FOREWORD

The modern concept of oxidative stress brought on by free radical-induced damage is now widely accepted in many disciplines of the biomedical field, including gerontology. The reason this theory has received such broad support stems from an appreciation of the inherent cellular damage produced by the ubiquitous free radical activity found in all respiring cells (1-3).

Emerging evidence claims new roles for reactive species as regulators of essential biochemical and physiological functions. Their apparently paradoxical characteristics (i.e., damage/regulation) create interesting and intriguing cellular reactions; as evidenced under conditions of physical exercise, these reactions underscore the important dual functions of defense systems to tightly control and regulate their activity. One situation where free radical reactions are seemingly out of control is in age-related disease processes. In recent years, many investigators have provided abundant evidence verifying the involvement of oxidative stress in the chronic diseases of aging (2). For example, current evidence supports the notion of reactive species as contributors to degenerative diseases such as atherosclerosis, diabetes, and neoplasm. This evidence is further supported by studies investigating the anti-aging action of dietary restriction. Now known as the most effective anti-oxidative deterrent in defense systems, dietary restriction is shown to simultaneously suppress free radical damage and enhance defense systems (3).

Highlighting the importance of oxidative stress and its possible modulation of the aging process, I have compiled seven reviews of current interest. Each is presented by well-qualified investigators, actively involved in research on their topic of discussion. The articles are presented in two separate issues of **AGE**, four in this volume and three in the volume to follow. Here I will briefly summarize the essence of each topic.

Issues related to the stability and maintenance of the membrane (a prime target of lipid peroxidation) is discussed by Dr. C. Pieri. This article highlights important new evidence on age-related membrane rigidity, a condition previously blamed on increased cholesterol (4). Recent findings show that membrane fluidity is exquisitely more sensitive to lipid peroxidation than to cholesterol accumulation. Dr. Pieri reviews the evidence, elucidating how the membrane's sensitivity to lipid modification is highly dependent on age-related, membrane lipid compositional changes, which are known to shift toward increases in peroxidizable polyunsaturated fatty acids. The significance of this increase is emphasized in an interesting recent report of G. Barja's group, showing that mitochondria isolated from pigeon (known to have lower lipid peroxidation and longer life spans than rats) have lower unsaturated fatty acid levels than rats (5,6).

Topics on oxidatively modified proteins are also of current gerontological interest. There is little doubt that protein oxidation can profoundly affect the structural

integrity and many enzymatic activities of the cell. Quantitative evidence for such modifications has been best documented in age-related carbonyl values. The significance of protein oxidation and improved methodologic procedures used in the detection and quantitation of carbonyls is carefully reviewed by Drs. S. Goto and A. Nakamura.

Another area of interest to many gerontologists is the ability of physical exercise to induce oxidative damage, yet reduce morbidity in the elderly. A possible resolution to this paradoxical damage/benefit effect may be found in the upregulation of anti-oxidative defenses induced by physical activity. Discussions related to the mechanisms that underlie the modulation of oxidative stress are presented in an article by Drs. L.L. Ji and S. Leichtweis. Physical exercise is also discussed by Drs. Ikeno, Bertrand, and Herlihy, who focus on the apparent effect of exercise on the attenuation of the disease status. Although the mechanisms underlying the disease-retarding action of exercise are complex, the authors present an interesting review that analyzes the current understanding of these effects on aging by bringing together what is known about the metabolic aspects of exercise and the life-prolonging effect of dietary restriction.

Recent interest in finding more effective antioxidants has led to the identification of several compounds. One well-tested and experimentally scrutinized compound is flavonoid-based, Ginkgo biloba. Although France and Germany have already approved this substance as a therapeutic drug for cerebral protection, its efficacy is less known in the United States. Dr. Droy-Lefaix introduces its efficacy and utilization based on research endeavors to characterize its potent anti-oxidative property.

To better understand cellular oxidative stress, it is important to define its cellular sources, besides mitochondria. One such source is free radical-generating xanthine oxidase. Although its participation in oxidative stress during ischemia/reperfusion is well-documented, almost no information is currently available concerning the status of xanthine oxidase with age, particularly on the regulation of xanthine oxidase/xanthine dehydrogenase conversion during normal aging processes. Dr. H. Y. Chung discusses the biochemistry of this enzyme system in relation to aging.

The molecular alteration of the genes responsible for mRNA expression and protein synthesis is an exciting approach gerontologists are using to gain greater insight into the roles of specific genes in the aging process. This approach opens new avenues by which to explore the poorly understood molecular mechanisms and interactions of genomic factors as well as oxidative modulation. Drs. M. Pahlavani and H. Van Remmen address these important questions by reviewing the current status and future directions of molecular applications in aging research.

It is my hope that the compilation of these seven articles will provide readers with valuable, updated information on the oxidative status of organisms during aging. As editor of this special issue, I hope these articles prove enlightening and useful. In presenting this many review articles, acknowledgments are due to many people. First, I would like to thank each author who willingly dedicated many hours to this worthwhile endeavor, as well as those who so adeptly reviewed these articles. My thanks also go to Ms. Corinne Price for her invaluable assistance in editing these articles and to Mrs. Kim Kennedy for preparing final versions for publication.

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Guest Editor

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