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## REDOX PIONEER #11

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# Redox Pioneer: Professor Joe M. McCord

David M. Schnell<sup>1</sup> and Daret St. Clair<sup>2</sup>



**Professor Joe McCord**

### Abstract

Dr. Joe McCord (Ph.D. 1970) is recognized here as a Redox Pioneer because he has published at least three articles on antioxidant/redox biology as first/last author that have been cited over 1000 times and has published at least 37 articles each cited over 100 times. Dr. McCord is known for the monumental discovery of the antioxidant superoxide dismutase (SOD) while a graduate student under fellow redox pioneer Irwin Fridovich and demonstrating its necessity to aerobic life. Beyond this, McCord's career is distinguished for bridging the gap from basic science to clinical relevance by showing the application of SOD and superoxide to human physiology, and characterizing the physiological functions of superoxide in inflammation, immunological chemotaxis, and ischemia-reperfusion injury, among other disease conditions. Work by McCord serves as the foundation upon which our understanding of how superoxide functions in a variety of physio-

logical systems is built and demonstrates how superoxide is essential to aerobic life, yet, if left unchecked by SOD, toxic to a multitude of systems. These discoveries have substantial significance in a wide range of studies with applications in cardiovascular disease, cancer, neurology, and medicine, as well as general health and longevity. Dr. McCord's contributions to free radical biology have been recognized through many prestigious achievement awards, honorary titles, and conferences around the world; each serving as a testament to his status as a redox pioneer. *Antioxid. Redox Signal.* 20, 183–188.

My advice to students is this: Science requires the same creativity, inventiveness, and passion that we expect from artists, composers, and writers. When you feel it, you know it. If you don't feel it, then science probably isn't the best career choice for you. This has little to do with whether science seems easy or difficult. It always seemed difficult to me as a student, as it probably should.

—Prof. Joe McCord

### Educational and Professional Training of Dr. McCord

Dr. Joe McCord earned his B.S. in chemistry from Rhodes College (formerly Southwestern at Memphis) in Memphis, Tennessee. He completed his Ph.D. under the direction of

fellow redox pioneer Dr. Irwin Fridovich in the Department of Biochemistry at Duke University in Durham, North Carolina. Dr. McCord stayed in the Fridovich laboratory to complete his postdoctoral training and continue his research in the physiological roles of superoxide dismutase (SOD).

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Reviewing Editors: *Irwin Fridovich, Barry Halliwell, Arne Holmgren, Ting-Ting Huang, and Gregg Semenza*

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*Author note:* Daret St. Clair is a leading SOD researcher and colleague of Joe McCord who has closely followed his work for more than 20 years. David M. Schnell is a graduate student under the direction of Daret St. Clair.

For a list of frequently cited articles published by Prof. Joe McCord, see Supplementary Tables S1 and S2, available online at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)

## Background, Development, and Training

McCord is a native of Memphis, Tennessee, where he graduated from Central High School. He stayed in Memphis for his bachelor's degree in chemistry at Rhodes College, where he spent two summers working in the laboratory of Dr. Harold Lyons. Dr. Lyons helped to cultivate McCord's interest in research and encouraged him to pursue a graduate degree in biochemistry at the Duke University. At Duke, McCord met Dr. Irwin Fridovich, who was at the time, the director of graduate studies. Attracted to Fridovich's approachable demeanor and love of teaching, McCord joined his laboratory for Ph.D. studies during which they discovered and characterized SOD. Recognizing the significance of SOD and the unique research conducted there, McCord stayed in the Fridovich laboratory to complete his postdoctorate work.

## Summary of Top Contributions

Dr. McCord's career in research began with the discovery of SOD and has since been devoted to understanding the mechanisms and physiological roles of superoxide radicals and SOD. His work serves as the foundation and fundamental understanding of superoxide radicals in aerobic metabolism as well as its role in a variety of pathophysiology, particularly inflammation and ischemia-reperfusion injury. Research orchestrated by McCord illustrates the double-edged sword of superoxide generation as both a highly destructive by-product of aerobic metabolism and as an essential actor in the immune response.

## Relevance of Findings to Human Health

Dr. McCord's research discovering and characterizing the physiological roles of SOD contributes to the foundation of

modern medicine's understanding of immune response and ischemia-reperfusion injuries and has helped to improve current treatments and medical procedures.

