

Book Reviews

Accepted for publication by Prof.B. Halliwell

Vitamin A and retinoids: an update of biological aspects and clinical applications.

**M.A. Livrea (Ed). Basel: Birkhauser Verlag
2000, 300 pp. ISBN 3-7643-5882-3**

This authoritative volume which is part of a series entitled *Molecular and Cell Biology Updates* edited by Angelo Azzi and Lester Packer, has no less than 45 authors from half a dozen countries. The topics are extremely various, covering every imaginable aspect of these vital molecules. After treatment of vitamins A in blood (M V Gamble and W S Blaner) and the enzymology of retinoic acid (J L Napoli) there is a comprehensive and definitive chapter entitled "Requirements and safety of vitamin A in humans" by J A Olson. He leads the reader through the complexities of dietary standards (as well as the old vexed question of international units) in relation to both the vitamin and provitamin series. He endorses the dangers of carotenoid ingestion in alcoholics and smokers, a theme which is taken up in the subsequent chapter, "Current views on carotenoids: biology, epidemiology and trials," by N I Krinsky and S T Mayne. There follow chapters on the eye, the immune system, and infectious diseases. In this last Dr R D Semba points out that vitamin A appears to have more effect on the severity of infections, rather than on their incidence. More

esoteric to the run of the mill scientist, although obviously not to those grappling with the complexities of polyexponential compartmental analysis, is "Physiologically based pharmacokinetic scaling in retinoid developmental toxicity", by C C Willhite and H J Clewell. Possibly "Retinoid treatment of photoaged skin" by A A Bajoghli and B A Gilchrest would be most useful for those with a reputation in the field of vitamin A biology and whose views are occasionally sought by the wrinkled public. This section gives an interesting summary of the difficulties which were faced by Dr Albert Kligman in having tretinoin therapy accepted by other authorities in dermatology.

There is no chapter on free radical aspects as such, nor do the terms "antioxidant" and "reactive oxygen species" appear in the index, probably because fifteen of the twenty-two chapters deal with various aspects of the retinoids as opposed to the carotenoids, although as might be expected there are scattered references throughout the text. In the chapter by Krinsky and Mayne there is a section on both the antioxidant and pro-oxidant roles of carotenoids. In respect of the former they note that lycopene seems to be the most effective. They leave open the question of whether carotenoids decrease the susceptibility of LDL to oxidative stress. Olson

mentions, in passing, that nutritionally inactive carotenoids *may* [my italics] have protective effects in reducing oxidative stress and some forms of chronic disease, and emphasises that it is unclear whether or not they affect the onset of chronic disease. So, in an oft-used phrase, there is much more work to be done!

Clearly this volume is a mine of information, covering the full spectrum of chemical, biological, and pathophysiological knowledge of vitamins A at the present time.

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A Rousing Chorus

Review of: **Wake up to Flavonoids**. Rice-Evans, C (Ed). London: Royal Society of Medicine Press, 2000. ISBN 1-85315-433-4

This is a short, 74 pp text, with eight contributing authors, the product of a symposium in July 1999 sponsored by the Brooke Bond Tea Company. A number of interesting areas are covered, including (for those not dealing with these complex substances on a daily basis) a very useful exposition by Prof J Harborne of their chemistry and nomenclature. Although the focus of the symposium is flavonoid-human interaction it is of interest to know why plants go to the trouble of synthesizing them – this may be due to their protective effect against ultraviolet radiation or herbivorous organisms or both. Prof Harborne also notes, in the context of possible harmful effects, that levels of minor flavonoids should be monitored when new plant species are introduced into the human diet.

Professor B Halliwell, in the next chapter, reviews antioxidant and other biological effects and is able under four heads to identify factors leading to current increased interest in this series of compounds. Importantly, he endorses current

evidence that flavonoids can be absorbed into the human body in amounts that are, “in principle”, sufficient to exert antioxidant activity. The qualification in inverted commas is interesting, and seems to be reinforced later in the chapter when he states that “Whether or not flavonoids are among these factors [‘classical’ antioxidants like vitamin E] also remains to be established”. One imagines that these words would be carefully weighed by the food industry in which the potential for replacing synthetic antioxidants like butylated hydroxytoluene with naturally occurring ones such as flavonoids is the fourth of Prof Halliwell’s heads of interest at the beginning of his discussion.

