Redox Pioneer: Professor Helmut Sies

Dean P. Jones¹ and Rafael Radi²

Abstract

Dr. Helmut Sies (MD, 1967) is recognized as a Redox Pioneer, because he authored five articles on oxidative stress, lycopene, and glutathione, each of which has been cited more than 1000 times, and coauthored an article on hydroperoxide metabolism in mammalian systems cited more than 5000 times (Google Scholar). He obtained preclinical education at the University of Tübingen and the University of Munich, clinical training at Munich (MD, 1967) and Paris, and completed Habilitation at Munich (Physiological Chemistry and Physical Biochemistry, 1972). In early research, he first identified hydrogen peroxide (H₂O₂) as a normal aerobic metabolite and devised a method to quantify H₂O₂ concentration and turnover in cells. He quantified central redox systems for energy metabolism (NAD, NADP systems) and antioxidant GSH in subcellular compartments. He first described ebselen, a selenoorganic compound, as a glutathione peroxidase mimic. He contributed a fundamental discovery to the physiology of GSH, selenium nutrition, singlet oxygen biochemistry, and health benefits of dietary lycopene and cocoa flavonoids. He has published more than 600 articles, 134 of which are cited at least 100 times, and edited 28 books. His h-index is 115. During the last quarter of the 20th century and well into the 21st, he has served as a scout, trailblazer, and pioneer in redox biology. His formulation of the concept of oxidative stress stimulated and guided research in oxidants and antioxidants; his pioneering research on carotenoids and flavonoids informed nutritional strategies against cancer, cardiovascular disease, and aging; and his quantitative approach to redox biochemistry provides a foundation for modern redox systems biology. Helmut Sies is a true Redox Pioneer. Antioxid. Redox Signal. 21, 2459–2468.

The joy of exploring the unknown and finding something novel and noteworthy: what a privilege!

—Prof. Helmut Sies

Background Development and Training

The 20th century culminated with the triumph of sequencing the human genome, but achievements in physiological chemistry and redox biology dominated life science research for most of the century. Warburg’s description of Atmungsferment (cytochrome c oxidase) as the central catalyst of aerobic life and Keilin’s description of cytochromes provide highlights. Krebs connected these to the citric acid cycle; Lipmann described ATP as the central energy currency; Lehninger and Chance demonstrated associations of these processes with mitochondria; and Mitchell

¹Department of Medicine, Emory University, Atlanta, Georgia.
²Departamento de Bioquimica, Center for Free Radical and Biomedical Research, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay.

Author note: Dean Jones is a long-term colleague who collaborated with Dr. Sies on updating the definition of oxidative stress and outlining central principles of redox biology. Rafael Radi is an expert in nitric oxide and peroxynitrite biochemistry and has enjoyed more than two decades of academic interactions and visits with Dr. Sies.

For a list of frequently cited articles published by Prof. Helmut Sies, see Supplementary Tables S1 and S2, available online at www.liebertpub.com/ars
provided the mechanism for electrochemical coupling of oxidative phosphorylation. Seminal discoveries linked oxidative mechanisms to disease, and included discovery of peroxisomes, the respiratory burst of phagocytes, radical mechanisms of CCl₄ toxicity, radical scavenging of vitamin E, selenium requirement for antioxidant proteins, discovery of thioredoxin and superoxide dismutase, and elucidation of nitric oxide (NO) and hydrogen peroxide (H₂O₂) signaling.

Helmut Sies stands among the preeminent scientists with his contributions to this pioneering redox research.

Sies was born in 1942 and grew up in northern Germany “at the border of meadows and hillside forests,” a place enchanted by colorful kingfishers, springtime lush with wildflowers, and metamorphosis of tadpoles into frogs (64). He cites his first elementary school teacher, Georg Henkel, for fostering curiosity that led to a lifelong pursuit of discovery. His formative education was rich with culture, achievement, and opportunity. He took demanding experimental physics, mathematics, and chemistry and credits study of Latin for providing logic and long-term perspective. At 17 years of age, he boarded a Greek liner along with 200 European exchange students traveling to the United States for studying abroad. He lived with a medical doctor in a small town near Cincinnati; the impressive life and dedication of the country doctor had a lifelong impact (64).

