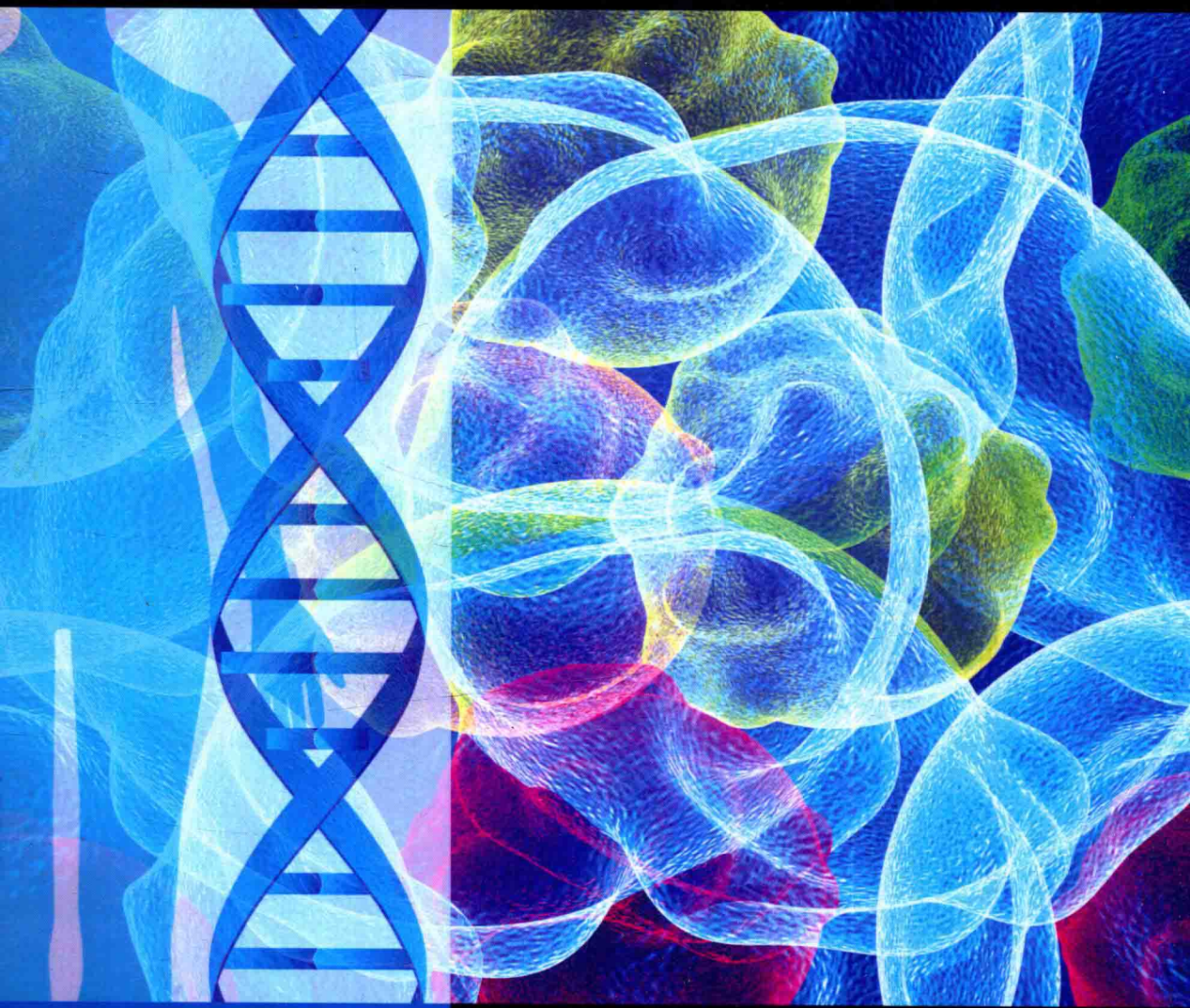
REACTIVE OXYGEN SPECIES in BIOLOGY and HUMAN HEALTH



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Preface

Reactive oxygen species (ROS) have been identified to play major roles in our lives. This is evident from the fact that since their first documented publication in 1945 by Stuffins and Weatherall [1] and in 1946 by Mann and Quastel [2], 161,400 research papers have been documented (PubMed, November 6, 2015). Indeed, ROS production, their interactions with a large number of biomolecules and the resulting damage and consequences, and their roles in inducing a large number of human diseases, also positively affecting certain metabolic processes and playing roles in aging, are highly complex areas of human biochemical metabolism and require much more studies to obtain a more complete picture.

