Nitrite and Nitrate in Human Health and Disease
The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews by the leading researchers in their respective fields, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and the consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research, and 9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

“Nitrite and Nitrate in Human Health and Disease”, edited by Nathan S. Bryan, Ph.D. and Joseph Loscalzo, M.D., Ph.D., clearly exemplifies the goals of the Nutrition and Health Series. For many of us who learned about the potential adverse effects of nitric oxide as an environmental air pollutant and the potentially carcinogenic effects of nitrosamines, seeing a volume on nitrate and nitrite may appear at first glance as a toxicology volume. This is not the case. Nitric oxide (NO) still remains an air pollutant; however, within human blood vessels, this short lived gas acts to dilate vessels and lower blood pressure and also maintains the integrity of platelets. This first comprehensive review of the science behind active nitrogen-containing molecules and their effects in humans is of great importance to the nutrition community as well as for health professionals who have to answer client questions about this new area of clinical research.
The two editors are highly qualified in nitrate and nitrite investigations. Dr. Bryan is currently Assistant Professor at the University of Texas Health Sciences Center’s Institute of Molecular Medicine in Houston TX. He has been a pioneer in recognizing the salubrious effects of dietary nitrite and nitrate and elucidating the novel metabolism of nitrate and nitrite in humans. He has published extensively in this area. Dr. Bryan is a member of the Society for Free Radical Biology and Medicine, American Physiological Society, Nitric Oxide Society, American Heart Association and the American Association for the Advancement of Science. Joseph Loscalzo, M.D., Ph.D is the Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School and serves as Chairman of the Department of Medicine and Physician-in-Chief at Brigham and Women’s Hospital in Boston, Massachusetts. Dr. Loscalzo is recognized as an outstanding cardiovascular scientist, clinician, and teacher. Dr. Loscalzo was one of the early pioneers in the nitric oxide field with many of his seminal publications and discoveries dating from the early 1980s. He was the first to demonstrate the formation of S-nitrosoproteins and to elucidate the antithrombotic and antiplatelet mechanisms of NO, as well as many other contributions to this field. He has received many awards, including the Clinician-Scientist Award, the Distinguished Scientist Award, the Research Achievement Award, and the Paul Dudley White Award from the American Heart Association; a Research Career Development Award, a Specialized Center of Research in Ischemic Heart Disease Award, and a MERIT Award from the National Institutes of Health; the George W. Thorn Award for Excellence in Teaching at Brigham and Women’s Hospital, and Educator of the Year Award in Clinical Medicine from Boston University; the Glaxo Cardiovascular Research Award, and the Outstanding Investigator Prize from the International Society for Heart Research; and election to the American Society for Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the National Academy of Sciences.

“Nitrite and Nitrate in Human Health and Disease” represents the first comprehensive compilation of the newest science of inorganic nitrite and nitrate in human health, and it is to the credit of Drs. Bryan and Loscalzo that they have organized this volume so that it provides an in-depth overview of the natural occurrence and biochemistry of relevant nitrogen-containing molecules; human exposure to nitrate and nitrite; and the latest research on the role of nitrate and nitrite in normal health, cardiovascular disease, and related conditions, as well as their use as therapeutic agents. Of importance, this volume includes an in-depth review in the final section that re-examines the role of nitrosamines (which can be formed from nitrite and nitrate) in human cancer risks.

