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The Oxygen Paradox, Oxidative Stress, and Ageing

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Abstract

Professor Helmut Sies is being lauded in this special issue of Archives of Biochemistry & Biophysics, on the occasion of his retirement as Editor-in-Chief. There is no doubt that Helmut has exerted an enormously positive influence on this journal, the fields of Biochemistry & Biophysics in general, and the areas of free radical and redox biology & medicine in particular. Helmut Sies' many discoveries about peroxide metabolism, glutathione, glutathione peroxidases, singlet oxygen, carotenoids in general and lycopene in particular, and flavonoids, fill the pages of his more than 600 publications. In addition, he will forever be remembered for coining the term 'oxidative stress' that is so widely used (and sometimes abused) by most of his colleagues.

Keywords

Oxidative Stress; Ageing; Glutathione and Glutathione Peroxidase; Singlet Oxygen; Peroxynitrite and Nitric oxide; Carotenoids; Flavenols; Flavonoids

Introduction

I first met Helmut Sies at the University of California at Berkeley in 1979. I was a graduate student working with Lester Packer, Bruce Ames, Paola Timiras, George Brooks, and Dan Koshland, and Helmut was a visiting Professor from Dusseldorf, Germany. Little did I know, at that time, that Helmut would become a valued and dear friend over the succeeding 35 years! Helmut became a frequent visitor to Berkeley over the next couple of years, but I suspect his enthusiasm was more a romantic interest in his future wife, Nancy, than an inability to stay away from the research we were all doing. In the end, Helmut managed to 'steal' Nancy away from us, which was certainly one of the most intelligent things he has ever done – and that's saying something!

Over the years, Helmut continued to collaborate on many projects with Lester Packer, including the early Oxygen Radicals Gordon Conferences, and the founding of the Oxygen Club of California. We are celebrating Helmut's many achievements over a long tenure as editor of *Archives of Biochemistry & Biophysics*, but it should also be remembered that Lester Packer preceded Helmut as ABB editor. As a member of Les's lab., I often dealt with ABB papers in those early days. There are frequently interesting relationships and even apprenticeships in 'scientific families' and so I suppose you could describe Helmut and I as

‘cousins.’ I took a term as President of the Oxygen Club of California (OCC) from 2002 to 2004, when Les Packer stepped back to become Founder & Honorary President. No huge surprise then to recollect that Helmut Sies became OCC President from 2004 to 2008 and, of course, did a fine job with the organization. Helmut and I then reversed terms as Presidents of the International Society for Free Radical Research (SFRR International), he from 1998 to 2000, and I from 2003 to 2005. Since both the OCC and SFRR International appear to be thriving, I will take the liberty of assuming that at least neither of us did irrevocable damage!

Helmut's contributions to our understanding of hydroperoxide metabolism, glutathione metabolism, peroxidases, and selenium have been tremendous. Similarly, Helmut's research made a huge impression on our appreciation of carotenoids (especially lycopene) flavonoids, flavenols, and polyphenols. Helmut has also made major contributions in the singlet oxygen field, and to our understanding of nitric oxide and peroxynitrite metabolism.

The Distinguished Scientist Fellowship Program of King Saud University indicates that Professor Helmut Sies has published over 600 scientific papers and book chapters. He won the Werner Heisenberg Medal, Alexander v Humboldt Foundation in 1999, an Honorary Ph.D. from the Universidad de Buenos Aires in 1996, the ISFE-Preis in 1994, the Claudius-Galenus-Preis in 1990, the Ernst Jung Preis für Medizin in 1988, the Silver Medal of the Karolinska Institute of Stockholm in 1986, and the FEBS Anniversary Prize from the Federation of European Biochemical Societies in 1978. Professor Helmut Sies is a past President of both the European Society for Free Radical Research and the International Society for Free Radical Research, and is a member of the Distinguished editorial Board of the journal, *Free Radical Biology & Medicine*. He has chaired both the Oxygen Radicals Gordon Conference and the Oxygen Radicals Gordon conference. He is a member of the German National Academy of Sciences, and a Fellow of the Royal College of Physicians, London. I could easily fill several pages of this article with Helmut's achievements, but I think that the point is made with even this abbreviated list.