## Area of Interest in Redox Biology

When Dr. McCord began his research career as a graduate student under the direction of Dr. Irwin Fridovich, the Fridovich laboratory was interested in the reduction of cytochrome c caused by xanthine oxidase. This reaction was observed in the presence of oxygen, but not in anoxic environments and was thought to be mediated by an electron bridge formed when a superoxide radical ( $O_2^{\bullet-}$ ) bound to xanthine oxidase (8). As a new member of the laboratory, McCord was assigned a project measuring the physical binding between xanthine oxidase and carbonic anhydrase, a proposed inhibitor of xanthine oxidase. Although thought to be a simple project, experiment after experiment failed to show the predicted binding between the two proteins. McCord began to reevaluate the hypothesis under which he was operating and considered other possible mechanisms for the decreased reduction rate of cytochrome c. He considered the reduction of cytochrome c as two half reactions with the possibility of superoxide acting as a free molecule in a solution. Superoxide had long been recognized as a product in xanthine oxidase catalysis (8); however, it had never been investigated as a free reducing agent of cytochrome c. With adjusted experimental direction, McCord discovered that cytochrome c did not bind to xanthine oxidase, nor did any other suspected inhibitors. This disproved the theory that cytochrome c was reduced by the xanthine oxidase-oxygen bridge complex and suggested that the reducing agent was instead a free superoxide radical produced by xanthine

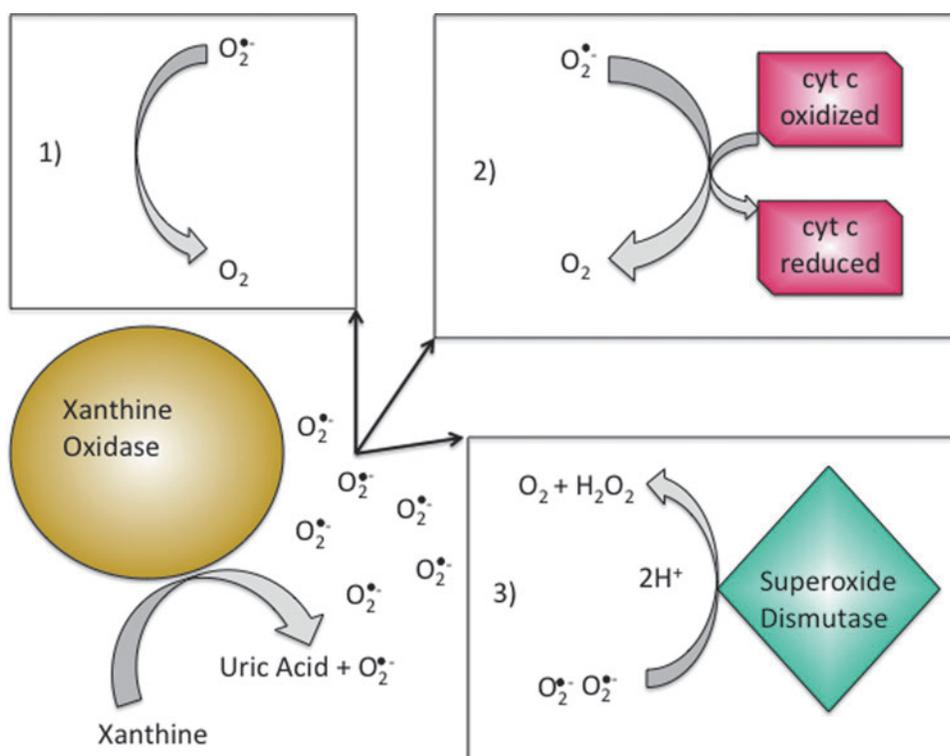


FIG. 1. The oxidation of xanthine to uric acid by xanthine oxidase produces superoxide ( $O_2^{\bullet-}$ ), which can undergo three possible fates: 1) spontaneous dismutation; 2) reduction of cytochrome c; or 3) reaction with superoxide dismutase to create  $H_2O_2$ . To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)

oxidase (19). The article describing these findings has been cited over 9000 times.

If cytochrome c was not a substrate of xanthine oxidase, and therefore was not outcompeted for xanthine oxidase binding sites by carbonic anhydrase, what was inhibiting the reduction? McCord and Fridovich recognized that the inhibiting factor would have to eliminate superoxide from the solution through catalyzing a dismutation reaction. The observed dismutase activity was initially attributed to carbonic anhydrase and myoglobin (18).