The volume is organized into three comprehensive sections. The first section includes four chapters that define the biochemistry, metabolism, and physiology of the nitrogen-containing compounds. The first chapters review the major processes involved in the biochemical steps from the capturing of nitrogen from the atmosphere through the generation of nitric oxide (NO), nitrite, and nitrate within the human body. The chapters provide the reader with a basic understanding of the interactions between the inert gas, nitrogen, that comprises 78% of our atmosphere and natural physical events, such as lightning strikes and volcanic eruptions, that result in the formation of active compounds. The most abundant source of active
nitrogen compounds result from plant fixation of nitrogen with the help of anerobic microorganisms that are capable of conversion of atmospheric nitrogen into inorganic nitrogen-containing compounds that can be incorporated into essential amino acids and proteins, nucleic acids, and enzymes. In addition to a full description of the traditional nitrogen cycle, there is also a complete and detailed discussion of the novel nitrogen cycle that was first elucidated in the 1980s and resulted in naming NO as the Molecule of the Year in 1992 and the awarding of the Nobel Prize in Medicine to Dr. Louis J. Ignarro, Robert Furchgott, and Ferid Murad. Dr. Ignarro has generously provided a most insightful Foreword for this important volume.

The two final chapters of the first section describe the formation of NO within the human body and its role in delivering oxygen to tissues under very low oxygen pressures. Nitrite binds to hemoglobin, and when it is delivered to ischemic or hypoxic tissue beds, it dilates the arterioles permitting more of the oxygen-carrying hemoglobin to reach these tissues. These highly complex reactions are excellently illustrated in the figures in the chapter. The genetic polymorphisms that are associated with alterations in the enzymes required for conversion of active nitrogen compounds and the effects on delivery of oxygen to tissues are also reviewed.

The next chapter, that follows logically from the previous chapter, discusses the sources of nitrate and nitrite, and reminds us that naturally occurring nitrogen-containing compounds have been used throughout human history to reduce heart pain (angina) as well as to reduce the spoiling of foods (salt peter, as an example). Ground water is a major source of nitrate, as are fruits and vegetables. This chapter also includes an examination of the potential sources of nitrosamines and reviews the environmental conditions that can result in their formation within the body. The take-home message from the introductory chapters and throughout the volume is that the level and duration of exposure to nitrate and nitrite is the keys to whether these molecules are of benefit or may be harmful to health.

The second section contains six chapters on food and environmental exposures to nitrite and nitrate. The chapter on the history of use of nitrate in foods postulates that one potential reason that many of the randomized controlled clinical trials of antioxidants have not shown significant decreases in cardiovascular disease is that there was no inclusion of nitrate or nitrite sources that may have helped optimize vascular function and health. There is an important review of the Mediterranean and DASH diets as these diets contain higher than average intakes of fruits and vegetables that are major sources of nitrate and nitrite. Dr. Willett, in the next chapter, outlines the critical issues involved in capturing the level of exposure to nitrate and nitrite in the human diet and examines the methodologies used in collecting epidemiological data on intakes and biochemical indicators of status. At present there is no validated assessment of nitrate or nitrite content in foods and the lack of this critical tool has resulted in many differing values for exposures. Also, there is no acceptable biomarker of long term intake. The suggestion is to utilize currently validated food frequency questionnaires, estimate nitrate and nitrite levels based upon published studies and measure intakes at multiple time points in prospective cohort studies as this model is the least compromised in terms of recall and other potential biases.
The next chapter reviews the sources of nitrate and nitrite in our food supply and environment. The novel discovery of the oral cavity's role in nitrate balance within the human body is explained with great depth. This chapter provides a clear understanding of the importance of anaerobic bacteria that live within the tongue and in our mouth and describes the metabolism of nitrate, its functions within the bloodstream, and its elimination. Salivary nitrate and nitrite levels are much higher than those in the blood and represent a recycling of both exogenous and endogenous sources. The potential effects of nitrate and nitrite are modulated by other constituents, such as antioxidant vitamins and flavanols, found in the same food sources.

