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McCord J M. Free radicals and inflammation: protection of synovial fluid by superoxide dismutase. *Science* 185:529-31, 1974.
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The paper demonstrates that enzymatically generated superoxide radical can depolymerize hyaluronic acid, whether purified or as bovine synovial fluid. It proposes a role for phagocyte-generated free radicals in the mechanisms of injury associated with the inflammatory process. [The *SCI*® indicates that this paper has been cited in over 470 publications.]

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Five years prior to this paper's publication Irwin Fridovich and I described a new enzyme, superoxide dismutase, that catalyzes the disproportionation of superoxide radicals.[1] Superoxide dismutase was viewed by many as "a solution in search of a problem," as there was no widespread appreciation at the time that oxygen-derived free radicals played significant roles in mammalian biochemistry. A profound piece of information, however, suggested otherwise: superoxide dismutase had been independently isolated from beef liver by Thomas L. Schulte, Wolfgang Huber, and others at a small California pharmaceutical company called Diagnostic Data, Inc. They had isolated the protein as a naturally occurring anti-inflammatory protein with no knowledge of its enzymatic activity. They called this protein orgotein[2] and quickly recognized its identity with superoxide dismutase based on the physical and spectral characteristics we had published.[1]

No apparent connection existed between superoxide radicals and inflammation until the missing link was provided by Bernard M. Babior in 1973.[3] Babior discovered that the rapid increase in oxygen consumption displayed by neutrophils when they phagocytose their prey was associated with the liberation of a substantial amount of superoxide radical. He correctly surmised that the toxic radical was produced intentionally by these kamikaze cells as part of their bactericidal armament.

For me it suddenly became clear: In an autoimmune disease such as rheumatoid arthritis, the inflammatory cells become "confused," attacking normal host tissue as though it were an invading microorganism. Thus, the superoxide-producing machinery would be directed against self, and the presence of a superoxide-scavenging enzyme in the interstitial fluid would intercept the radical and protect the tissues. Superoxide dismutase, by this logic, would be an anti-inflammatory protein. How could this hypothesis be tested?

One clinical manifestation of an inflamed joint is the loss in viscosity of the synovial fluid filling the joint space. This viscosity change reflects a decrease in the molecular weight of the linear polysaccharide hyaluronic acid. I purified hyaluronic acid from human umbilical cords and purchased normal bovine synovial fluid. These were exposed to an enzymatic source of superoxide and hydrogen peroxide generation, xanthine oxidase, and hypoxanthine. Sure enough, the viscosity dropped as the reaction proceeded. (Relative viscosity, by the way, was measured with a 29-cent viscometer by timing the drainage of a solution between gradations on the barrel of a disposable plastic syringe through a needle of appropriate bore.) The change in viscosity could be nearly completely suppressed by a few micrograms of either superoxide dismutase or catalase, implicating the secondarily derived hydroxyl radical as the actual depolymerizing species.

This paper has been much cited because it offered the first simple, logical proposal for a pathological role for oxy radicals. Today, much is known about the pathophysiology of superoxide, and additional pathways have been delineated for its production in other disease states such as injury due to ischemia/reperfusion[4] and for its role in linking inflammation with ischemia.[5]

1. **McCord J M & Fridovich I.** Superoxide dismutase: an enzymic function for erythrocuprein (hemocuprein). *J. Biol. Chem.* 244:6049-55, 1969. (Cited 2,485 times.) [See also: **McCord J M.** Citation Classic. (Barret J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 189.]
2. **Marberger H, Bartsch G, Huber W, Menander K B & Schulte T L.** Orgotein—new drug for treatment of radiation cystitis. *Curr. Ther. Res.* 18:466-75, 1975. (Cited 20 times.)
3. **Babior B M, Kipnes R S & Curnutte J T.** Biological defense mechanisms. The production by leukocytes of superoxide, a potential bactericidal agent. *J. Clin. Invest.* 52:741-4, 1973. (Cited 980 times.)
4. **McCord J M.** Oxygen-derived free radicals in post-ischemic tissue injury. *N. Engl. J. Med.* 312:159-63, 1985.
5. ———. Superoxide radical: a likely link between reperfusion injury and inflammation. *Adv. Free Radical Biol. Med.* 2:325-45, 1986.

IA-2