Free Radicals in Biology

VOLUME IV

Edited by
William A. Pryor

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General Preface

This multivolume treatise had its genesis in April, 1970, when a number of chemists and biologists interested in free radical biology met in Atlantic City at the President's Symposium of the American Society for Experimental Pathology [*Federation Proceedings* **32,** 1859–1908 (1973)]. In a discussion following the meeting, the speakers all agreed that no adequate textbook or monograph existed in the fascinating and diverse field of free radical biology. This lack is felt both by workers studying one aspect of the field who would like a broader grasp of other areas and by biologists and physicians who are not working in the field but who wish to learn of recent developments.

The areas included under the general rubric of free radical biology are so varied that no single author could possibly have expertise in all of them. For example, relevant topics include the organic and physical-organic chemistry of free radicals; the various reactions of oxygen, including autoxidation, reactions of the superoxide radical, and reactions of singlet oxygen; the chemistry of antioxidants, including vitamin E; oxygen toxicity; the chemistry of polyunsaturated fatty acids and their role in membrane chemistry and physics; photochemistry, photobiology, and radiation biology; oxidases, hydroxylating enzymes, and detoxification systems; electron-spin resonance studies of enzymes and substrates, spin-label studies, and esr studies of tissue samples; the toxicity of chlorinated hydrocarbons; the chemistry and biochemistry of smog; the chemistry of cigarette smoke; carcinogenesis of aromatic hydrocarbons, amines, and other compounds; and, finally, the role of free radicals in the time-dependent degradation we call "aging."

In view of the need for an up-to-date review of free radical biology and the enormous diversity of the areas involved, the participants in the 1970 Atlantic City FASEB meeting agreed that a series of monographs was needed. It has been my pleasure and privilege to serve as editor of these volumes.

I have asked the authors involved in this project to write both for novices and for specialists. I wanted chapters that would not only serve as précis and a "first place to look" for an introduction to a field, but also as up-to-date reviews for experts. This has proved to be a difficult task. So many areas, representing such a diverse background of skills, need to be reviewed that the problem is especially acute. In some cases the subject matter could easily be presented at an elementary level; in others, however, the very nature of the material dictated a more detailed and advanced review. I hope, nonetheless, that most of the chapters in these volumes are at a level that allows them to serve both as a brief introduction to each area and also as an up-to-date survey of each topic.

It seems particularly appropriate that the first of these volumes was published on the two-hundredth anniversary of the discovery of oxygen by Joseph Priestley. Certainly the necessity of organisms tolerating oxygen in their energy-producing systems gives rise to many of the problems and interesting topics in this field. Had glycolysis, or some similar anaerobic process, never been replaced with respiration, organisms would not have had to learn to protect themselves against the oxidative threat that oxygen presents. Also, oxygen appears to be particularly susceptible to one- as well as two-electron transfers, and thus is responsible for producing some of the one-electron intermediates found in the cell.

I hope that these volumes, which bring together many of the diverse subjects in free radical biology, will make these topics accessible to chemists, biologists, and physicians. I also hope that the reader will agree that this is a fascinating, sometimes controversial, and important field.

William A. Pryor

Preface to Volume IV

The rapid development of free radical biology is attested to both by the variety and the importance of the topics treated in the chapters of this volume. The scope of the chapters included in this fourth volume encompasses radiation biology, lipid peroxidation (which continues to occupy a key position in this field), radical-mediated liver pathology, chemical carcinogenesis, radical mechanisms in prostaglandin biochemistry, and the use of electron spin resonance (esr) and spin trap methods to probe mechanisms of radical reactions in biological systems.

The polyunsaturated fatty acids (PUFA) in lipids are among the biological target molecules that are most easily attacked by free radicals. An extensive literature clearly demonstrates that radical attack on PUFA initiates their autoxidation, and this can trigger membrane disruption, cell leakage, and ultimately death. Detailed treatments of lipid peroxidation were given in earlier volumes in this series; the reader may wish to consult, for example, Volume I, Chapter 2 by James F. Mead and Chapter 6 by Irwin Fridovich; Volume II, Chapter 3 by Christopher S. Foote and Chapter 6 by Daniel B. Menzel; and Volume I, Chapter 1 by myself.

This volume includes two chapters on lipid autoxidation and related subjects. In Chapter 1, Al L. Tappel, one of the pioneer workers in free radical biology and a person who has contributed enormously to our understanding of lipid peroxidation, reviews mechanisms of lipid peroxidation and potential protective mechanisms. Chapter 1 covers the chemistry of fluorescent products from *in vivo* lipid peroxidation, the production of pentane in the expired breath of animals exposed to oxidative threats, and the chemistry of the enzyme glutathione peroxidase, one of the enzymes that detoxifies lipid peroxides.