During a visit by Britton Chance to Benno Hess at the Max-Planck-Institut für Ernährungsphysiologie, Dortmund, Enrique Cadenas recalls Chance’s reference to Sies as an “outstanding biologist who could see how concepts developed in the future.” In redox biology, Sies led others to discovery through his vision of oxidative stress, defined in 6.5 pages in *Oxidative Stress: Introductory Remarks* (58).
developed in a review in Angewandte Chemie (59). He brought together findings from biochemistry, chemistry, physics, radiology, medicine, nutrition, cell biology, physiology, and cancer biology, to provide a roadmap for upcoming decades as he conceptualized the consequences of an imbalance of pro-oxidants and antioxidants in terms of macromolecule damage to DNA, lipids, and protein (Fig. 2).

During this seminal period, he discovered that ebselen, an organoselenium compound, is a GSH peroxidase mimetic (33, 38, 39, 61, 62). His description of redox cycling linked a broad range of redox-active enzymes to mechanisms of macromolecular damage and cell toxicity (23) in a process driven by enzymatic activity and not requiring radical propagation for toxicity. Sies contributed to the understanding of *NO (24, 25, 27), the nitroxy anion (35), a method to capture *NO (26), detect S-nitrosylated and S-glutathionylated proteins (22) and nitrite as a precursor to *NO (93). He characterized reactions of organoselenocompounds with peroxynitrite (3, 6, 7, 29) and showed that GSH peroxidase is a peroxynitrite reductase (76). He showed that plasma selenoprotein P protected low-density lipoprotein (LDL) against oxidation (94) and astrocytes (90) and endothelial cells from damage (91). He also examined a relationship of high selenium intake to type 2 diabetes risk (40, 92).

**Translation of Basic Science to Health Practices in Studies of Carotenoids and Flavonoids**

In a third key finding, Sies (14) showed lycopene to be the most efficient carotenoid quencher of singlet oxygen (Fig. 3).
Lycopene, present in different foods (83–87), showed preferential availability from processed tomato products (86). With Stahl, he extended lycopene research to humans, notably regarding skin damage from sunlight (Fig. 3). Applying noninvasive measurement and identifying dermal carotenoid products (82), his pioneering research demonstrated protection against ultraviolet light in humans (5, 17, 81, 82), and it is now extended to lycopene research worldwide, particularly in prostate cancer and cardiovascular disease. It should be noted that Sies studied carotenoids in a nutritional biochemical context, not as dietary supplements which, at high doses, proved counterproductive in human studies.

In diet and health research, Sies advanced a mechanistic understanding of flavanols on pro-oxidative enzymes (46–49, 88, 89) and showed that flavanol-rich cocoa protects against inflammatory events (30). In human volunteers, high-flavanol cocoa increased the level of bioactive protein-bound NO in the blood and improved endothelial function (Fig. 3) (19, 20). The effect was mimicked by (-)epicatechin isolated from cocoa (50). He found flavanol-rich cocoa to diminish plasma F2-isoprostane in humans (100) and showed beneficial vascular effects in smokers (21), photoprotective and cosmetic effects in the skin (18, 36), and longer-term health benefits (20) distinct from acute vascular responses (65). In other research, Sies studied vitamin E in viral hepatitis (95–97) and inactivation of virus in human plasma (32). He contributed to human research on aging (43), diabetics, congestive heart failure, ischemic stroke, and dementia (28, 41–43, 45). Stretching forward from his key findings on singlet oxygen, reactive carbonyls, carotenoids, and other antioxidants, Sies provided pioneering leadership in the roles of vitamins, essential minerals, and phytochemicals in promoting optimum health and preventing disease.

