Free Rad. Res., Vol. 27(4), pp. 437–443
Reprints available directly from the publisher
Photocopying permitted by license only

Book Reviews

Antioxidants in Disease Mechanisms and Therapy
Helmut Sies, Volume Editor
Advances in Pharmacology Series, Volume 38
Academic Press, 1997
ISBN 0-12-032939-5
691 pages

Following the tradition of OXIDATIVE STRESS (1985) and OXIDATIVE STRESS: OXIDANTS AND ANTIOXIDANTS (1991), **ANTIOXIDANTS IN DISEASE MECHANISMS AND THERAPY** (1997), edited by Helmut Sies, is a must in the library of researchers in the area of free radical biology. Although this new volume focuses on some new strategies of antioxidant defense in terms of new pharmacologically active agents, it presents an invaluable in-depth critical coverage of topics inherent in the 'antioxidant literature' and ranging from basic physical chemistry concepts to clinical therapy, prevention, and epidemiological perspectives.

ANTIOXIDANTS IN DISEASE MECHANISMS AND THERAPY belongs to the Advances in Pharmacology series edited by Academic Press. The book is divided in four parts: Natural Antioxidants, Synthetic Antioxidants and Enzyme Mimics, Antioxidant Enzyme Induction and Pathophysiology, and Disease Processes. Each of these carefully selected parts contains several chapters written by authorities in the field. An important aspect of this book is not only that the topics selected in each chapter are thoroughly and critically addressed, but it depicts a comprehensive arrangement formulated by the entire goals of the book. This is also strengthened by the excellent print style of the book, which is uniform and has been carefully edited. The reader will also benefit by a complete subject index.

Part I, Natural Antioxidants, lists eight chapters written by experts in the field. Following an introductory chapter on the basics of antioxidant mechanisms, updated reviews on the antioxidant properties of vitamins C and E and of glutathione/glutathione delivery compounds are included. The most salient features of Part I are a critical and exhaustive coverage of the antioxidant properties of melatonin and polyamines as well as the potential role of lipoic acid as a redox modulator of transcription, this addressing the possible therapeutic roles of lipoate in processes involving modification of NF-κB activity. The last chapter in this part of the book addresses interesting aspects on the antioxidant properties of flavonoids, including cytotoxic effects against tumor cells and the mutagenic/antimutagenic character of these compounds.

Of necessity, any book on Antioxidants is expected to cover enzyme mimics and some of the synthetic antioxidants. Although this is a difficult and controversial field, the chapters in Part II have been carefully selected and they convey a sense of useful knowledge in the area, usually difficult to achieve. The glutathione peroxidase-, superoxide dismutase-, and catalase mimics are dutifully covered and, as a token, the novel activity of Ebselen as a scavenger of peroxynitrite and its clinical assessment as an anti-inflammatory antioxidant are discussed.

Of equal excellent quality are the two other chapters in this part of the book: that on iron chelators provides useful chemical concepts—usually disregarded—, a good classification of these compounds, and a critical assessment of iron chelation therapy. That on the thiol-containing compound *N*-acetylcysteine is a complete view on different aspects of this compound: biopharmaceutical and pharmacological aspects, pharmacokinetics, cell and gene modulatory effects, and the role of *N*-acetylcysteine in several disease states.

The six chapters contained in Part III of **ANTIOXIDANTS IN DISEASE MECHANISMS AND THERAPY** feature recent aspects of one of the most interesting areas in the field: Antioxidant Enzyme Induction and Pathophysiology. Following the basic concepts of inherent in antioxidant drug targeting (towards organs, desired cell types, and particular intracellular metabolic pathways or signal transduction systems), a chapter on expression of antioxidant-inducible genes in mammalian cells provides a complete survey built on typical inducers acting on specific tissues. Two chapters are concerned with redox signaling as it effects cell growth and death as well as transcription factors and inflammation, they feature prominent key issues in the field and they are a pleasure to read. The more circumscribed effects of nitrone-based free radical traps on oxidative damage to the central nervous system and of the role of oxygen radicals in Downs syndrome are the subjects of the other two chapters in part III of this book.