Helmut's famous paper on the concept of Oxidative Stress was extremely influential for many (if not most) of us working in the free radical field (1-4). The impact of the simple statement that, “...*oxidative stress denotes a shift in the prooxidant/antioxidant balance in favor of the former*” really cannot be overestimated. In addition, Helmut presented the whole concept of Oxidative Stress within the context of “...*normal aerobic life,...*” and not as some rare or aberrant occurrence. Indeed, he proposed that, “Diverse biological processes such as inflammation, carcinogenesis, ageing, radiation damage and photobiological effects appear to involve reactive oxygen species. This field of research provides new perspectives in biochemical pharmacology, toxicology, radiation biochemistry as well as pathophysiology.”

Helmut's Oxidative Stress concept is, of course, a complex outcome of a much more simple phenomenon for which I coined the term, “The Oxygen Paradox” (5). Simply stated, the Oxygen Paradox proposes that although Oxygen is essential for aerobic beings, it is also inherently dangerous to the very same lifeforms; in other words, it is very difficult to live without Oxygen, but it is also very difficult to live with Oxygen. Oxidative Stress and the Oxygen Paradox, therefore, form a complementary dyad which leads us to look for the

mechanisms by which life on earth has managed to find ways to profit from an Oxygen environment without immediately falling prey to the dangers of oxidation.

Glutathione, Selenium, and Glutathione Peroxidases

Having worked with Britton Chance at the Johnson Foundation in Philadelphia in the 1970's, it is surprising that Helmut Sies became a champion of the antioxidant role of glutathione peroxidases. This is because the Chance lab., in those days, was a staunch proponent of catalase as the major intracellular peroxide-metabolizing enzyme, a position strengthened by the rather amazing catalytic activity exhibited by catalase. The turning point, at least for Helmut Sies, seems to have been discussions with Leopold Flohé that resulted in a series of 'challenge' experiments that the two scientists then performed. The results of these groundbreaking trials led both to agree on the importance of glutathione peroxidase (6-8) and, ultimately, changed the direction of an entire field, and even the mind of Brit Chance (9)! Of course, we now know that catalase and glutathione peroxidases are largely compartmentalized, which limits their actual 'competition' *in vivo*. In the absence of such 'geographic' knowledge, however, the studies of Sies and Flohé (6-8) can fairly be described as seminal.

Helmut Sies went on to study glutathione metabolism and transport, and to establish that proteins could undergo glutathiolation and glutathionylation both *in vitro* and *in vivo*. Years later, when my own group found that glutathiolation can modulate the activity of the proteasome, and that such glutathiolation reactions may actually be used physiologically to regulate proteasomal activity and selectivity during cellular stress (10), we leaned heavily on Helmut's work as we tried to understand the chemistry and biochemistry of glutathione reactions.

Most glutathione peroxidases (but not all) are seleno-enzymes, and selenium metabolism and chemistry became an important part of Helmut Sies research (11-13). In typical Helmut style, however, he was not content with chemistry and biochemistry alone, but went on to make significant nutritional contributions dealing with selenium bio-availability, intestinal uptake, and incorporation into seleno-proteins (14-17).

Singlet Oxygen, Nitric Oxide, Peroxynitrite, Carotenoids, Flavenols, and Flavonoids

Helmut Sies has published a wealth of experimental evidence detailing the importance of various carotenoids, particularly lycopene, in protection against singlet oxygen and UV light, and of the importance of flavonoids, flavenols, and carotenoids in human health (18-28). At the same time, he also managed to undertake groundbreaking research with nitric oxide and peroxynitrite (15, 35, 36). These studies span an immense scientific arena, as they run the gamut from chemistry and biochemistry; to nutrition and intestinal absorption studies; to physiology, pathology, and medicine (18-22). Very few (if any) researchers in the free radical field can claim to have undertaken anything like the comprehensive approach to the study of antioxidants that Helmut Sies has made a trademark.