Protein-polyphenol interaction is dealt with in an article by Professor E Haslam, Dr M Williamson and Mr Adrian Charlton. Flavonoids can complex with salivary proline-rich proteins and caseins, almost certainly decreasing their bioavailability. Following from this, Mr S Wearne discusses “Estimating dietary intakes of flavonoids”; teas, onions and apples are the main sources in North American and European populations. Red wine and soya beans have their own aficionados.

The crucial question of the bioavailability of flavonoids is then discussed by Dr P Hollman; studies of quercetin glycosides administration to ileostomy subjects lacking a colon with bacterial flora show that the glycosides do not have to be bacterially degraded for absorption to be substantial – indeed the presence of the glucose moiety enhances it. Dr M Gaziano discusses flavonoids in relation to coronary heart disease and after a survey of the relevant clinical trials cautiously concludes that a precise aetiological mechanism for their reduction of CHD risk has yet to be established. Subsequently in his section on flavonoids and platelet function, Professor A Beretz accepts that they inhibit aggregation, but discusses uncertainties as to which flavonoids are active, as well as mechanism of action.

In her concluding comments Professor Catherine Rice-Evans notes the questions which need

“urgent elucidation and clarification.” They constitute quite a list! To quote but one sentence: “We know flavonoids are powerful antioxidants in vitro, but what is their overall function in vivo – antioxidant, inflammatory, enzyme inhibitor, enzyme inducer, inhibitor of cell division, or another role?” Her summary reflects the general caution of the participants in coming to conclusions about specific health benefits of flavonoids – to the irritation, no doubt, of the general public, who believe, it seems, that the expenditure of research funds must result in certainties. Of course it is workers in the antioxidant and cardiovascular fields who will find this volume informative and rewarding.

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Manganese and its Role in Biological Processes

Metal Ions in Biological Systems, Vol. 37, edited by A. Sigel and H. Sigel, Marcel Dekker Inc, New York, 2000.

Manganese is a fascinating metal, toxic in excess yet essential to life (in small amounts). I was therefore pleased to see a whole volume of the well-known series *Metal Ions in Biological Systems* devoted to this inspiring transition element whose name is thought to be derived from the Greek word for *magic* (page 90). All aspects of manganese are reviewed: its distribution in the environment, uptake by bacteria, yeasts, higher plants and animals (including humans), manganese neurotoxicity, consequences of manganese deficiency and its use as a ‘probe’ of enzyme mechanism. The important manganese-containing proteins are reviewed in detail, including MnSOD, phosphoenolpyruvate carboxykinase, arginase I, manganese-containing catalases, the photosystem II water-splitting

mechanism, and manganese-dependent peroxidases.

Overall, this is an excellent book. I recommend it to all manganophiles, although caution them to avoid *Locura Manganica*.

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Different Pathways through Life **Biochemical Aspects of Plant Biology and Medicine**

Editors: A. Denke, K. Dornisch, F. Fleischmann, J. Grassmann, I. Heiser, S. Hippeli, W. Oßwald, and H. Schempp

Publisher: Lincom Europa, 1999 ISBN 3-89586-645-8

Different Pathways through Life was dedicated to Professor Erich F. Elstner on the occasion of his 60th birthday. Several distinguished scientists have met to publish this *Festschrift* as a birthday present for Erich Elstner. Within five sections, the corresponding chapters cover a wide scientific field ranging from biochemistry and plant physiology to plant and human pathology. The first section of this book, *Biochemistry of Activated Oxygen*, provides through authoritative chapters some critical views of the field of free radical biology: current concepts of oxidative stress emphasizing important distinctions and parallelisms among oxidative stress, reductive stress, and nitrosative stress; an accurate description of the current methods to determine antioxidant activities; a critical evaluation of the participation of hydroxyl radicals in reactions occurring in cells or tissues; a much needed perspective on the role of mitochondria and oxidative stress with implications for pathophysiological situations and, finally, an overview of the key enzyme of the nitric oxide/cGMP pathway: soluble guanylate cyclase, its expression and

mechanisms of activation. This section of the book succeeded in introducing an up-to-date status of key issues of free radical biology.

