EDITORIAL

Free Radicals and the Pathogenesis of Disease

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In this issue of the Medical Journal of Malaysia, A. S. Salim reports on his experience with free radical scavengers in the treatment of refractory peptic ulceration[1]. Although the number of patients in his study was small and the trial was open and non-comparative, the results obtained are interesting enough to justify further research into the role of free radicals in the pathogenesis of peptic ulceration. Oxygen derived free radicals has also been shown to be involved in the pathogenesis of acute gastric ulceration induced by indomethacin[2]. Thus after acid, pepsin and *Helicobacter pylori*, the generation of free radicals could well become another major factor to contend with in the management of peptic ulcers.

A free radical is a molecule with a solitary unpaired electron. This lone electron will seek to become paired thus free radicals are highly reactive and short-lived. Free radicals are dangerous since it interacts readily with other biomolecules including nucleic acids, proteins and free amino-acids, lipids and carbohydrates. Such interactions can result in impairment of cellular membrane function, metabolic processes and genetic expression.

Free radicals derived from oxygen are produced by all respiring cells. These radicals are formed through reduction of oxygen in the presence of metals such as iron and copper. Oxygen derived radicals include hydrogen peroxide, the hydroxyl radical and singlet oxygen. Fortunately cells have a number of enzymic and non-enzymic mechanisms to protect against these free radicals and as long as homeostatis is maintained, cellular damage is limited. In situations where the defenses cannot cope, either as a result of increased oxygen concentrations or a decrease in antioxidant defense mechanisms, a state of oxidative stress occurs. This can result either in immediate death of cells or more subtle and chronic damage like the development of malignant change. Antioxidant strategies include removing the free radicals through specific enzymes like superoxide dismutase and glutathione peroxidase or preventing the generation of the free radicals through the use of agents like xanthine oxidase inhibitors.

As free radicals can be produced in almost all tissues it is not surprising that free radical generation has been implicated in the pathogenesis of a wide variety of human diseases[3]. Such disorders include aging, cancer, poisonings, cardiovascular disease, complications of diabetes mellitus, multiorgan failure secondary to sepsis, cataracts and illnesses related to chronic alcohol consumption, to name but a few.

There is now increasing evidence that tissue damage that accompanies the aging process is due to free radicals[4]. Support for this is derived from studies on the origin of life and evolution, studies on the effects of ionising radiation on living things, the effect of dietary manipulations on endogenous free radical reactions and the growing number of studies that implicate free radicals in the pathogenesis of disease. On the basis of present data it has been postulated that life expectancy can be increased

by five years or more through dietary modifications. In the field of cancer, measures designed to block formation of free radicals or to intercept them before their interactions with biomolecules are attractive proposals for protection against cancer[5].

Oxygen derived free radicals have also been implicated in the pathogenesis of hypercholesterolaemia induced atherosclerosis[6]. Even though clinical benefit can be derived from lipid-lowering regimens, the magnitude of angiographic regressive changes is relatively small and alternative approaches including the use of antioxidants will have to be explored[7]. Free radicals are also the cause of tissue damage in ischaemia-reperfusion injury[8]. Nevertheless one clinical study has failed to demonstrate any benefit with allopurinol, a xanthine oxidase inhibitor in preventing myocardial infarct extension[9]. Antioxidant therapy has also been proposed as adjunctive therapy in the management of septicaemia where ischaemia-reperfusion injury is believed to be the basis of multi-organ failure[10]. Microangiopathy of diabetes mellitus is also believed to be caused by free radical injury and the role of antioxidants in the treatment and prevention of diabetic complications is currently being assessed[11].

The use of antioxidants in the treatment and prevention of a wide variety of diseases is an exciting prospect. This is especially so in Malaysia since palm oil contains Vitamin E and its analogues as well as βcarotenes which are potent antioxidants[12]. It is hoped that the role of these antioxidants will soon be established for the benefit of mankind in general and Malaysian palm oil in particular.

References

1. Salim AS. Oxygen-derived free radical scavengers: A new approach to the problem of refractory peptic ulceration. Med J Malaysia 1993;48 : 392-396
2. Vaananen PM, Meddings JB, Wallace JL. Role of oxygen-derived free radicals in indomethacin-induced gastric injury. Am J Physiolol 1991;261 : G470-5.
3. Cross CE. Oxygen radicals and human disease. Ann Intern Med 1987;107 : 526-45.
4. Harman D. Free radical involvement in aging. Drugs Aging 1993;3 : 60-80.
5. Kensler TW, Trush MA, Guyton KZ. Free radicals as targets for cancer chemoprotection : prospects and problems. In: Steele VE, Boone CW, Stoner GD and Kelloff GJ (eds) Cellular and molecular targets for chemoprevention. Boca Raton: CRC Press Inc, 1992 : 173-86.
6. Prasad K, Kalra J. Oxygen free radicals and hypercholesterolaemic atherosclerosis: effect of vitamin E. Am Heart J 1993;125 : 958-73.
7. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Cayatte AJ, Mowery J. Atherosclerosis. Potential targets for stabilisation and regression. Circulation 1992;86 (6 Suppl): III17-23.
8. Kukreja RC, Hess ML. The oxygen free radical system: from equations through membrane-protein interactions to cardiovascular injury and protection. Cardiovasc Res 1992;26 : 641-55.
9. Parmley LF, Mufti AG, Downey JM. Allopurinol therapy of ischaemic heart disease with infarct extension. Can J Cardiol 1992;8 : 280-6.
10. Mileski WJ. Sepsis. What is it and how to recognise it. Surg Clin North Am 1991;71 : 749-63.
11. Chittenden SJ; Shami SK. Microangiopathy in diabetes mellitus: I. Causes, prevention and treatment. Diabetes Res 1991;17 : 105-14.
12. Chandrasekharan N. An appraisal of the nutritional and health aspects of palm oil. Med J Malaysia 1992;47 : 93-8.