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Book Reviews

The Biology of Nitric Oxide, vol. 3. Physiological and Clinical Aspects; vol. 4. Enzymology, Biochemistry and Immunology, *Portland Press, 1994*

Although many aspects of the physiology of nitric oxide remain controversial there can be little doubt that this simple free radical gas has excited the interest of researchers from virtually all fields of biology and medicine.

These two volumes represent the proceedings of the 3rd International Meeting on Nitric Oxide (Cologne, Germany) held in 1993. Each contains a synthesis of information about the biochemistry and biological effects of nitric oxide which will undoubtedly prove of value to researchers in this field. Indeed, the expression, 'something for everybody' springs to mind whilst leafing (possibly not the correct word) through in excess of 1000 pages and 270 individual papers contained therein. Coverage of the area is extensive and includes the various proposed physiological and pathophysiological functions of nitric oxide in the cardiovascular and nervous systems coupled to the potential clinical significance for blood pressure control, migraine, liver and gut disease (volume 3) as well as in immunology and inflammation, perhaps curiously linked in, with the biochemistry and molecular biology of nitric oxide synthase. The biological relevance of nitric oxide donors and nitric synthase inhibitors has also not been forgotten and contributions have been made from all over the world including the 'great and the good' in this field notably Robert Furchgott who most would consider to have started the ball rolling with the discovery of endothelium derived relaxing factor (EDRF) some 15 years ago and Salvador Moncada who identified EDRF as nitric oxide some years later.

My only slightly negative comment is the perhaps inevitable one that events have moved swiftly since the meeting in Cologne and the publication of these volumes and some of the contributions now appear to be either dated or have not stood the test of time. On the other hand, it is fascinating to observe that some authors obviously used this conference as a 'sounding board' for their ideas which were later developed and published in full and now form part of the dogma.

Overall, these volumes represent an excellent source of information (and perhaps new ideas) for biological scientist and clinicians interested in nitric oxide and nitric oxide synthase and should, assuming the expense account is up to it, prove an invaluable asset to their bookshelves.

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Mitochondrial Diseases
Editors: L. Ernster, R. Luft and S. Orrenius
Publishers: Elsevier

The book "Mitochondrial Diseases" contains the proceedings of Nobel Symposium 90, "Mito-

chondrial Disease", which took place in Saltjobaden, Sweden in 1994. As you initially thumb through the book it become immediately obvious that each chapter is set out in a research paper format. Indeed, the book consists of 39 papers which are subdivided into seven topic areas, plus a keynote lecture by Professor G. Schatz: *Beyond oxidative phosphorylation*.

The opening chapter by R. Luft: *The development of mitochondrial medicine*, gives an informative and interesting background to the main milestones in mitochondrial research—from the discovery of the first mitochondrial disorder 'Luft's disease' in 1959 to the involvement of abnormal mitochondrial function in the wealth of CNS and peripheral disorders known to date. This chapter sets the scene for the rest of the book and is an essential read for those already involved in mitochondrial research and others who have a vague interest in this highly important organelle.

The first topic area: *Biochemistry of mitochondrial diseases*, contains two chapter by Chance *et al* and Radda *et al* on non-invasive methods for the detection and quantification of functional mitochondrial abnormalities in skeletal muscle. Although there is some repetition between chapters the authors give an interesting insight into the physical background of the MRS and NIRS techniques which are currently under investigation and how these techniques can be applied in the clinic as an adjunct to other biochemical tests. Such biochemical test on isolated mitochondria can serve as tools for identifying the site(s) of impairment, however as with many research fields the results obtained are only as good as the methods used! In the next chapter in this section: *Biochemical studies of isolated mitochondria from normal and disease tissue*, the author C. P. Lee outlines how the literature is full of conflicting data on the abnormalities seen in isolated mitochondria from the same disease types. Lee stresses the importance of the preparation of mitochondria in such studies and details the problems associated with the isolation of mitochondria from different tissues. Using specific examples from his own research on mitochondrial myopathy and brain ischemia Lee then details how a systematic search using recognised and reproducible techniques can be conducted to isolate a mitochondrial defect. This chapter is highly informative and is essential reading for established mitochondrial researchers and anyone wishing to embark on this type of research. Such a chapter sets the standard for the quality of the research presented in the rest of the book and should form an opening chapter in many a research text book.