Finally, part IV—on Disease Processes—includes eleven chapters, each one standing on its own in terms of metabolic equilibria, clinical significance, pathobiological considerations, therapeutic strategies, emerging issues, and future directions. The disease processes treated are atherosclerosis, adult respiratory distress syndrome, cystic fibrosis, cataract and age-related macular degeneration, neurological disease, HIV infection, alcoholic and nonalcoholic liver diseases, diabetes, photoaging of connective tissues of skin, and an epidemiological perspective on antioxidant nutrients, cancer incidence, and mortality. Part IV is as exhaustively complete as it can be defined by quality and limited by space.

In summary, **ANTIOXIDANTS IN DISEASE MECHANISMS AND THERAPY** is an excellent book, highly recommended, on topics of great current interest.

Enrique Cadena

Present Knowledge in Nutrition (Seventh Edition)
Ed E.E. Zeigler and L.J. Filer jr
1996 ILSI Press Washington DC

As a lecturer in nutrition, I was delighted to receive this very interesting book for review. The editors are to be congratulated on managing a good balance, in this reference book, between the generality of a text book and the speciality of an advanced research book. Indeed this approach of each author producing a highly referenced though relatively short contribution, is one that has now been adopted by a number of text books. This approach indicates the enormous body of knowledge encompassed by the title nutrition. Indeed, around 64 different areas of nutrition are covered.

The book starts with energy requirements then moves *via* hunger and appetite to obesity. The macronutrients are considered next, followed by dietary fibre and then the vitamins and minerals (a separate chapter is devoted to each). The contributions on nutrition and disease cover diabetes, atherosclerosis and cancer. Other topics of particular interest are covered by the contributions on toxic substances in foods, drug-nutrient and gene-nutrient interactions and antioxidants. The book is very topical and up-to date: the sec-

tion on macronutrient replacements even considers the sucrose polymer Olestra, which is currently being proposed as a fat substitute.

The book could possibly have placed more emphasis on the role of dietary phytochemicals in general and in particular the flavonoids, in human health. Flavonoids include the potent antioxidant quercetin found in apples, red wine and tea and the oestrogenic isoflavones such as genistein found in soya products. Phytoestrogens including isoflavones may protect against hormonal-dependent cancer and heart disease. Indeed, flavonoids are the focus of our current research and perhaps they are candidates for more indepth coverage in the eighth edition of this most useful book.

The illustrations are adequate and presumably colour diagrams have not been used to ensure a reasonably low cost. Overall I am pleased to be able to thoroughly recommend this book.

Helen Wiseman
Nutrition, Food and Health Research Centre
King's College London

Cytokines Produced by Polymorphonuclear Neutrophils: Molecular and Biological Aspects
Cassatella, Marco A
Springer-Verlag, Berlin, 1996

The purpose of this book, as stated in the preface, is "to present current knowledge on the production of cytokines by neutrophils in an efficient and organized manner". It succeeds admirably. From a succinct description of neutrophils (Chapter 1) and cytokines (Chapter 2), the book moves on to consider what cytokines are produced by human neutrophils, *in vivo* and *in vitro* and how this production is regulated both in health and disease. Overall, the book is nicely presented and a useful review of the field, and I am pleased to have it on my bookshelf.

Barry Halliwell
Neurodegenerative Disease Research Centre
King's College London

Tamoxifen: Beyond the Antiestrogen
Edited by J.A. KELLEN
Birkhäuser Verlag: Basel
x+ 377 pages
ISBN 3-7643-3842-3. 1996

Tamoxifen: Beyond the Antiestrogen comprises of a collection of papers from notable experts that have worked for a number of years with the drug. Tamoxifen (ICI 46,474 Nolvadex) is a non-steroidal antiestrogen with demonstrated anti-infertility properties in mice and rats. It has been shown to have efficacy in the treatment of advanced breast cancer and has been evaluated as a preventive agent in women at the risk of breast cancer [Jordan (1993) *British Journal of Pharmacology* **110**, 507–517].