The next chapter reviews the important role of flavanols and polyphenols in affecting the activity of the key enzyme involved in NO generation within blood vessels, endothelial nitric oxide synthase, that results in vascular dilation. The chapter includes an extensive discussion of methodologies used to measure vascular health as well as the biochemistry of NO synthesis. Two unique chapters complete this section of the volume. The first examines the critical role of nitrate and nitrite found in human breast milk. Colostrum contains higher concentrations than later milk and may be involved in protecting the neonate from infections when the immune system is not yet fully developed. The concentrations of nitrate and nitrite in human milk are compared to those found in infant formula, cow's milk and soy milk formulas, all of which have lower concentrations than seen in human breast milk. FDA regulations of infant formula levels are reviewed and this information complements the next chapter that describes the numerous regulations in the US and globally of nitrate/nitrite levels in ground water and processed meats. Regulatory bodies include the EPA, FDA, USDA, and the WHO. The regulations include the addition of antioxidants to processed meats to reduce potential nitrosamine formation. Often, the concentrations that represent the upper levels of intake by the regulatory bodies are significantly lower than the concentrations found naturally in certain foods such as spinach. Several authors suggest that regulations be re-examined based upon the new data on the importance of nitrate and nitrite for cardiovascular health and other health benefits. Authors and the editors agree that using a process such as that used by the US Institute of Medicine to determine intake levels for essential nutrients, may be of value in determining safe and effective levels of intake for nitrate and nitrite.

The third section reviews the newest data on nitrate and nitrite use in therapeutics and disease conditions and includes seven chapters. In order to develop therapies that utilize the synthesis of NO, there must be a clear understanding of the enzymatic reactions that naturally result in NO formation, the dietary sources of precursor molecules, and the endogenous and environmental factors that modulate the formation as well as destruction of these biologically active nitrogen-containing species. The next chapters review these reactions and provide relevance to the studies of L-arginine as a precursor and the development of NO forming drugs used to treat angina and erectile dysfunction by dilating relevant blood vessels. Inhaled NO is currently being used in serious therapeutic cases to increase pulmonary vasodilation. Owing to the potential for NO to combine with oxygen and create highly reactive molecules that can damage the lung and other tissues, the control of the
concentration of NO that is utilized is critical. This is especially true when NO is used in the treatment of premature infants who lack maturity in their lungs and may develop bronchopulmonary dysplasia. Inhaled NO is also used to treat acute respiratory distress syndrome and acute lung injury. There are detailed descriptions of the animal models that have been developed to better understand the value and limits of NO inhalation in severe lung diseases. The medical conditions associated with the use of nitrovasodilators are described in detail in the next chapter. Nitrovasodilators are used in the treatment of stable and unstable angina, congestive heart failure and myocardial infarction. The complex pharmacology and metabolism of the drugs are reviewed. As an example, cyanide radical is released when sodium nitroprusside is metabolized; control of exposure to this toxic molecule is obviously essential.

The next three chapters examine the potential for nitrate and nitrite to serve as therapeutic agents under different disease conditions. The chapter on ischemia-reperfusion (IR) injury describes the effects of IR injury on the heart, lungs, liver, kidney and brain. Active nitrogen-containing molecules can blunt the formation of reactive oxygen radicals known to be the major causes of IR injury. Other conditions that are also prone to IR cellular damage include sickle cell anemia and peripheral artery disease and low dose nitrite therapies are being explored as therapies in these and other relevant conditions. Traditional Chinese Medicines (TCM) that have been used for thousands of years for cardiovascular indications are often composed of the roots, stems and leaves of plants. The plants have been recently analyzed for their nitrate, nitrite contents, the values are tabulated in the next chapter, and a full discussion of the combinations of herbs and other plants are described in detail. As indicated earlier, the question of the association of nitrate and nitrite with cancer risk is examined in great detail in the next chapter. It appears that there are inconsistent data from human epidemiological studies. The literature consistently reports a decreased risk of many cancers, including lung, breast, and colorectal in populations with the highest intakes of fruits and vegetables, especially green and yellow vegetables that have high concentrations of nitrate and nitrite. The literature also reports a higher risk of stomach cancer in individuals with the highest intakes of pickled, processed, and cured meats that are also concentrated sources of nitrate and nitrite. The laboratory animal studies may not be relevant to human intake levels as animals are often exposed to very high intakes of nitrate and nitrite. One argument that is raised is that stomach cancer has significantly decreased over the past decades and this may be linked to the addition of antioxidants to cured meats. The critical issue, discussed in the final chapter written by the volume’s editors, is the perception of the negative effects of nitrate and nitrite in the minds of many health professionals based upon the early findings of increased cancers in animals exposed to very high intakes of nitrate and nitrite and the well recognized fact that nitrosamines are mutagenic and may be carcinogenic under the appropriate conditions. This volume presents compelling data to support a paradigm shift in the understanding that nitrate and nitrite can be of great benefit to health if consumed at the right levels and if used therapeutically with the proper precautions.
The logical sequence of chapters enhances the understanding of the latest information on the current standards of practice for clinicians, related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist, and others involved in the team effort required for successful treatment of cardiovascular and other relevant diseases, as well as conditions that adversely affect normal metabolic processes. This comprehensive volume also has great value for academicians involved in the education of graduate students and post-doctoral fellows, medical students, and allied health professionals who plan to interact with patients with disorders that can be beneficially affected by the addition of nitrate and nitrite to the diet or by use of pharmacological agents that utilize active nitrogen-containing drugs.