ROS are unstable reactive molecules, have one or more unpaired electron(s), and are able to oxidize nearby molecules to gain an electron to enter the ground states. A number of ROS in biological systems include lipid peroxides, nitric oxide (NO), singlet oxygen ($^1O_2$), ozone (O_3), and hypochlorous acid (HOCl); however, superoxide anions ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2) are the three most important ROS playing dual roles in biological systems. Interestingly, these three ROS are interconvertible, in that the oxygen molecule can be converted to $O_2^{\bullet-}$ by accepting an electron. In turn, the dismutation reaction by superoxide dismutase (SOD) can convert $O_2^{\bullet-}$ to H_2O_2, and this finally may be partially reduced to $^{\bullet}OH$ or fully reduced to water.

ROS can be produced endogenously or exogenously. Endogenously, they are produced naturally and continuously in biological systems as a result of leakage of electrons from the electron transport chain in mitochondria. Additionally, they are produced by various enzyme reactions in the systems such as those carried out by xanthine oxidase and by cytochrome P450. Also, autoxidation of small molecules (e.g., catecholamine), response to xenobiotics and exogenous environmental exposures, ischemia, and inflammatory stimuli are also responsible for the production of ROS. Endogenously, ROS are also produced through the ROS NADPH oxidase (NOX) complex in the cell membrane, mitochondria, peroxisomes, and endoplasmic reticulum.

A number of exogenous agents playing roles in ROS production include xenobiotics, pollutants, drugs, smoke, tobacco, and radiation. A good example of production of ROS by ionizing radiation is a set of reactions in which water is converted to $^{\bullet}OH$, then to H_2O_2 and to $O_2^{\bullet-}$, and ultimately to oxygen.

ROS being highly reactive can cause damages to biological systems, including DNA strand breaks, base modifications leading to mutations, inhibition of RNA and protein synthesis, protein damage including disruption of amino acid bonds and also their cross-linking, oxidation of membrane phospholipids, lipid peroxidation, disruption of membrane ion gradients, and depletion of cellular levels of ATP leading to cellular dysfunction. Mitochondria, having the highest turnover of oxygen, involving enzymes of the respiratory chain, are the specific targets of ROS. Out of the three ROS, $^{\bullet}OH$ is the most reactive and can immediately interact with any molecule in its vicinity and can remove electron, turning that molecule into a free radical, giving rise to chain reactions. $^{\bullet}OH$ specifically induces hydroxylation of deoxyguanosine in DNA forming 8-OH-dG, which can be a site for mutagenesis and, possibly, cancer. $O_2^{\bullet-}$ in comparison to $^{\bullet}OH$ is not that much reactive by itself but can initiate lipid peroxidation in its protonated form or can inactivate certain specific enzymes. H_2O_2 has low reactivity, is more stable, and hence can travel into the nucleus and can react with important components such as nucleic acids and nuclear proteins besides other cellular components such as lipids.

ROS are beneficial at physiological levels and assist in maintaining normal cell function; it is therefore essential that they be maintained at homeostatic levels. The beneficial roles of ROS include induction of host defense against a variety of pathogens. Defense against viral infections is carried

out by potentiating RIG-like helicase-1 and mitochondrial antiviral signaling protein. ROS have also been implicated with mobilization of the ion transport system and a variety of inflammatory responses, including cardiovascular disease (CVD) and ischemic injury and also in hearing impairment due to ototoxicity by cisplatin and congenital deafness. Interestingly, people suffering from granulomatous disease, in which ROS production is reduced or absent, become more susceptible to infection by a range of pathogenic bacterial species.

Nature has endowed living systems with a number of protective mechanisms mostly involving enzymes whose roles are to scavenge excessive and unwanted ROS present in the system. ROS scavenging enzymes include catalase and peroxidase (for H_2O_2) and SOD that catalyze the dismutation of $O_2^{\bullet-}$ into oxygen and H_2O_2. Catalase converts H_2O_2 to oxygen and $2H_2O$. Also in the system, low-molecular-weight antioxidants such as ascorbic acid, α-tocopherol or vitamin E, and glutathione are present. In a recent article, it has been shown that mitochondria are the major source of MnSOD, and this enzyme constitutes an essential defense against $O_2^{\bullet-}$; further, this and other nitrogen species are responsible for various redox-related diseases and aging. A number of neurodegenerative diseases (NDs) associated with ROS include amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease (AD), and Huntington's disease (HD) (for more details, see [3]), as well as age-related macular degeneration, atherosclerosis, and various types of cancers.