The book contains 17 well written and presented chapters. The excellent introductory chapter by Kellen is complemented with a review of the use of Tamoxifen in treatment of malignancies other than breast cancer. Rowlatt discusses 'neoplasia' in the second chapter—the reader is reminded that scientists are still dependent on clinical judgements which appear subjective in the absence of a verifying hypothesis. Other chapters "Interactions of Tamoxifen with lipid signal transduction cascades" (Cabot and Giuliano); "Carcinogenicity of Tamoxifen" (Sasco and Gendre)—an excellent account of randomised controlled clinical trials in

the 1970–1980s which suggests the risk of endometrial cancer among women receiving Tamoxifen; "Mechanisms of resistance to antiestrogens and their implications for crossresistance" (Clarke and Lippman); "Tamoxifen and multidrug resistance in cancer" (Kellen); "The effect of Tamoxifen on the immune response" (Baral, Nagy and Berczi); "Cellular effects of early exposure to Tamoxifen" (Iguchi and Ohta); "The covalent binding of Tamoxifen to proteins and DNA" (Kupfer); "Tamoxifen metabolism and oestrogen receptor function—implications for mechanisms of resistance in breast cancer" (Johnston and Dowsett); "Tamoxifen and the E-cadherin/catenin complex" (Bracke, Van Roy, Castronovo and Mareel); "Regulation of growth factor gene expression by Tamoxifen" (Murphy and Murphy); "Tamoxifen and drug metabolising enzymes" (Ahotupa); "Membrane antioxidant-mediated cardioprotective anti-carcinogenic actions of Tamoxifen" (Wiseman); "Antiestrogen regulation of *erb*B2 expression in human breast cancer cells" (Wärri and Härkönen) and a concluding chapter by Kellen. As an add on to the involvement of Tamoxifen in oxidative reactions, this reviewer found that Tamoxifen reacts very rapidly with peroxyl radicals—intermediate species in the process of lipid peroxidation, with a calculated rate constant of 4.7×10^7 $M^{-1}s^{-1}$ and its hydroxylated metabolite (discussed in Chapter 10 by Johnston and Dowsett) also reacts rapidly with peroxyl radicals with a rate constant of 5.3×10^7 $M^{-1}s^{-1}$.

In general the book gives an impressive account of the complex biopharmacy and pharmacology of Tamoxifen. The sense of accomplishment which elates the reader is borne out of the unique 'curtain raiser' and the 'final curtain' of quotes: "to single out causes, one must make loose assumptions"—Levy 1995, and, according to Abraham Lincoln, "with high hope for the future, no prediction is ventured."

This is probably one of the better books on Tamoxifen in recent years.

Dr. Okezie I. Aruoma
Pharmacology Group
University of London King's College

Neurodegeneration and Neuroprotection in Parkinson's Disease
Edited by: C. W. Olanow, P. Jenner & M. Youdim
Publishers: Academic Press

Parkinson's disease (PD) is a progressive movement disorder characterised by a relatively selective degeneration of dopaminergic neurones in the substantia nigra. Despite the fact that the main pathological and biochemical changes in PD have been known for many years, the exact mechanism by which the neurones degenerate is not known and current therapy can only treat the clinical symptoms of the disease. This latest book in the 'Neuroscience Perspectives' series published by Academic Press aims to review the various factors which are thought to contribute to the neurodegenerative process in PD. In addition the book outlines novel therapeutic strategies which may counteract such mechanisms, hence serving as neuroprotective agents.