Cutting edge discussions of the roles of signaling molecules, growth factors, hormones, cellular and nuclear receptors, and all of the cells directly involved in NO metabolism are included in well-organized chapters that put the molecular aspects into clinical perspective. Of great importance, the editors have provided chapters that balance the most technical information with discussions of its importance for clients and patients as well as graduate and medical students, health professionals and academicians.

The volume contains over 40 detailed tables and figures that assist the reader in comprehending the complexities of the nitrogen cycles and the metabolism of nitrate and nitrite within the body. The over-riding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of this relatively new field of investigation. Hallmarks of the 17 chapters include, key words, and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 1,400 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments, and preventive strategies that are involved in the understanding of the role of a critical gas, NO, in the control of blood flow through the body as well as the modulation of platelet function. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, “Nitrite and Nitrate in Human Health and Disease,” edited by Nathan S. Bryan, Ph.D., and Joseph Loscalzo, M.D., Ph.D., provides health professionals in many areas of research and practice with the most up-to-date, well referenced and comprehensive volume on the current state of the science and medical uses of active nitrogen-containing molecules. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D, FACN
Series Editor
The short-lived, free radical molecule nitric oxide (NO) has emerged as one of the most versatile cell signaling transmitters produced by mammalian biological systems. NO, identified as ‘endothelium-derived relaxing factor’ and proclaimed ‘Molecule of the Year’ in 1992, functions critically in physiology, neuroscience, and immunology. The vascular effects of NO alone include vasodilatation, inhibition of platelet aggregation and leukocyte adhesion to the endothelium, scavenging of superoxide anions, and inhibition of smooth muscle cell hyperplasia. Early studies on NO stemmed from work with nitroglycerin in an attempt to elucidate the mechanism through which it relieved pain due to angina pectoris. It was discovered that the formation of NO from nitroglycerin accounts for its therapeutic efficacy for angina by dilating constricted and diseased blood vessels in the heart. Not surprisingly, some of the most prevalent diseases result, at least in part, from decreased NO availability, for example, hypertension, atherosclerosis, diabetes mellitus, and hypercholesterolemia.

The discovery of the formation of NO from the semi-essential amino acid L-arginine through one of three isoforms of nitric oxide synthase provided a key therapeutic target, which is still the focus of much research today. Dietary supplementation of L-arginine has been shown to enhance NO production in healthy individuals (despite already saturated extracellular concentrations), and this may provide both cardiovascular protective effects and enhance athletic performance. Indeed, endothelial dysfunction, an early sign of cardiovascular disease, has been reversed through enhanced NO production. This observation leads us to believe that intervention through the NO-pathway is a viable route for treatment and prevention of vascular dysfunction.