McCord set out to purify the SOD-containing enzyme from bovine erythrocytes and produced a vivid, blue-green colored copper-containing protein exhibiting a specific activity of 3300 units per milligram (19). McCord and Fridovich identified this blue-green enzyme to be the same as the copper storage proteins, erythrocuprein, hemocuprein, cerebrocuprein, hepaticcuprein, and cytocuprein. Upon recognizing these supposedly unconnected and enzymatically inactive proteins were, in fact, all the same enzyme and moreover highly active in the dismutation of superoxide, McCord and Fridovich coined the name *superoxide dismutase* (19) and defined its activity as shown in reaction 1 (see also reaction 2 in Fig. 1).



### Description of Key Finding 1

#### *SOD is essential to aerobic life*

After isolating and identifying SOD, the next investigative step was to determine its physiological role on a grand scale through the examination of SOD activity in a variety of aerobic and anaerobic bacteria. Oxygen toxicity was previously thought to be a result of hydrogen peroxide accumulation and therefore managed by catalase. However, McCord showed that catalase could not predict aerotolerance with 100% fidelity (20), suggesting the involvement of another actor in aerotolerance. McCord and coworkers examined catalase and SOD activity in 26 microorganisms and showed that SOD was active in all examined bacteria capable of aerobic metabolism. Aerotolerant anaerobes, preferential anaerobes capable of aerobic metabolism, contained no catalase activity, but did exhibit SOD activity similar to and even exceeding their aerobic counterparts. This experiment was crucial in understanding the role of SOD in reactive oxygen species management and aerobic life.

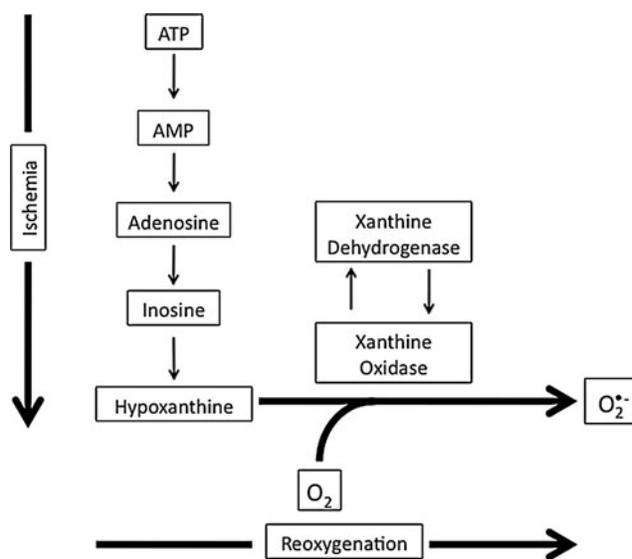
Further research from the Fridovich laboratory showed that the copper-containing SOD, formerly identified as the cuprein family of proteins, was not the only variety of SOD. Working with Bernard Keele, McCord was part of the research group that discovered a second type of SOD in *Escherichia coli*. Through ultracentrifugation and dialysis, Keele isolated 16 mg of a red-purple protein exhibiting 3800 units of SOD activity per mg (16). Electron paramagnetic resonance spectroscopy and quantitative colorimetric analysis identified 1.6–1.8 atoms of manganese per molecule of enzyme, distinguishing it as a completely new variety of SOD. Structurally and evolutionarily unrelated to the cupric SOD discovered in 1969 (CuZnSOD, SOD1), this manganese superoxide dismutase (MnSOD, SOD2) showed convergent evolution of SOD, emphasizing the necessity of SOD in a variety of biological systems.

