



## Free Radicals in Biology and Medicine. Fifth Edition. By Barry Halliwell and John M. C. Gutteridge. Oxford University Press, 2015. Pp. xxxviii + 905. Price GBP 70.00 (paperback, ISBN 9780198717485), GBP 125.00 (hard- back, ISBN 9780198717478).

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*Free Radicals in Biology and Medicine*, which first appeared in 1985 (Bannister, 1986; Kovacic, 1986), has now reached its fifth edition. Despite their thirty-year experience, the authors do not seem to have lost a bit of enthusiasm, as one can tell from the preface, where they announce a probable future sixth edition.

This textbook is an absolute reference (one could probably say *the* reference without fear of sounding disrespectful to other authors) in the field, covering the whole spectrum of free radical (and beyond, dealing with reactive species in general) biology and its physiological and pathological implications. The back cover states that two new chapters have been added, discussing *in vivo* and dietary antioxidants; however, the fifth edition contains one chapter more (11) than the fourth edition. The additions and updates, which are extensive (about 250 pages), are widespread through several chapters, making this new edition a significant revision with respect to the previous one. The authors have made an impressive effort to be clear and understandable to every reader who has a basic knowledge of chemistry and biology. An appendix *Some basic chemistry* (also present in the previous edition) helps those who may need to be refreshed, and makes sure that nobody is left by the wayside.

To get an idea of how impressive the work is, one can start at the end with the list of references, which spans 116 pages and includes 4071 citations. It is followed by an 83-page index that allows the reader to trace back each and every detail (s)he may wish or need to access directly. At the opposite end (thus, the beginning) of the book we find seven pages of abbreviations. One could not ask more!

From quantity to quality, the tune does not change and the reader cannot help being impressed by the rigour of the presentation and analysis. The authors are never tired of drawing attention to the traps one may fall in. A few examples should illustrate the point.

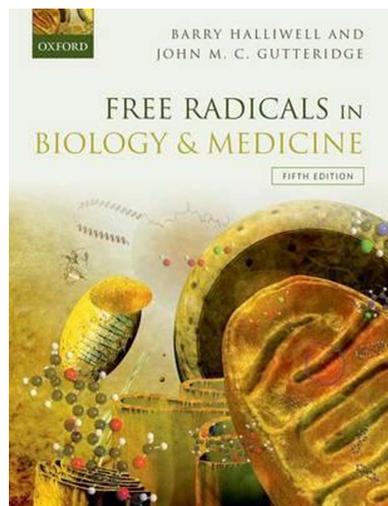
*In vitro* results should not be assumed to necessarily apply *in vivo*: plasma levels of antioxidants may be insufficient, or the antioxidant may be rapidly excreted, or metabolized to inactive products, or may not reach the targeted site. On the contrary, compounds without antioxidant activity *in vitro* can be metabolized to active compounds *in vivo*.

The *in vivo* effect may not be the one expected from *in vitro* or theoretical considerations (e.g. mitochondrially targeted agents that utilize the membrane potential may not reach the targeted damaged mitochondria because of their lower membrane potential).

An antioxidant effect may result from mild oxidative stress that triggers antioxidant defences.

Encouraging results on animal models are often of limited application to clinical situations, the difference in the physiology and metabolism making the direct transfer hardly significant.

The first two chapters can be seen as an airlock where the reader gets the necessary background to start the journey through cells, organelles and enzymes. Chapter 1 introduces the chemistry and biochemistry of oxygen, the *Dr Jekyll and Mr Hyde* that allowed the emergence of life as we know it, yet it threatens living beings by producing a



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series of reactive oxygen species, one more dreadful than the other. Chapter 2 presents thermodynamics and kinetics of redox chemistry and a comprehensive survey of reactive species (RS), classified as free radicals and non-radicals, and as oxygen, chlorine, bromine and nitrogen species (ROS, RCS, RBS, RNS). The fundamental role of transition metals, especially iron (Fenton chemistry) and copper in the generation of RS is duly emphasized, as it is returned to again and again in the following chapters.