In the second chapter devoted to lipid peroxidation, Lloyd A. Witting, in Chapter 9, reviews kinetic aspects of lipid peroxidation, a topic he has been interested in for many years. In this review, he clarifies the multiple ways in which autoxidants can react, a subject that often causes confusion.

In Chapter 2, Edward S. Reynolds and Mary Treinen Moslen review mechanisms of hepatoxicity by synthetic chemicals present in the environment. A variety of xenobiotic compounds cause damage to the liver; in many cases the mechanism is thought to involve the transformation of the toxin to a reactive free radical that can initiate lipid peroxidation. Reynolds and Moslen review the significance and reliability of the available criteria for the involvement of radicals, including pathological, metabolic, and biochemical data. A considerable portion of the chapter is concerned with halomethanes such as CCl_4, an important liver toxin that has been studied in detail. Readers interested in the toxicity of carbon tetrachloride may also wish to consult Volume III, Chapter 3 by Richard O. Recknagel *et al.* on this subject.

L. S. Meyers, Jr. reviews direct mechanisms of radiation damage to nucleic acids in Chapter 3. Radical involvement in radiation biology was treated by Thornod Henriksen and co-workers in Chapters 8 and 9 in Volume II. These chapters describe radical damage to proteins and radical reactions of nucleic acids in crystal systems. Radiation biology was also reviewed in detail in Chapters 1 and 2 of Volume III; in these chapters Benon H. J. Bielski and Janusz M. Gebicki treated the application of radiation chemistry to biological problems, and Gerald E. Adams and Peter Wardman explained the pulse radiolysis approach.

The extremely rapid pace of the development of our understanding of prostaglandins has provided new examples of the roles of radicals in normal biological processes. The prostaglandin synthetase enzyme system produces a range of cyclic peroxides and lipid hydroperoxide molecules, establishing for the first time that animals as well as plants have lipoxygenase activity. Clearly, this is a field that will have enormous implications in free radical biology. In Chapter 8, Ned A. Porter reviews useful synthetic approaches to prostaglandin molecules. He also argues that the biosynthesis of the key prostaglandin endoperoxide, PGG, involves radical reactions controlled by the prostaglandin enzyme systems.

There is considerable inferential evidence for the involvement of radicals in chemical carcinogenesis. For example, antioxidants protect against almost every class of chemical carcinogen in a range of animal and tumor models. A detailed examination of the mechanisms for the conversion of arylamines to carcinogenic activity is described by Robert H. Floyd in Chapter 6; this is an extremely interesting system in which radicals are clearly involved. Readers may also wish to consult Volume I, Chapter 3 by Donald C. Borg on the application of esr methods to biology, since this chapter reviews the evidence for the involvement of radicals in several systems where carcinogenic activity has been demonstrated, and the general review in Volume III, Chapter 7 by Paul O. P. Ts'o *et al.* on the involvement of radicals in chemical carcinogenesis.

The use of esr is becoming more and more important in the study of biological free radicals, and this volume provides several chapters on this subject. In Chapter 7, the group at the Medical College of Wisconsin describes the structure and reactivity of melanins, a class of pigments that contains stable free radicals that are most conveniently studied by esr techniques. In Chapter 10, Kazimierz Ostrowski and co-workers describe radiation-induced radicals in mineral tissue and calcified tissue.

The relatively new technique of spin trapping greatly extends the number of systems that can be studied by esr techniques. Frequently, radicals that are not sufficiently stable to be directly detectable by esr can be captured and studied by the spin trap method. (Spin traps are molecules that react with reactive free radicals to form stabilized radicals that can be studied more conveniently by esr methods.)

In Chapter 4, Edward G. Janzen, one of the inventors of the spin trap method, describes the chemical background of this method and some of its biological applications. In Chapter 5, Paul B. McCay *et al.* apply the method to the study of enzyme systems, including the system that converts carbon tetrachloride to a reactive and toxic free radical. In this chapter, McCay and his group also describe, for the first time, the use of a spin trap in living animals. They show that spin traps can be fed to animals at the same time that toxins are administered and spin adducts can be isolated from the liver, demonstrating the production and reaction of radicals *in vivo*. This clearly is an exciting advance that will be followed up in many laboratories.

William A. Pryor

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