**Other Achievements and Current Position**

As founder of the concept of oxidative stress, Professor Sies set the foundation for the integration in a rational way of the biochemical observations toward the field of biomedicine. With the advance in knowledge on the role of redox processes in biology, the concept of oxidative stress was updated to include the role in redox signaling (75). He is a pioneer in quantitative redox biology and a trailblazer in exploring mechanisms and impacts of dietary constituents on a large variety of disease conditions and even in the aging process. His concepts opened new avenues for the possibility of modulating redox processes in vivo through dietary or pharmacological means, an area that continues to be highly active and now extends to roles of oxidative processes in cell signaling. He continues his leadership role in basic and translational science as Professor Emeritus, Department of Biochemistry and Molecular Biology I, Faculty of Medicine, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.

Professor Sies has frequently lectured at international scientific meetings and has also been active in dissemination of research to the public, through lectures to lay audiences, at nutrition meetings, at academies, and through television.
He has frequently credited his close associates, Dieter Häussinger (13, 15, 16, 74), Enrique Cadenas (9–11, 67, 70), Paolo diMascio (14), Theo Akerboom (1, 2), Wilhelm Stahl (78, 83–87), and many others cited in the references, as well as support from the National Foundation for Cancer Research (Bethesda), Alexander von Humboldt Foundation, Deutsche Forschungsgemeinschaft, and others. In 1996, he received an Honorary Ph.D. degree from the University of Buenos Aires from Prof. Boveris’ institution, and in 2010, he received an Honorary M.D. from Dr. Radi’s institution, Facultad de Medicina, Universidad de la República, Montevideo, for his outstanding contributions to unravel molecular mechanisms in physiology and pathology and to celebrate the 25th anniversary of the emergence of the Oxidative Stress concept.

He has received FEBS Anniversary Prize (1978), the Ernst-Jung-Prize for Medicine (1988), the Claudius-Galenus-Prize (1990), the Werner-Heisenberg-Medal of the Alexander von Humboldt Foundation (1999), the Linus Pauling Institute Prize for Health Research (2013), and the Trevor Slater Award of the Society for Free Radical Research International (2014).

He has been an instrumental force in scientific leadership for decades, editing scientific journals and books and providing leadership, such as President of the Society for Free Radical Research International, an umbrella organization that encompasses the regional societies in America, Europe, Asia, and Australasia, and of the Oxygen Club of California. He has served as President of the Northrhine-Westphalian Academy of Sciences and is a Member of the German National Academy of Sciences Leopoldina. He has helped lead scientific education, fostering the highest standards in research conduct and dissemination. He stands staunchly on the shoulders of his distinguished scientific pedigree: a student of Theodor Bücher, who descends from Nobel Prize awardees Otto Warburg and Emil Fischer, who traces back to Justus von Liebig, the founder of nutritional biochemistry. Professor Sies extends this tradition with research transcending science to address the health of our society.
Participants at the 25. *Konferenz der Gesellschaft für Biologische Chemie* at Reisensburg Castle, Germany, July 8–11, 1978; organized by Helmut Sies and Albrecht Wendel. Next to GSH sign: Sir Hans Krebs, right, Alton Meister, left. Front row, Leopold Flohé and Albrecht Wendel, 3rd and 4th from right. Helmut Sies (with sunglasses) is two rows at the back of A. Wendel. Coauthor, Dean Jones (with glasses), is two rows at the back of A. Meister.

Alberto Boveris, Nozomu Oshino, and Helmut Sies (left to right) at the Society for Free Radical Research International meeting in Kyoto, 2000.
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References


Address correspondence to:
Dr. Dean P. Jones
Department of Medicine
Emory University
Whitehead Bldg., Rm 205P
Atlanta, GA 30322
E-mail: dpjones@emory.edu

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Abbreviations Used

H$_2$O$_2$ = hydrogen peroxide

NO = nitric oxide