Mitochondria are not only potential sources of highly damaging free radical species but are also susceptible to free radical attack. The second topic area: *Mitochondria and oxidative stress*, deals with this important issue. The well written opening two chapters by Alton Meister and Reed *et al* in this section discuss how the antioxidant glutathione can markedly influence mitochondrial function. Since nearly 4% of mitochondrial O_2 is incompletely reduced and that mitochondria do not possess catalase, glutathione forms an important anti-oxidant. Liver mitochondria do not possess the synthetic enzymes necessary for the synthesis of glutathione, but as Meister describes mitochondria can actively sequester glutathione under conditions of glutathione depletion within the cell so as to protect themselves against internal free radical damage. Apart from being a potential source of free radicals, mitochondria are capable of the metabolic activation of drugs to form toxic metabolites. M. W. Anders in his chapter on: *Mitochondrial bioactivation of cysteine S-conjugates and 4-thiaalkanoates*, gives an interesting account of how toxic cysteine S-conjugates are formed by mitochondrial glutathione S-transferase-catalysed addition of glutathione to haloalkenes. Cysteine S-conjugates can bring about glutathione depletion and altered mitochondrial function, thus affecting cell survival. The final three chapters in this section of the book all deal with apoptosis (programmed cell death) and how mitochondrial derived free radicals

may have a role in triggering this process. Indeed, Slater in his chapter on "*The role of intracellular oxidants in apoptosis*" and Richter and colleagues in their chapter "*Oxidants in mitochondria: from physiology to disease*" eloquently detail how exposure of cells to low levels of oxidants e.g. H_2O_2, can trigger apoptosis. Indeed, TNF-α, a known inducer of apoptosis, is thought to produce its effects by altering mitochondrial function leading to an increased production of reactive oxygen species (ROS). Hence, could mitochondrial derived ROS play a signalling role in apoptosis?

The five chapters which form the third topic area: *Regulation of mitochondrial function in health and disease*, emphasise the diverse number of external and internal factors which can regulate mitochondrial function. Since the majority of mitochondrial proteins are encoded by nuclear DNA there are a number of factors which can influence their synthesis. Hoek *et al* and Nelson *et al* in their chapters describe how hormones can influence the expression of such proteins. As Hoek *et al* also point out hormones can also influence mitochondria directly by increasing cytosolic Ca^{2+} concentrations which act as a messenger to activate intramitochondrial metabolic processes and can also influence their susceptibility to Ca^{2+} induced swelling. At the other end of the spectrum mitochondria can be involved in auto-immune diseases. The fascinating chapter by Harold Baum on this subject details how anti-mitochondrial antibodies can be generated in diseases like primary biliary cirrhosis where the close similarity between mitochondrial peptides e.g. oxo-acid dehydrogenase complex, and their counterparts in bacteria can trigger auto-immune diseases.

Sandwiched in the middle of the book is the keynote lecture: *Mitochondria—beyond phosphorylation* by Gottfried Schatz; in which he addresses the fact that mitochondria perform many other important cellular functions e.g haem synthesis, apart from oxidative phosphorylation. Assuming that some key processes found in bacteria are also present in mitochondria, Schatz utilising modern molecular biology techniques is starting to shed some light on the true functions of the mitochondria.

The molecular biology theme is then carried on into the fourth topic of the book: *The mitochondrial DNA and cellular dysfunction*. Although the mitochondrion is composed mostly of nuclear encoded proteins, surprisingly few nuclear mutations that affect mitochondrial function have been identified. The five chapters which make up this section detail how molecular biology techniques have allowed us to gain an insight into the causes of mitochondrial DNA mutations e.g damage caused by free radicals, how such mutations can be inherited and which diseases bear this trait and very importantly how ageing can influence such processes.

The ageing process and the appearance of accelerated ageing in many neurodegenerative disease has long fascinated scientists. A basic understanding of the ageing process may provide vital clues towards a better understanding of many disease processes. To emphasize the importance of ageing the fifth topic of the book has been devoted to "*Oxidative stress and ageing*". The six well written research papers which form this section can be split into two complementary sections. Firstly, the respective papers written by Ames *et al*, Cortopassi and Wang, and Ozawa discuss in depth the fact that although mitochondria are the greatest source of oxidants, mitochondria are highly susceptible to oxidative damage and such damage plays a major role in ageing. Mitochondrial DNA is more susceptible to oxidative damage than nuclear DNA and the most common mutations occur in DNA encoding for complex I of the respiratory chain. Cortopassi and Wang detail how such defects in complex I can lead to increased formation of the superoxide radical, which in turn can stimulate further cellular damage or trigger apoptosis. However, other molecules are also susceptible to oxidative damage e.g lipids, indeed a decrease in mitochondrial membrane