### Description of Key Finding 2

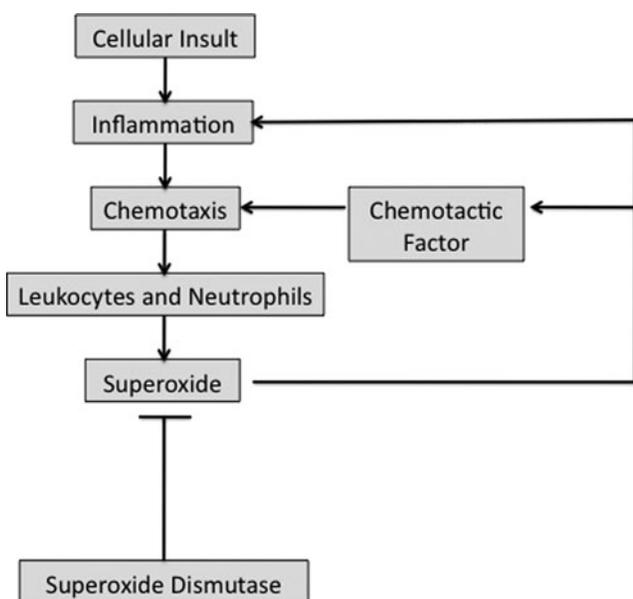
#### *SOD and inflammation*

Shortly after McCord and Fridovich published their work describing SOD, Diagnostic Data, Inc. of California contacted McCord informing him that they had isolated the same copper-containing protein and were marketing it as a veterinary anti-inflammatory drug. The medical application of SOD was of great interest to McCord, leading his work to diverge from Fridovich's kinetic and mechanistic research of SOD and focusing instead on SOD's role in pathophysiology. Around the same time that McCord developed an interest in the physiological roles of SOD, Dr. Bernard Babior of Harvard Medical School published a seminal article showing the production of superoxide radicals by leukocytes during phagocytosis (1). This burst of oxidative activity was one of the first instances showing a beneficial role of superoxide and provided the missing link between superoxide and physiology that McCord was looking for. With this, McCord directed his research toward the role of superoxide and SOD in inflammatory disease, particularly the deterioration of synovial fluid in arthritis.

In his first article as an independent researcher, Dr. McCord established the role of superoxide in the deterioration of synovial fluid through a mechanism of free radical induced depolymerization (21). He showed that this oxidative depolymerization of hyaluronic acid could be inhibited by either SOD or catalase, suggesting that the oxidative species responsible was neither superoxide nor hydrogen peroxide alone, but a product of a reaction between the two: the

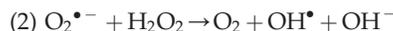


**FIG. 2. Granger and McCord's proposed model for superoxide production in the ischemic bowel.** As ischemia progresses, ATP is catabolized to AMP and further to hypoxanthine, a substrate of xanthine oxidase. In the hypoxic environment, xanthine oxidase is unable to oxidize hypoxanthine to xanthine and hypoxanthine concentrations within the cell increase. Upon reoxygenation of oxygen, xanthine oxidase is again able to oxidize hypoxanthine, which is available at very high concentrations. The rapid oxygenation of hypoxanthine produces superoxide faster than it can be scavenged by superoxide dismutase causing an increase in cellular-free superoxide and oxidative damage. AMP, adenosine monophosphate; ATP, adenosine triphosphate.

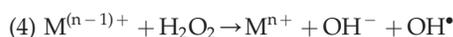
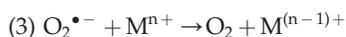


**FIG. 3. The inflammation superoxide-positive feedback loop.** Upon cellular insult and inflammation, chemotactic factors attract leukocytes and neutrophils that produce mass quantities of superoxide as part of phagocytosis and immune response. The produced superoxide in turn further stimulates chemotactic factors and causes more inflammation, attracting more immune cells that produce more superoxide. SOD can manage superoxide produced by phagocytes during the immune response preventing the feedback loop and attenuating inflammation. SOD, superoxide dismutase.

hydroxyl radical ( $\text{OH}\cdot$ ), a product of the Haber–Weiss reaction as depicted in reaction 2.



However, while the stoichiometry was accurate and the reaction is thermodynamically favorable, several studies (13, 17, 26) showed that the Haber–Weiss reaction did not occur naturally at any significant rate. In response to this, McCord separated the reaction into halves, investigating the possibility of chelated iron compounds as intermediaries (22). The enzyme kinetics showed a competitive relationship between SOD and  $\text{Fe}^{3+}$ -EDTA for the removal of superoxide, supporting McCord's theory of chelated iron intermediates to hydroxyl radical formation as shown in the reactions 3 and 4.



### Description of Key Finding 3

#### *A new look at ischemia reperfusion*

By the late 1970s, it was clear that superoxide had both deleterious and beneficial roles in multiple physiological systems. The superoxide radical had been implicated in oxygen toxicity resulting from normal oxidative metabolism (18), necessitating obligatory expression of SOD by aerobic and aerotolerant or-

ganisms to manage oxidative damage (20). It was also produced in large amounts through an oxidative burst during phagocytosis by neutrophils, monocytes, and macrophages as an essential component of the immune response (2). Individuals lacking NADPH oxidase, the enzyme that creates the superoxide radicals in phagocytes, exhibit chronic granulomatous disease and are extremely susceptible to infection (6), often succumbing to fatal infections at a very young age.