In this book, attempts have been made to cover as much information about ROS as possible with the exception of their role in aging, which is still at the hypothesis stage.

For the readers' easy reading the contents of the chapter has been sectionalized below.

Section I includes Chapters 1 through 6 in which the introduction, detection, and production of ROS are described. In Chapter 5, special emphasis is given to phenolic compounds and vitamin E for their abilities to act as antioxidants; however, due to their overall low concentrations, doubt has been casted on their *in vivo* effectiveness. Chapter 6 highlights the role of lipoprotein-associated oxidative stress and suggests that its assessment in plasma may be used as the best biomarkers of oxidative stress.

Section II embraces Chapter 7 in which Carmen et al. have intricately addressed the importance of accumulation of iron in the brain resulting in the development of a group of neurodegenerative disorders. Several causative genes for neurodegeneration with brain iron accumulation (NBIA) have been identified, which are associated with Parkinsonism-related disorders. It is suggested that increased knowledge of NBIA genes and their functions should help to better understand the clinical picture, MRI findings, and disease mechanisms.

Section III discusses a number of NDs. In Chapter 8, Perry addresses one of the most important diseases, ALS, also known as motor neuron disease. Despite a large number of studies being carried out, its exact mechanism still remains unclear. One important finding linked with the disease is the mutation in SOD-1 (coding for Cu, Zn SOD), which may be responsible for the disease pathology. Chapter 9 presents the complexity of AD and its therapeutic strategies. HD, another ND, which is associated with mitochondrial dysfunction, has been addressed comprehensively in Chapter 10, and readers may gain considerable insight from it. In Chapter 11, epilepsy, another ND caused by ROS and reactive nitrogen species (RNS) associated with mitochondrial dysfunction, is described. Mitochondrial DNA and phospholipids have specifically been identified as the targets of ROS and RNS. Interestingly, certain psychological disorders have also been associated with ROS-induced brain injury, which is critically addressed in Chapter 12. In Chapter 13, studies on another frequently found neurological disease, multiple sclerosis, and the latest treatment regimen worthwhile to be studied are presented.

Section IV addresses autoimmune diseases caused by ROS. In Chapters 14 and 15, two important diseases are included: asthma, caused by the dysregulation of the oxidant–antioxidant balance, and autoimmune liver diseases, caused by oxidative stress from cigarette smoking, wherein the smoke contains a large number of toxic, carcinogenic, and mutagenic chemicals. Chapter 15 also includes other autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, thyroid disease,

and primary biliary cirrhosis. The use of immunosuppressants has been recommended as a possible regimen. Systemic lupus described in Chapter 27 is another ROS-activated autoimmune disease that can affect several organs, including the kidneys, skin, lungs, brain, and heart. Oxidative stress, leading to oxidative modifications of functional proteins, lipid, and DNA, ultimately results in the breakage of immune tolerance, apoptosis, necrosis, autophagy, and increased tissue damage.

Section V includes Chapters 16 through 19 that address a number of different types of cancers, including lung cancer, breast cancer, and melanoma. Detailed analyses of these cancers alongside their possible treatment regimens are intricately presented and deserve priority in the reading list.

Section VI discusses CVDs induced by ROS. They too are a highly important set of diseases. In Chapters 20 and 21, Johnson and Shimokawa, respectively, present their in-depth knowledge of this subject. CVDs remain the leading cause of human death and much information about their causes, mechanisms, and treatments is available. Mangge in Chapter 22 intricately presents the ROS-associated complex biochemical processes inducing inflammation as an important cause of CVDs. Chapter 23 explains the roles carotenoids play in preventing CVDs and how this agent can improve cardiovascular health. These authors recommend more studies to be carried out to minimize the risk of CVDs.