fluidity is associated with ageing. Secondly, the final three papers in this section by Linnane *et al*, Ernster and Dallner, and Wong have given support to the concept that oxidative damage to mitochondria is involved in ageing by demonstrating in experimental models that supplementation of mitochondrial antioxidant e.g ubiquinone, or by the induction of mitochondrial MnSOD can afford some protection against oxidative damage and thus ageing. The beneficial effects of such treatments in diseases associated with accelerated ageing however have not been fully evaluated.

The sixth topic area: *Molecular basis of mitochondrial disorders*, is a very broad topic area and is reflected by the diversity in the five chapters in this section. The chapters range from the basic science, dealing with investigations into the structures of the respiratory enzyme complexes by J. E. Walker which will ultimately benefit the understanding of mitochondria disorders, to how man made toxins e.g MPTP (Singer *et al*) and fungal derived toxins (Siedow *et al*) can affect mitochondrial function. The final chapter in this topic area by Attardi and colleagues gives an interesting account of how cell culture techniques can be used to investigate disease-causing mitochondrial DNA mutations. In such techniques mitochondria from myoblasts or fibroblasts of patients with mitochondrial DNA linked diseases are transfected into human cell lines depleted of mitochondrial DNA by long term exposure to ethidium bromide so as to investigate the effect of the mutated mitochondrial DNA on cell function.

The final topic area in the book: *Clinical aspects of mitochondrial disease*, can be split into three subsections. The first contains two chapters by Holme *et al* and M. L. Savontaus, who address the important issue of inheritance and expression of mitochondrial DNA point mutations in diseases like Leber's optic neuropathy. Secondly how mitochondria feature in the aetiology and pathogenesis of diseases like diabetes mellitus (by Gerbitz *et al*) and Parkinson's disease (by Mizuno *et al*). The final and third sub-section contains two chapters where coenzyme Q_{10}, vitamin K and other antioxidants have been successfully used to treat mitochondrial encephalomyopathy e.g MELAS (by P. L. Peterson) and where coenzyme Q_{10} has been successfully used to treat muscular dystrophy's and neurogenic atrophies (by Folkers and Simonsen), suggesting that some mitochondrial disorders can be partly corrected by drug treatment.

The papers which make up this book were presented at the Nobel Symposium 90 on Mitochondrial Diseases which brought together experts in a variety of mitochondrial research areas. This is reflected in the very high standard of the book which forms a 'state of the art' reference on mitochondrial disease. The book will be an essential reference for those involved in the mitochondrial research field and will give any scientist an insight into this fascinating organelle.

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Biothiols in Health and Disease
Editors: Lester Packer & Enrique Cadenas
Publishers: Marcel Dekker, Inc.

This book provides in-depth information concerning the role of thiols in redox reactions as well as molecular mechanisms underlying the multiple functions of thiols in biological systems. The following is a brief description of the contents.

Chapter one discusses a variety of oxidation processes conducted by thiyl and perthiyl radicals and then their biological significance. This chapter also discusses antioxidant and prooxidant properties of thiol and thiyl-radicals as well as the potential use of thiols as free radical scavengers. This chapter also provides valuable tables with rate constants of oxidation of a wide range of biomolecules by thiyls.

In chapter two, the emphasis is placed on the role of thiols in clinical conditions associated with oxidative stress. This chapter also discusses the strategies for increasing cellular thiol content as a therapeutic agent in prevention of free radical mediated pathological disorders as well as biochemical and clinical implication of phospholipid hydroperoxide glutatione peroxidases and glutatione transferases.

Chapter three mainly deals with lipoic acid (1,2-dithiolanc-3-pentanoic acid), describing its antioxidant properties as well as its use as a therapeutic agent in the treatment of diabetic neuropathy. Lipoic acid is widely distributed in animals and plants. It acts a cofactor of different multienzyme complexes involved in decarboxylation of α-keto acids.

The book should prove of value to all who work in the field of free radical research or are interested in the topics related to the role of free radicals in diseases associated with oxidative stress.

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