The second section, *Oxidants and Antioxidants in Humans and Plants*, addresses more specific aspects of free radical functions, but there is a recurring theme that emerges with different intensity in the individual chapters: the redox regulation and/or redox control of a wide variety of processes from protein phosphorylation in signaling cascades in human leukocytes to the function of ascorbate transport systems in plant membranes and through disease or physiological situations as varied as diabetes and photosynthesis. All eleven chapters in this section are solid contributions with sound chemistry and innovative biology.

The third section, *Signaling in Phytopathology*, contains five chapters and was an enticing and learning experience for this reviewer: the status of phytotoxin research, the genes responsible for disease resistance in plants and the signaling pathways in plant-microbe interactions and the interesting ozone sensitive of tobacco are some examples.

The fourth section, *Impacts and Detection of Pollutants*, adds a practical dimension to the previous chapters addressing, among others, topics such as the toxic effects of anthropogenic components of the atmosphere -soot particles and mechanisms of health effects, exhaust gas emission and air quality, and the uptake and assimilation of atmospheric nitrogen dioxide by Norway spruce in photochemical equilibrium with ozone.

The fifth and last section, *Remarkable Aspects of Plant Biology*, is perhaps far away from the central theme of "Biochemistry of Activated Oxygen"; this does not detract from the importance of the chapters herein and, as indicated in the section's title, there are some remarkable aspects of plant biology to become acquainted with: plant growth under severe drought, seasonal fluctuations of food reserves in woody axes, and how the shape of a molecule is related to smell,

an interesting excursion into the relation between odour and pharmacology.

Overall, this is an excellent book that warrants strong recommendation to potential readers and, above all, a unique recognition of Professor Erich Elstner's scientific accomplishments and vision.

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Free Radicals in Brain Pathophysiology

Edited By G. Poli, E. Cadenas and L. Packer Marcel Dekker Inc., New York, 2000

This book, a member of the series *Oxidative Stress and Disease*, discusses the role of reactive species and antioxidants in brain pathophysiology, including ischaemic damage and the major neurodegenerative diseases. It begins with good chapters on how free radicals are generated in the brain and the roles that they play, with a special focus on excitotoxicity and nitric oxide. Mechanisms of cell death in stroke are well covered, as is monoamine metabolism and its relevance to Parkinson's Disease, with an especially-interesting chapter on MAO-"knock out" mice. Several chapters cover the roles of NO[•], ONOO⁻, GSH, mitochondrial defects, catecholamine oxidation and neuromelanin in PD. Alzheimer's disease is also well considered, particularly the role of free radicals and Ca²⁺ in the mechanisms of toxicity of amyloid-β protein. The link between oxidative damage and genetic factors predisposing to AD is well-considered in the chapter by Mattson, which complements the discussion of transgenic animal models of AD by Pappolla *et al* in chapter 17. I also enjoyed chapter 18, dealing with oxidative protein damage in Alexander's disease. The role of SOD mutations

in ALS is also covered in the book. Possible neuroprotective agents, such as *Ginkgo biloba*, apomorphine, idebenone and oestrogens, are also reviewed.

Overall, a useful book that I recommend to graduate students to gain a knowledge of current thinking and research in this area.

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***Experimental Protocols For Reactive Oxygen
And Nitrogen Species***

N. Taniguchi and J.M.C. Gutteridge
Oxford University Press, Oxford, UK, 2000

This nice-looking small book (an elegant cover in black, white and grey) is an expanded and updated version of a Japanese text published in 1994. The two editors, both acknowledged experts on reactive species, have drawn together a wide range of contributors from various laboratories in Japan and a few overseas. How does this volume compare with established series such as *Methods in Enzymology*? To my mind, it score points because, although each chapter is brief-there is no background to the topic or discussion of it, the chapters detail precisely what reagents will be needed and how to make them up, in a form that could easily be used *ab initio* by a technician or new graduate student.