Recently, the oxidative ‘waste’ products of nitric oxide, nitrite and nitrate, have been evaluated in a new context, due to their ability to form NO independent of nitric oxide synthase enzymes, through reductive electron exchanges. Since nitrate (as well as nitrite) are primarily ingested in the form of fruits and vegetables, which have been known for some time to protect against diseases from atherosclerosis to cancer, a new paradigm has emerged regarding the role of these once feared nitrogen oxides. Both public and scientific perception of nitrite and nitrate still revolve around fears of nitrosamine formation and carcinogenesis. What has not been considered, however, is the fact that consumption of antioxidants with nitrite and nitrate (both significant components of fruits and vegetables) inhibits the formation of nitrosamines in the gastric milieu. Furthermore, a human nitrogen cycle consisting...
of commensal bacteria in the oral cavity, which serve a reductive role in the conversion of approximately 20% of ingested nitrate to nitrite, now appears to provide a significant NOS-independent source of NO generation.

This body of work may have revolutionary implications in terms of developing strategies to combat heart disease and many other contemporary diseases associated with a NO deficiency. Furthermore we may finally have an explanation for the many known and undisputed benefits of the Mediterranean diet. Perhaps now we should consider nitrite and nitrate as the bioactive food components that account for the protective benefits of certain foods and diets. Numerous clinical trials of supplementation with various antioxidants borrowed from heart-healthy diets, such as those typical of Mediterranean countries, have consistently failed to replicate the protective effects of the foods themselves. Consistently absent, but the primary human source, is dietary nitrate and nitrite. Recent work has shown various cardio-protective effects from modest supplementation of nitrite and nitrate. Nitrite, in particular, has been shown to prevent hypercholesterolemic microvascular inflammation and protect against injury from ischemic events.

The broader context of research regarding nitrate, nitrite, and nitric oxide suggests these simple nitrogen oxides serve as a critical dietary component for protection against various chronic diseases. Currently, heart disease and cancer lead the nation in cause of deaths. Concurrently, the dietary patterns of the West have transitioned towards heavily processed foods and lack significant quantities of fruits and vegetables. The explanations have been varied but overlook simple molecules known to play critical roles in multiple organ systems through the chemical messenger NO. The dietary contributions to normal NO homeostasis would not only help explain significantly lower rates of cardiovascular disease in those who regularly consume fruits and vegetables, but also arm scientists and physicians with a relatively simple and inexpensive therapeutic intervention.

This text effectively overviews the important role nitrite and nitrate play in biological systems and NO homeostasis. A risk benefit analysis has shown nitrite and nitrate present no danger when consumed in modest quantities and preferably with antioxidants. In fact, research appears to suggest nitrite acts as a redundant NO reservoir when NOS activity is insufficient or stress requires a secondary source. The future use of nitrite/nitrate in dietary considerations will likely have a significant impact on current public health policy. This book brings the NO-story full circle and presents novel thought on the future treatment for many of the country’s most pressing health issues. This is a relatively new area of nitric oxide research but a very exciting one. The L-arginine pathway for NO synthesis may turn out to be only part of the story. The symbiosis between humans and the bacteria that reside in and on our body may be just as important in terms of utilizing nitrate and nitrite to make NO under conditions when the oxidation of L-arginine is dysfunctional. Drs. Nathan S. Bryan and Joseph Loscalzo have assembled the world’s experts to present a first of its kind, comprehensive work on nitrite and nitrate in human health and disease, carefully examining the context for a risk benefit assessment.