Oxidative Stress

Certainly, no single term is so clearly associated with the Name Helmut Sies as is 'Oxidative Stress.' For many years, Helmut's concept of 'oxidative stress' guided our investigation of antioxidant enzymes; antioxidant compounds, and especially damage removal and repair systems such as lipolytic enzymes; proteolytic enzymes (proteasome, Lon, autophagy); and DNA repair enzymes (39-43). Although today the emphasis in the field has shifted to more discrete (and trendy), 'redox' control of signaling pathways, 'oxidative stress' still appears to be an entirely valid terminology when applied to the frankly toxic effects of very high concentrations of oxidizing species (or repeated or chronic exposures to such agents). Thus, toxicologists, pathologists, and many physicians will likely continue to find value in, and applicability of the term 'oxidative stress' for the foreseeable future. There is no doubt that 'oxidative stress' has been misused by some, as have fluorescent dyes, and terms such as reactive oxygen species or 'ROS' (37,38), but Helmut has himself cautioned against such broad and undefined usage (4).

Perhaps the greatest value of Helmut's 'oxidative stress' concept is that it had immediate currency for those who were not familiar with biological oxidation/reduction reactions. In an effect similar to the way that the discovery of superoxide dismutase by Joe McCord and Irwin Fridovich (44,45) convinced hard-core biochemists that free radicals had real roles to play in living organisms, Helmut's 'oxidative stress' terminology 'spoke' to a wide miscellany of biologists and physicians. I am convinced that this accessibility engendered by Helmut's 'oxidative stress' terminology was a significant factor in gaining 'respectability' for the fledgling free radical field.

Of Storks and the (West) German Birthrate

In 1988 Helmut demonstrated his keen understanding of the real-life significance of statistical correlations, along with a wonderfully wry, and dry, sense of humor. In a letter-to-the-editor of *Nature* magazine, entitled "*A new parameter for sex education*," (46) Helmut suggested an explanation, in the form of a graph, for the falling birth rate in what was then the state of West Germany; an explanation he suggested, "...that every child knows makes sense." All Helmut presented in his letter was a simple graph showing the declining number of newborn (human) babies in West Germany between 1965 and 1980, and the declining population of breeding pairs of storks. Since the slopes of the two declining lines exhibited an almost perfect correlation, the unstated conclusion (that storks actually do deliver babies unless there are too few birds to cope) would be obvious even to children! This is a lesson I never fail to introduce to graduate students and post-doctoral fellows in my laboratory, and I highly recommend it to everyone.

The Oxygen Paradox, Oxidative Stress & Ageing

The influence of Helmut's work on carotenoids in protecting skin against UV and singlet oxygen photo-damage (*e.g.* 18-23) has been enormous. Essentially every cosmetic company in the world has used the results of Helmut's research as the basis for producing products that 'prevent skin aging.' One imagines that Helmut has had to deny ever making such

claims himself on many occasions. Nevertheless, it does seem clear that repeated photo-oxidative insults to the skin impair its long-term health and vitality, and Helmut's work has shown that carotenoids can mitigate against such injuries (18-23).

Helmut has also made significant forays into the major age-related diseases of our time, including the fields of dementia, including Alzheimer disease (47-49); stroke (50); and heart failure (51). Perhaps only the fact that he remains so young at heart has kept Helmut from spending more of his time studying gerontology, although one notices that he has placed a strategic 'foot-in-the-door' by starting to unravel the secrets of healthy centenarians (52)!

Conclusions

It is both a pleasure and a privilege to be invited to contribute to this homage to my friend, Helmut Sies. Although my mini-review of his career hardly does justice to the broad array of major contributions he has made to science, it hopefully is sufficient to at least convince the reader that a giant is about to retire from our midst. Knowing Helmut, however, this 'retirement' is likely just a smokescreen, or a red herring, to lure us all into complacency; it won't work Helmut – we still expect many more great things from you in the years to come!

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Fig. 1.
The author (right) and Professor Helmut Sies (left) at a meeting in November 1999. The author has clearly been impressed by a comment of Prof. Sies. Lester Packer can (just) be seen in the background.

Fig. 2.

Above we see Prof Enrique Cadenas (left), Helmut Sies, the author, and Prof. Giuseppe Poli (right) on October 3, 1996 in Barcelona, Spain, at the VIII Biennial Meeting of the International Society for Free Radical Research.

Fig. 3.
Prof. Helmut Sies with Prof. Christine Winterbourn on November 20 2014 in Seattle, Washington, USA, at the annual Editorial Board meeting of the journal Free Radical Biology & Medicine. Both Profs. Sies and Winterbourn were inducted as members of the FRBM Distinguished Editorial Board at the meeting.