Oxidative stress (OS) has been implicated in many neurodegenerative diseases including PD where the role of OS has been extensively researched. Indeed, OS is extensively covered in the first of the seven sections covered by the book. The opening chapter in this section by *Halliwell & Gutteridge*—'Oxidative stress, brain iron & neurodegeneration. Basic principles'—clearly and concisely deals with the principles of free radical formation, the bodies antioxidant mechanisms, the role of iron in free radical production, molecular targets of OS and the specific susceptibility of

the brain to OS. This chapter forms a good basic foundation facilitating a clearer understanding of the data presented in the remaining five chapters in this section. The second chapter in this section by *Jenner & Olanow* deals with pathological evidence in support of a role for OS in PD. Although a large percentage of the data presented in this chapter is several years old the chapter does provide a useful review of how alterations in iron metabolism and increased OS may play a role in the pathological mechanisms involved in PD. Since most of the evidence in support of a role of OS has come from post-mortem studies on brain tissue collected from patients at the end stage of the disease, it is difficult to conclude whether OS is a primary feature of the pathological process or whether it is a secondary phenomenon. In an attempt to address the question of whether OS is a primary or secondary event the authors present data from a study on incidental Lewy body disease. Such clinically normal individuals have been termed pre clinical PD patients since when examined at post-mortem they have moderate cell loss in the substantia nigra and Lewy bodies. Data from these studies have shown no gross changes in iron metabolism, suggesting changes in iron metabolism are a secondary phenomenon. However, OS was still evident even at this early stage of the disease process. The authors conclude that whether OS is a primary or secondary event it may still play an important role in the disease process and be a potential target for drug therapy.

The topic of iron and OS in PD is revisited in the fourth chapter by *Olanow & Youdim*—'Iron & neurodegeneration: prospects for neuroprotection'. Although there is considerable overlap with previous chapters the authors do discuss the important question of whether the iron which accumulates in PD is in a reactive form and what may be the potential source of the increased iron load. However, the authors coverage of the use of iron chelators as neuroprotective agents is sadly lacking and dated. The authors conclude this section by discussing the futuristic development of iron chelators which can penetrate the CNS. Such chelators have been in existence for several years and have been shown to be effective in animal models of iron overload but have not been clinically tested in PD. In contrast *Floyd & Carney* in chapter 5—'Nitrone radical traps protect in experimental neurodegenerative diseases'—give an interesting insight into the development of nitrone-based free radical traps and how they can be used as neuroprotective agents in animal models of neurodegenerative disease where OS is known to be involved e.g ischaemia, MPTP model of PD. The authors then go on to discuss why such compounds are neuroprotective and what mechanisms are involved. Such mechanisms appear to be dose related; at high doses nitrone compounds act as true scavengers of oxygen radical and/or secondary free radical products, whilst when given at low doses in a chronic fashion nitrone compounds alter the biological system e.g cytochrome P_{450} mediated metabolism, such that the body can more adequately withstand OS. Such compounds may be potentially useful in the treatment of neurodegenerative disease.

Although nitric oxide (NO), synthesised by nitric oxide synthase (NOS), has many useful biological functions e.g. messenger molecule in the CNS, the toxic effects of NO have been implicated in several neurodegenerative diseases including PD. *Beal* in his chapter on 'Therapeutic effects of NOS inhibition in neuronal injury' gives a clear account of how NO may bring about its toxicity. *Beal* also details how the NOS inhibitor 7-Nitroindazole, which has a high specificity for the neuronal isoform of NOS, is neuroprotective in a variety of animal models of neurodegenerative disease including the MPTP model of PD. One of the proposed mechanisms of NO toxicity is the inhibition of mitochondrial function which ties in well with the next section by *Schapira* on 'Mitochondrial dysfunction in neurodegeneration: prospects for neuroprotection', who gives a clear cut introduction to the function and structure of the various complexes

of the mitochondrial respiratory chain and how such complexes can be inhibited by man made and natural toxins. The chapter then discusses diseases which have been associated with a mitochondrial defects, paying particular attention to PD where there is a selective complex I defect. *Schapira* gives a balanced review of the wealth of data relating to the complex I deficit in brain and other tissues in PD and discusses how OS may affect mitochondrial function. The chapter concludes with an interesting insight into how the dysfunction in complex I in PD links in with the proposed mechanisms of cell death in PD and what neuroprotective strategies may be applied to limit such mitochondrial dysfunction.