Louis J. Ignarro, Ph.D.
1998 Nobel Laureate in Medicine
Preface

Our major objective and driving force in developing *Nitrite and Nitrate in Human Health and Disease* is to consolidate all the key research and knowledge in one volume in order to establish a framework based on the totality of evidence for nitrite and nitrate and the effects of these two anions on human health and disease. Although the biomedical science community is excited and optimistic about the potential for developing new therapeutics and perhaps regimens of disease prevention based on their ability to generate nitric oxide under appropriate conditions, epidemiologists, nutritionists, and cancer biologists have cause for concern due to the inherent nitrosative chemistry of nitrite and NO that could form potentially carcinogenic N-nitrosamines. This is the first book in the Springer/Humana Nutrition Series dedicated to understanding the nutritional aspects of nitrite and nitrate for human health. It is our intent to deliver a comprehensive review of nitrite and nitrate, from basic biochemistry to the complex physiology and metabolism of these two naturally occurring molecules in the human body.

Overall, the book contains well-organized and well referenced chapters by respected scientists and physicians that covers the rich history of nitrite and nitrate, sources of exposure and physiological effects when consumed through foods containing nitrite and nitrate. The first portion of the book describes the biochemistry, metabolism, and physiology of nitrite and nitrate, how these molecules get incorporated into the foods we eat, and how they are systematically metabolized to bioactive nitric oxide. This involves the environmental processes of nitrogen fixation and the presence of a human nitrogen cycle involving symbiotic bacteria that reside in and on the human body. The book then shifts focus to the sources of exposure to nitrite and nitrate, both environmental and dietary, as a means to quantify exposure estimates and what this may mean for human health. We discuss the epidemiology and dietary effects on the nitric oxide pathway. This portion of the book also examines systems in nature in which this pathway is exploited, including the breast milk of nursing mothers. Finally, the last section of the book discusses nitric oxide-based therapeutics and how nitrite and nitrate biochemistry can be harnessed safely and efficaciously to improve human health through the production of nitric oxide. We end with a summary of the collective body of knowledge presented in the book and what we might expect going forward. Each chapter begins with Key Points that
outline the concepts presented to assist the reader in understanding the fundamental principles presented.

It is undisputed in the biomedical community that NO is one of the most important molecules the human body produces. If NO is such an important molecule in practically every organ system in our body, why, then, is there only a singular pathway for its production, i.e., the complex oxidation of l-arginine? Phosphorylation is another fundamental cellular process that is just as important in cell signaling, with over 500 recognized kinases and many phosphatases to regulate this biochemical process; by contrast, there is only one class of enzymes, the nitric oxide synthases, to produce NO. Most physiological systems are rich in redundancy, allowing backup systems to support the primary system. The provision of nitrate and nitrite as sources of NO may then be viewed as a system of redundancy. After all, a one-electron reduction is energetically and kinetically favorable to a five-electron oxidation.

According to the World Health Organization, cardiovascular disease is the number one killer of both men and women in the United States. These deaths represent a staggering 40% of all deaths. Close to 1 million people die each year and more than 6 million are hospitalized due to cardiovascular disease. Therefore, developing new strategies to correct NO insufficiency and replete NO availability is of paramount importance and could potentially save millions of lives worldwide and lessen the burden on the health care system. We now appreciate that reduced or insufficient NO production or activity is a hallmark of a number of disorders, including many complex, chronic cardiovascular diseases and even Alzheimer’s diseases. Therefore, developing new strategies to restore and replete bioactive NO is of paramount importance and could potentially lessen the burden of disease for society. Thus, understanding the biological activity of nitrite and nitrate may not only lead to novel treatments for disease but may lead to strategies to prevent disease development or progression and even the physiological basis for the benefits of certain diets such as the Mediterranean diet. To achieve this laudable goal, we must first establish the context for potential benefit while preventing unwanted risks or harm. We hope the information provided in this text will begin to help define that context, be a source of valuable information, and be useful for anyone who wants the most important and updated information about nitrate and nitrite.