Section VII includes Chapters 24 through 39 addressing other human diseases induced by oxidative stress. These include sickle cell disease (Chapter 24), which is a group of complex genetic hemolytic disorders associated with high morbidity and mortality and which still remains to be fully understood. Nonalcoholic steatohepatitis (Chapter 25) addressed by Yamamoto is more commonly found in patients suffering from diabetes. ROS have been accepted as the main inducers of this disease in which liver fat deposition commonly prevails. In Chapter 26 on retinopathy, one of the several diabetic complications, the authors have ascertained that oxidative stress is the central factor involved in its pathology and the polyol pathway plays key roles in the production of ROS. Fibromyalgia, addressed by Fatima in Chapter 28, is one of the least understood human diseases caused by imbalance between malondialdehyde and SOD, and patients suffering from this disease sustain persistent and widespread pain and tingling sensations, muscle spasms, limb weakness, nerve pain, and muscle twitching. Unfortunately, the etiology of this disease is not well known, and only limited treatments are available. Chronic obstructive pulmonary disease, asthma, and pulmonary hypertension are shown, by Zuo in Chapter 29, to be induced by excessive ROS production. Further studies have been suggested to unravel the complete picture and successful treatment. Chapters 30 through 32 are dedicated to human fertility, and its awareness may assist those suffering from infertility. Chapter 33 presents a detailed study on the aging of human skin by ROS, and, more importantly, a good number of color figures have been added to enrich the chapter. Also, awareness has been included on how to avoid or minimize skin aging specially when induced by exogenous agents. Ataxia telangiectasia, an inborn genetic disease, has been shown, by Nakajima in Chapter 34, to be due to a mutation in the ATM gene, and the regulation of this gene expression is carried out by oxidative stress. It is intriguing to learn in Chapter 35 by Hong that oxidative stress can have profound effects on viral pathogenesis and on the host, and this is due to an imbalance between pro- and antioxidants leading to inflammatory response, viral replication, and apoptosis. Hargreaves in Chapter 36 highlights the importance of organophosphates, the highly toxic group of chemicals that can affect the nervous system by exerting its toxicity via oxidative stress. Conclusion is drawn on the basis of antioxidants attenuating some of the toxic effects. Chapters 37 through 39 address the roles of ROS in morphine addiction, exercise, nitric oxide, and epigenetics, respectively.

It is hoped that the material presented in this book will stimulate both experts and novice researchers in the field with excellent overviews of the current status of research and pointers to future research goals. Clinicians, nurses, carers, and families should also benefit from the information presented in handling and treating their specific patients. Also, the insights obtained should prove valuable for further understanding such a large number of diseases at the molecular level and

allow the development of new biomarkers, novel diagnostic tools, and highly effective therapeutic drugs to treat patients suffering from these devastating diseases.

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REFERENCES

1. Stuffins, C.B. and Weatherall, H., Determination of the peroxide value of oil and fat, *Analyst*, 70, 403, 1945.
2. Mann, P.J.G. and Quastel, J.H., Toxic effects of oxygen and hydrogen peroxide on brain metabolism, *Biochemistry*, 40, 139, 1946.
3. Ahmad, S.I. (ed.), *Neurodegenerative Diseases*, Springer-Verlag, New York, 2012.

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Editor

Shamim I. Ahmad, after earning his master's degree in botany from Patna University, Bihar, India, and his PhD in molecular genetics from the University of Leicester, England, joined Nottingham Polytechnic as a grade 1 lecturer and was subsequently promoted to the senior lecturer post. Nottingham Polytechnic subsequently became Nottingham Trent University, where, after serving for about 35 years, he took early retirement, yet continued serving as a part-time senior lecturer. Dr. Ahmad is now spending much of his time producing/writing medical books. For more than three decades, he researched on different areas of molecular biology/genetics, including thymineless death in bacteria, genetic control of nucleotide catabolism, development of anti-AIDs drug, control of microbial infection of burns, phages of thermophilic bacteria, and microbial flora of Chernobyl after the accident at the nuclear power station. But his main interest, which started about 30 years ago, is DNA damage and repair specifically by near-ultraviolet light, especially through the photolysis of biological compounds, production of reactive oxygen species, and their implications on human health, including skin cancer. He is also investigating near-ultraviolet photolysis of nonbiological compounds such as 8-metoxypsoralen and mitomycin C and their importance in psoriasis treatment and in Fanconi's anemia. In collaboration with the University of Osaka, Japan, in his recent research publication, Dr. Ahmad and his colleagues were able to show that a number of naturally occurring enzymes were able to scavenge the reactive oxygen species.

In 2003, Dr. Ahmad received the prestigious "Asian Jewel Award" in Britain for "Excellence in Education." He has been editor for the following books published by Landes Bioscience/Springer: *Molecular Mechanisms of Fanconi Anemia* (2006), of *Xeroderma Pigmentosum* (2009), of *Cockayne Syndrome* (2009), of *Ataxia Telangiectasia* (2009), *Diseases of DNA Repair* (2010), *Neurodegenerative Diseases* (2012), *Diabetes: An Old Disease, a New Insight* (2013), and *Obesity: A Practical Guide* (2016).

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