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McCord J M. Oxygen-derived free radicals in postischemic tissue injury. *N. Engl. J. Med.* 312:159-63, 1985.
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This paper reviewed the emerging relationship between the production of oxygen-derived free radicals and postischemic tissue injury. It examined evidence for free-radical-mediated injury in laboratory models of intestinal and myocardial ischemia, circulatory shock, and organ transplantation. It provided a biochemical mechanism that focused on the role of xanthine oxidase as a primary source of superoxide radical production in reoxygenated tissues. [The *SCI*® indicates that this paper has been cited in more than 1,240 publications.]

A Radical Review of Ischemia

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The discovery of superoxide dismutase in 1969[1] caused a certain amount of bewilderment in some scientific circles. The enzyme was ubiquitous among aerobic cells and had the sole apparent function of eliminating a peculiar free-radical form of oxygen—the superoxide radical. For many, superoxide dismutase was a solution in search of a problem, because it was not accepted that cells produced superoxide or that it would be harmful, even if it were produced. In the decade that followed, it became clear that the superoxide radical played significant pathophysiological roles in the bactericidal action of neutrophils and in the process of inflammation.[2,3]

In 1980, a role for superoxide was clearly demonstrated in the mechanism of tissue injury by ischemia/reperfusion.[4] Two of my colleagues, D. Neil Granger, a gastrointestinal physiologist, and G. (Franco) Rutili, a visiting scientist from Sweden, were subjecting feline ileum to one hour of ischemia followed by reperfusion in vivo. Measurement of increased capillary permeability was the end point, and several pharmacological interventions were tried in order to probe the mechanism of injury. Antihistamines and steroidal or nonsteroidal anti-inflammatory drugs provided no protection. Franco had heard of the anti-inflammatory properties of superoxide dismutase, so they gave it a try. It worked!

As I was the local free-radical guru, they immediately sought my advice as to what was going on and what to do next. We formulated a hypothesis based on circumstantial evidence already in the literature in which the enzyme xanthine oxidase was the source of the free radicals. (Unknown to us at the time, Ola D. Saugstad, a pediatric surgeon in Oslo, had speculated that free-radical production via xanthine oxidase might result from the high levels of hypoxanthine known to accumulate during hypoxia.[5]) Within days of the initial observation, a very productive collaboration emerged that eventually dictated the directions of future research for both Neil and myself.

The idea of a role for a free-radical-mediated component of reperfusion injury caught on quickly and resulted in the attraction of several new groups of researchers to the "freeradical bandwagon," which now includes physiologists, cardiologists, neurologists, and transplant surgeons. The next several years saw many additional publications exploring the roles of xanthine oxidase and the superoxide radical in gastrointestinal ischemia, as well as in myocardial, cerebral, hepatic, and renal ischemia. Because reperfusion injury following heart attack and stroke represents a major source of morbidity and mortality in this country, many are now interested in the therapeutic potential of superoxide dismutase and related radical-scavenging drugs.

In 1984, I received a call from Franklin Epstein, an editor of the *New England Journal of Medicine,* asking if I would be interested in reviewing the field for the journal's "Mechanisms of Disease" feature. I jumped at the opportunity. I believe the review has been highly cited because it represented the first major review of a new and rapidly developing area of research and it appeared in a highly visible journal.

1. **McCord J M & Fridovich I.** Superoxide dismutase: an enzymic function for erythrocuprein (hemocuprein). *J. Biol. Chem.* 244:6049-55, 1969. (Cited 3,275 times.) [See also: **McCord J M.** Citation Classic. (Barrett J T. ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 189.]
2. **McCord J M.** Free radicals and inflammation: protection of synovial fluid by superoxide dismutase. *Science* 185:529-31, 1974. (Cited 585 times.) [See also: **McCord J M.** Citation Classic. *Current Contents/Life Sciences* 31(8):12, 22 February 1988.]
3. **Petrone W F, English D K, Wong K & McCord J M.** Free radicals and inflammation: superoxide-dependent activation of a neutrophil chemotactic factor in plasma. *Proc. Nat. Acad. Sci. USA* 77:1159-63, 1980. (Cited 305 times.)
4. **Granger D N, Rutili G & McCord J M.** Superoxide radicals in feline intestinal ischemia. *Gastroenterology* 81:22-9, 1981. (Cited 345 times.)
5. **Saugstad O D & Aasen A O.** Plasma hypoxanthine concentrations in pigs: a prognostic aid in hypoxia. *Eur. Surg. Res.* 12:123-9, 1980.

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