Around the time of SOD's discovery, xanthine oxidase was strongly connected to hemorrhagic shock (5) and ischemic damage (7). Knowing xanthine oxidase's role in producing oxygen radicals, McCord examined the role of superoxide in ischemia in the feline bowel as part of a team from the University of South Alabama led by Neil Granger. Their work showed that treatment with SOD before reperfusion of a 60-min ischemic insult prevented ischemia-induced increase in capillary permeability (11). They hypothesized that during ischemia, adenosine triphosphate (ATP) was reduced to adenosine monophosphate (AMP), which was further catabolized to hypoxanthine. Upon tissue reoxygenation, xanthine oxidase rapidly converted hypoxanthine to xanthine, generating large quantities of superoxide. This model recognized that tissue damage was not caused by the lack of oxygen, but instead by free radical production during reperfusion, fundamentally changing medicine's understanding of ischemia-reperfusion injury and treatment (Fig. 2) (10).

### Other Achievements

During research examining the production of superoxide by leukocytes and neutrophils, McCord recognized that



Professor McCord and his research group at University of Colorado Denver.

superoxide acts as an initiator of immune cell chemotaxis (23). Building on this discovery, McCord's laboratory showed that administration of SOD before an inflammatory challenge through injection of xanthine oxidase (a superoxide generator) could preclude up to 99% of neutrophil recruitment, while treatment with catalase could only prevent 28% of neutrophil recruitment (25). This model of superoxide-initiated chemotaxis (outlined in Fig. 3) represented a breakthrough in the understanding of superoxide and perhaps the first instance in which superoxide was demonstrated as a cellular signaling molecule.

McCord has also made major contributions to the understanding of reactive oxygen species and SOD in the immune system. His work has shown localized superoxide production in polymorphonuclear leukocytes as a bacteriocidal mechanism (27) and the use of SOD as a protective measure in phagocytosing leukocytes (28). He was also a contributor to groundbreaking work implicating superoxide in myocardial damage from ischemia reperfusion (3, 4) in a fashion similar to that seen in intestinal ischemia. Expanding on this work, McCord showed that xanthine oxidase inhibitors are capable of preventing oxidative damage in both myocardial and intestinal ischemia-reperfusion injuries (4, 12).

Beginning even before the discovery of its enzyme activity, a great deal of time and money has been spent in trying to make SOD into a clinically useful therapeutic agent to protect against inflammation, reperfusion injury, and oxidative damage. However, none of these attempts have achieved clinical success. In 2003, McCord and colleagues synthesized a chimeric SOD combining the body of SOD1 with the heparin-binding domain of SOD3 with improved pharmacological properties (9, 14). However, a much more efficient and practical method of increasing human *in situ* antioxidant activity was recognized through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor referred to as the "master regulator of antioxidant enzymes." Nrf2 regulates the expression of not only SOD, also catalase, glutathione peroxidases, and many other enzymes active in the prevention and cleanup of oxidative damage. In recent years, McCord has developed a composition of five highly synergistic natural Nrf2 activators as a dietary supplement called "Protandim<sup>®</sup>" (15, 24, 29).

### Current Position

Dr. McCord has held faculty positions at Duke University, the University of South Alabama, and the University of Colorado. He served as the Chairman of the biochemistry department at the University of South Alabama for 9 years before relocating to the Webb-Waring Institute at the University of Colorado Anschutz Medical Campus in 1990 as the head of the Division of Biochemistry and Molecular Biology. As a Professor of Medicine at the University of Colorado, McCord held joint appointments in Biochemistry, Microbiology, and Toxicology until his retirement in 2011. Dr. McCord currently maintains an appointment as Clinical Professor of Medicine at the University of Colorado and serves as Chief Science Officer of LifeVantage Corp., which produces the Nrf2-activating dietary supplement Protandim. According to Prof. Joe McCord, "My advice to students is this: Science requires the same creativity, inventiveness, and passion that we expect

from artists, composers, and writers. When you feel it, you know it. If you don't feel it, then science probably isn't the best career choice for you. This has little to do with whether science seems easy or difficult. It always seemed difficult to me as a student, as it probably should."

### Acknowledgments

Dr. McCord credits a number of individuals as having had great influence on the direction his career has taken, including a few who may not have been aware of their influence. Among the most notable, he mentions his mentor and friend Irwin Fridovich, his undergraduate mentor Harold Lyons, and colleagues Bernard Babior, Neil Granger, and Charles Baugh. McCord notes that a successful career is driven by connections not only between data sets, but also people: a scientist cannot be successful in isolation.

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#### Abbreviations Used

AMP = adenosine monophosphate  
 ATP = adenosine triphosphate  
 CuZnSOD = copper-zinc superoxide dismutase  
 EDTA = ethylenediaminetetraacetic acid  
 MnSOD = manganese superoxide dismutase  
 Nrf2 = nuclear factor erythroid 2-related factor 2  
 SOD = superoxide dismutase