The effects of an impairment in mitochondrial energy metabolism that is seen in PD and other neurodegenerative diseases is discussed further in section 3—Excitatory Neurotoxicity, by *Greene & Greenamyre*. Glutamate acts not only as a neurotransmitter, but also as an excitotoxin. Under such circumstances stimulation of the glutamate receptors leads to an increase in intracellular calcium which triggers many cellular processes e.g. increased free radical formation, mitochondrial dysfunction, ultimately leading to cell death. Although evidence linking glutamate excitotoxicity as a primary cause of PD is speculative, *Greene & Greenamyre* give an interesting account of a "weak excitotoxic hypothesis" where glutamate may play a secondary role in cell death in PD and other neurodegenerative disorders. In PD where there is an impairment in energy metabolism there may be insufficient energy to maintain normal membrane potential. Under such circumstances the magnesium blockade of the NMDA glutamate receptor is eased facilitating activation of the receptor by glutamate (under normal circumstances activation would not have occurred). Such activation may trigger a rise in intracellular calcium which may ultimately lead to cell death. Therefore, glutamate levels need not be elevated to cause cell death. Support for such a hypothesis has come from in vivo studies with factors which affect energy metabolism e.g. MPTP model of PD, in which NMDA receptor antagonists have been shown to be neuroprotective.

Two fundamental cellular mechanisms underlie neuronal death: necrosis and apoptosis. Section four by *Nicotera & Orrenius* deals with the role of calcium in these cellular processes. The section opens with a clear review of calcium homeostasis and the cellular effects of calcium overload. The authors then eloquently give a step by step guide of the various stages at which calcium may play a role in apoptosis e.g trigger mechanism, nuclear alteration, regulation of pro-apoptotic genes etc. and then review the evidence linking increased intracellular calcium levels and apoptosis in a variety neurodegenerative disease and their respective animal models. The theme of apoptosis is continued in section 7 by *Tatton et al* who discusses the mechanisms by which small molecules e.g trophic factors and drugs, can reduce neuronal apoptosis. In an excellent review by *Altar and colleagues* in section 5 it is clear that neurotrophic factors can act as neuroprotective/neurorestorative agents and hence may be potentially beneficial in neurodegenerative disorders. However, due to severe side effects resulting from their systemic use, the use of trophic factors may be limited by their need for local application. However, as *Tatton and colleagues* clearly demonstrate with their work on deprenyl (drug used in the treatment of PD), other small molecules may have trophic-like activity which are safe to use systemically. Indeed, deprenyl reduces apoptosis by altering the transcription/synthesis of 40 or more genes/protein, many of which are anti-apoptotic or free radical scavengers. The precise mechanism by which deprenyl produces such changes are not known but such research may lead to the development of novel neuroprotective agents.

Until fairly recently the brain was considered to be an immune privileged site, however in the final book section (section 6) covered by this review, *Appel and colleagues* have demonstrated that autoimmunity may play a role in certain

neurodegenerative diseases e.g amyotrophic lateral sclerosis (ALS). In the sporadic form of ALS antibodies have been detected to the voltage sensitive calcium channels (VSCC) which may result in altered channel function and in increase in intracellular calcium levels and ultimately cell loss. Although, the evidence for an auto immunity involvement in PD is tenuous the authors have utilised immunological methods e.g antibodies harvested from guinea-pigs immunised with dopaminergic cells, to demonstrate that structures involved in PD can be potentially targeted and damaged by immune attack.

Overall, the book cannot be called a 'classic' reference book but it does contain some well written chapters which are not only informative, up to date but also thought stimulating and will be a regular source of reference for anyone owning this book. Sadly, there are small number of chapters which are poorly written and/or have not been fully researched. In addition some of the chapters contain data which is relatively old, so even if you are only relatively up to date with that pile of PD published papers on your desk that you must read, some of the chapters will not tell you anything startlingly new.

Dr. David Dexter
Pharmacology Department
Chasing Cross & Westminster Medical School
London, UK.