Another strength of the book is its comprehensive nature. It covers the measurement of the major reactive species, $O_2^{\bullet-}$ (by NBT and adrenalin assays and by chemiluminescence), H_2O_2 (by peroxidase-based assays and histochemical staining), OH^{\bullet} (deoxyribose assays), NO , $ONOO^-$, nitrosothiols, phospholipid hydroperoxides (by HPLC), cholesterol and its oxidation products, fluorescent end-products of lipid peroxidation, TBARS, 4-hydroxy-2-nonenal and

reactive dicarbonyls (including methylglyoxal). Methods to generate these species and to prepare neutrophils and subcellular organelles for studies of reactive species generation are also well-described. Assays of extracellular antioxidant activities (eg. iron-binding, iron-oxidizing, caeruloplasmin) as well as those of the major antioxidant defence enzymes (CuZnSOD, MnSOD, EC-SOD, catalase, peroxiredoxin, glutathione peroxidase and reductase) and their substrates (GSH, GSSG, thioredoxin) are included, as are assays for many of the diet-derived antioxidants (vitamin E, vitamin C, catechins) and putative antioxidants (ubiquinol, vitamin A, carotenoids). Also included are assays of the glutathione transferases, γ -glutamyl transpeptidase, γ -glutamylcysteine synthetase, NOS, myeloperoxidase, haem oxygenase, ferritin, total plasma copper and iron, UIBC, percentage transferrin saturation and xanthine oxidase. Techniques for LDL isolation, its *in vitro* oxidation (by Cu^{2+} or lipoxygenase) and measurement of its uptake by macrophages are also covered, as are the use of DCFH-DA to measure cellular peroxide levels and the bleomycin and phenanthroline assays in their various forms, as well as the calcein method to quantitate intracellular iron "pools".

Part 2 of the book, entitled "gene analyses", is similarly comprehensive, covering analysis of the expression of genes encoding NOS, MnSOD, glutathione peroxidase or catalase and how to measure protein levels for thioredoxin and peroxiredoxin, as well as the over-expression of bcl.2 and gulonolactone oxidase in cells. It also includes techniques for measuring 8OHdG and other aspects of oxidative and glycative nuclear DNA damage, 8OHdGTP hydrolase enzyme activity, mtDNA damage, plasma protein carbonyls (but, surprisingly, not tissue carbonyls) and *ortho*-, chloro-, and nitro-tyrosines.

Part 3 deals with "experimental pathophysiological models", ie. systems of an order of magnitude greater complexity. Coverage includes the Langendorf perfused rat heart, *in vivo*

open-chest dog model of myocardial-reperfusion injury (probably covered too briefly given the difficulty of this model), GI tract ischaemia-reperfusion, brain ischaemia in the gerbil model, skin damage by UV light, the longevity of *C. elegans*, effects of SOD on ovulation and fertilization, *in vivo* measurements of NO[•] scavenging, assay of cGMP in brain slices, how to impose oxidative stress on *E. coli* and how to set up animal models of carcinogenesis progression, copper-overload and iron-overload.

Given the breadth of coverage, it is easy to find a few minor things to quibble about in this book. The index is sketchy. Vinylpyridine may be better than N-ethylmaleimide in removing GSH for determination of GSSG in mixtures of the two Hydrogen peroxide may be a better sub-

strate for assay of "real" glutathione peroxidase than t-butyl hydroperoxide, and one should not hydrolyse proteins in HCl before measuring chlorotyrosine. A more serious criticism is the lack of critical evaluation of each technique. What are the possible artefacts and how could they be handled?

However, these are minor comments. The book overall is excellent and I recommend it strongly. It is not on my bookshelf, but on the laboratory bench, already in use.

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