The next two chapters are devoted to antioxidants: those synthesized *in vivo* (Chapter 3) and those obtained from the diet (Chapter 4). The reader is constantly reminded that the antioxidant role of a compound (especially one obtained from the diet) is not limited to its direct activity. In particular, the antioxidant capacity depends, among other factors, on the presence or absence of catalytic metals, so that the overall physiological effect often goes well beyond the simple, direct antioxidant activity. Several epidemiological studies are reviewed, leading to the (good sense!) conclusion that supplements will never replace a good diet rich in fruits and vegetables, with its balanced and synergistic intake of natural antioxidants.

Chapter 5 is an extensive presentation of the cellular mechanisms of regulation and adaptation to oxidative stress and of its biological consequences. Here and in the following the accent is put on the fact that RS action is both favourable (*e.g.* in promoting wound healing and acting as signal modulators) and harmful (*e.g.* by contributing to atherosclerosis, cancer, rheumatoid arthritis and fibrosis) depending on the amount and the situation. For example, cell injury and senescence participate in ageing, but are also a defence strategy against cells proliferating abnormally. The damage effects and mechanisms are analysed in detail for each of the RS main targets: DNA, lipids, proteins.

Chapter 6 is devoted to experimental techniques for measuring reactive species. ESR and spin trapping are obviously most popular, but approaches specific to each reactive species (superoxide, nitric oxide, peroxyxynitrite, halogen species, singlet oxygen, hydrogen peroxide) are also presented in detail, together with the use of products that can be traced back to oxidative attack (biomarkers). For each assay the possible artefacts and the precautions of how to prepare and deal with the sample are carefully pointed out.

Chapter 7 deals with the threats that RS represent for organisms, and the defences they have developed against these. The analysis starts with the animal body (threats to the gastrointestinal tract, the respiratory tract, erythrocytes),

continues logically to parasites, which have to cope with the pro-oxidants they release from their victims, to plants, which have to face intense oxidative stress from the oxygen they produce themselves. The reader cannot help but be fascinated by the remarkable equilibrium Nature has established, with the right amount of antioxidants needed to resist oxidative stress yet not so large as to hinder an adaptive response. The second part of the chapter describes specific targets of reactive species, and the associated pathologies: the eye, the reproductive system, the ear, the skin, the skeletal muscle. This leads to a natural transition to the following two chapters, where useful (Chapter 8) and poisonous (Chapter 9) roles of RS are presented. Here are a few examples to give the reader an idea of the variety of topics presented: the role of RS in the action of phagocytes; in the synthesis of thyroid hormones; in the regulation of blood pressure; in the aggregation of platelets; in bone turnover; in the germination and senescence of plants; in the cascade of the eicosanoids; and in the attack of toxic compounds like CCl<sub>4</sub>, pesticides, drugs, alcohol and air pollutants (organic compounds, nanoparticles, metals). These two chapters are those where a biology and biochemistry background is needed more.

The last two chapters, devoted respectively to disease and ageing, are the most medically oriented. The roles of RS in the diseases of affluence (atherosclerosis, obesity, cancer, diabetes); cystic fibrosis; various autoimmune diseases; disorders of the nervous system related to oxidative stress and the corresponding antioxidant defences; pain; and viral infections are analysed in detail. The long journey ends with a critical analysis of the 'free-radical' theory (actually, RS theory, given that many RS are not free radicals) of ageing, the direct link being less certain today than was previously believed.

The content of *Free Radicals in Biology and Medicine* is as wide as the horizon and as deep as the ocean: nobody can ever dream to satisfactorily capture it in the limited space available for a book review. The target audience that will undoubtedly profit from this gigantic work is equally wide: biologists, biochemists, medical doctors, nutritionists, therapists with a sound background. It stands as an invaluable reference to be consulted without moderation, although a deep understanding certainly requires repeated reading and study.

## References

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