It reacts in a non-specific fashion with anything it contacts and is trapped by its own microenvironment. Therefore it is argued that it does not have a specific quencher.<sup>5</sup> The fact that the authors were not able to influence the inflammatory process with dimethyl sulphoxide does not exclude the hydroxyl radical as a contributory agent.

Finally, it is not surprising that the xanthine oxidase pathway is not a major source of reactive oxygen metabolites in colitis of a non-ischaemic origin, as in aerobic conditions xanthine oxidase exists mainly as xanthine dehydrogenase<sup>6</sup> and in response to ischaemia xanthine dehydrogenase undergoes irreversible limited proteolysis by a calcium activated protease to form xanthine oxidase.<sup>7</sup> Xanthine oxidase can generate superoxide anions but this would only become an important source in the presence of gut ischaemia.

Free radical production by neutrophils may be an important mechanism of tissue injury in the experimental colitis described,<sup>1</sup> and inflammatory bowel disease in humans, and modification of this may have important implications for treatment. The key, however, to the pathogenesis of inflammatory bowel

disease is the determination of the stimulus which initiates the inflammatory response.

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- 1 Keshavarzian A, Morgan G, Sedghi S, Gordon JH, Doria M. Role of oxygen metabolites in experimental colitis. *Gut* 1990; 31: 786-90.
- 2 Goldstein IM, Cerqueira M, Lind S, Kaplan HB. Evidence that the superoxide generating system of human leukocytes is associated with the cell surface. *J Clin Invest* 1977; 59: 249-54.
- 3 Halliwell B, Gutteridge JMC. *Free radicals in biology and medicine*. Oxford: Clarendon Press, 1985: 118.
- 4 Fantone JC, Ward PA. Role of oxygen-derived free radicals and metabolites in leukocyte-dependent inflammatory reactions. *Am J Path* 1982; 107: 397-418.
- 5 Halliwell B, Gutteridge JMC. Oxygen free radicals and iron in relation to biology and medicine: some problems and concepts. *Arch Biochem Biophys* 1986; 246: 501-14.
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- 7 Granger DN, Hollwarth ME, Parks DA. Ischaemic reperfusion injury: role of oxygen derived free radicals. *Acta Physiol Scand* 1986; [Suppl 548]: 47-63.

### Reply

SIR,—I thank Dr Williams for his interest in our work. We agree that superoxide anion is generated by neutrophils by a membrane-bound NADPH dependent oxidase. As we indicated in our paper, several authors have stated that superoxide anions can cause tissue injury in vivo (through pathways that are stated in Dr Williams's letter) only through their metabolites, hydroxyl radicals, or hypochlorous acid.<sup>1,2</sup>

We believe that the lack of any protective effect of either a hydroxyl radical scavenger or an iron chelating agent, that inhibit production of hydroxyl radicals, on colitis strongly suggests that hydroxyl radicals do not play a major part in our colitis model. Dr Williams's argument in favour of hydroxyl radicals cannot reconcile the fact that deferoxamine did not influence the colitis. We conclude that our data only suggest that hypochlorous acid is a major reactive oxygen metabolite in colitis. Our conclusion is supported by others.<sup>1,3</sup>

Several authors have suggested that ischaemia may have a role in inflammatory bowel disease. We therefore thought that the xanthine oxidase pathway should be evaluated as a possible source of reactive oxygen metabolites. Our data indicated that this pathway is not important in our colitis model.

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- 1 Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; 320: 365-76.
- 2 Grisham M, McCord J. Chemistry and cytotoxicity of reactive oxygen metabolites. In: Taylor A, Matalon S, Ward P, eds. *Physiology of oxygen radicals*. Bethesda: American Physiological Society, 1986: 1-18.
- 3 Aruoma O, Wasil M, Halliwell B, Hoey BM, Butler J. The scavenging of oxidants by sulfasalazine and its metabolites: a possible contribution of their anti-inflammatory effects. *Biochem Pharmacol* 1987; 36: 3739-42.

## NOTES

### New journal

The Romanian Society of Gastroenterology is launching the *Romanian Journal of Gastroenterology* in 1991 and the journal is particularly keen to attract contributions from Western Europe and the United States. Reviews, original articles, and case reports are welcome. Further details from Professor Dr Stefan Popescu, Editor, IIIrd Medical Clinic, Str Croitorilor no 19-21, RO 3400 Cluj Napoca, Romania.

### British Society of Gastroenterology Endoscopy Committee

The second basic theory course on endoscopy, approved and organised by the Endoscopy Committee of the British Society of Gastroenterology, will be held on the afternoon of Friday, 12 April 1991 at the Manchester meeting of the British Society of Gastroenterology. This course is aimed at trainee endoscopists and endoscopy assistants. Full details and registration forms are available from Ms Anne Pearson, Confrex, PO Box 963, Brighton, East Sussex BN1 6TN.

### French digestive pathology course

The French speaking Congress on Digestive Pathology (Les Journées Francophones de Pathologie Digestive) will take place in the Corum of Montpellier from 16-20 March 1991. Information: CPS 168, quai Louis-Blériot - 75016 Paris. Tel: 45.24.34.63.