We have invited the world’s leading experts to share their research and perspectives which we hope will help define the context for benefits vs. any potential risks associated with nitrite and nitrate, either through dietary ingestion or therapeutic dosing. This diverse collection of authors includes muscle biologists, physiologists, physicians, epidemiologist, cancer biologist, registered dietician, chemist, and public health experts from five countries around the world in both academia and government. This approach provides a fair and balanced view of nitric oxide biochemistry, nitrite and nitrate biochemistry in physiology and in the food sciences. As a result, we are indebted to these many individuals. We realize the time and dedication it takes to compose a book chapter on the latest body of knowledge, and, thus, appreciate these authors’ taking time to help up develop this volume. We also sincerely thank Springer-Humana Press for including this body
of work in the Nutrition and Health Series with Dr. Adrianne Bendich as Series Editor. This is an exciting time in NO and nitrite-based research. This has been – and we predict will continue to be – an area of intense research in the future. It is our hope that the information contained herein will educate and inform scientists, physicians, health care professionals, nutritionists, dieticians, and even the general public on the effects of nitrite and nitrate in human health and disease.

Houston, TX                        Nathan S. Bryan Ph.D.
Boston, MA                          Joseph Loscalzo M.D., Ph.D.
## Contents

**Series Editor Page**

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>v</td>
</tr>
</tbody>
</table>

**Foreword**

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>xi</td>
</tr>
</tbody>
</table>

**Preface**

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>xiii</td>
</tr>
</tbody>
</table>

### Part I  Basic Biochemistry, Metabolism, and Physiology

1. **Introduction**
   - Nathan S. Bryan and Joseph Loscalzo
   - Page 3

2. **From Atmospheric Nitrogen to Bioactive Nitrogen Oxides**
   - Mark Gilchrist and Nigel Benjamin
   - Page 9

3. **The Nitrate–Nitrite–Nitric Oxide Pathway in Mammals**
   - Jon O. Lundberg, Eddie Weitzberg, Sruti Shiva, and Mark T. Gladwin
   - Page 21

4. **Sources of Exposure to Nitrogen Oxides**
   - Andrew L. Milkowski
   - Page 49

### Part II  Food and Environmental Exposures to Nitrite and Nitrate

5. **History of Nitrite and Nitrate in Food**
   - Jimmy T. Keeton
   - Page 69

6. **Nutritional Epidemiology of Nitrogen Oxides: What do the Numbers Mean?**
   - Martin Lajous and Walter Willett
   - Page 85

7. **Nutritional Impact on the Nitric Oxide Pathway**
   - Wing Tak Wong and John P. Cooke
   - Page 97
8 Dietary Flavonoids as Modulators of NO Bioavailability in Acute and Chronic Cardiovascular Diseases ........................................ 123
Matthias Totzeck, Malte Kelm, and Tienush Rassaf

9 Nitrite and Nitrate in Human Breast Milk: Implications for Development ........................................................................ 139
Pamela D. Berens and Nathan S. Bryan

10 Regulation of Dietary Nitrate and Nitrite: Balancing Essential Physiological Roles with Potential Health Risks .................. 155
Norman G. Hord

Part III Nitrite and Nitrate in Therapeutics and Disease

11 Nitric Oxide Signaling in Health and Disease ........................................ 169
Nathan S. Bryan and Jack R. Lancaster Jr.

12 Inhaled Nitric Oxide ........................................................................ 187
Kenneth D. Bloch, Andrea U. Steinbicker, Lisa K. Lohmeyer, and Rajeev Malhotra

13 Pharmacology of Nitrovasodilators .................................................. 207
Nathaniel A. Page and Ho-Leung Fung

14 Nitrite and Nitrate in Ischemia-Reperfusion Injury ........................... 225
Madhav Lavu, Susheel Gundewar, and David J. Lefer

15 The Nitrate–Nitrite–Nitric Oxide Pathway in Traditional Herbal Medicine for Heart Disease ........................................... 247
Yong-Jian Geng

16 Nitrite and Nitrate in Cancer .............................................................. 263
David M. Klurfeld

17 Looking Forward .............................................................................. 279
Nathan S. Bryan and Joseph Loscalzo

Index .................................................................................................. 293
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