Chapter 22
Looking Forward

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Introduction

Eating a well-balanced, nutritious diet and performing moderate exercise comprise the ideal model of routinely good health and disease prevention. Probably not coincidently, these two activities are known to affect positively nitric oxide production, which, one can argue, is a key molecular mediator of the salubrious effect of both interventions. What is becoming more apparent is that NO derived from dietary sources of nitrite and nitrate comprises another key pathway in NO biology. Notwithstanding the essential nature of nitrite and nitrate in the environmental nitrogen cycle, historical use of nitrates and nitrites as medicinal agents, and the fact that these anions are produced naturally in the body from the oxidation of nitric oxide, public perception remains that these are harmful substances in our food and water supply [**1**].

There exists a number of nitrogen-containing molecules that are essential and fundamental for all life. Nitrogen is the largest single constituent of the earth's atmosphere; it is created by fusion processes in stars, and is estimated to be the seventh most abundant chemical element by mass in the universe. Nitric oxide, nitrite, and nitrate in the environment and in the body make up part of the overall biological nitrogen cycle along with proteins and nucleic acids, and are important intermediates or mediators of a number of biological actions. The realm of nitrogen-based chemistry is historical and complex. Just as Alfred Nobel found great irony in the fact that he was prescribed nitroglycerin for his angina later in life, which was the very substance that he had patented for safe delivery of dynamite, the current view of the biological activity of nitrite and nitrate shares similar historical irony. The discovery that a poisonous and toxic gas (NO) was produced by the inner lining of our

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Fig. 22.1 The labels from a cylinder of nitric oxide gas, and bottles of sodium nitrite and sodium nitrate

blood vessels was shocking and revolutionary. This is not to say that NO is not poisonous or dangerous because its chemical properties define it as a poison or toxin; however, in the right context and in an ideal environment, it is without doubt the most important molecule produced in blood vessels. The same argument can be made for nitrite and nitrate. Their inherent chemistry makes them toxic, but in the right context and the right environment, they can have extremely beneficial actions in the human body. The illustration in Fig. 22.1 shows the label of NO, sodium nitrite, and sodium nitrate as poisonous and toxic. Yet, we appreciate and understand the essential functions NO has in the body. Becoming more apparent is the same beneficial effects of nitrite and nitrate *in the proper context*. As an analogous example, water is absolutely essential to all life on earth and is completely safe and innocuous; however, if one were to drink a large excess of water within a few minutes, the cells in the body would swell and burst owing to the hypotonic effects. In the words of Paracelsus, "the dose makes the poison." With respect to nitric oxide and nitrite, one could add the duration, location, context of exposure, and method of delivery.

Despite NO being recognized by the scientific and medical community as one of the most important molecules produced within the body and being named "Molecule of the Year" by *Science* in 1992 and a Nobel Prize in Physiology or Medicine awarded for its discovery in 1998, there are currently only three products on the market directly related to NO: (1) organic nitrates, such as nitroglycerin for the treatment of acute angina (these have been used for many decades long before the discovery of NO); (2) inhaled NO therapy for neonates for treatment of pulmonary hypertension due to underdeveloped lungs; and (3) phosphodiesterase inhibitors, such as sildenafil (Viagra®), which do not directly affect NO production per se but act through affecting the downstream second messenger of NO, cyclic guanosine monophosphate (cGMP). There are a number of other NO-based therapies in development, including technologies designated to affect post-translational protein modifications through S-nitrosation. The method of delivery of NO, nitrite, and nitrate is of utmost importance. We know that delivery of NO through controlled and enzymatic metabolism of organic nitrates is safe and effective acute treatment for angina, but still not without some adverse effects as presented in Chap. 15. The safe delivery of NO gas through inhalation therapy is also now in practice. Inhaled NO is currently approved by the U.S. Food and Drug Administration for hypoxemia in term and near-term infants with pulmonary hypertension. Although more clinical trials are underway in other disease states, currently, this is the only approved use of inhaled NO. However, many physicians use this off-label in adults with pulmonary hypertension, transplantation, and cardiothoracic surgery.

We expect the same considerations for the safe and effective delivery of nitrite and/or nitrate. Understanding their underlying chemistry and metabolism is intrinsic to developing strategies for delivery. The risk-benefit spectrum from nitrite and nitrate may very well depend upon the specific metabolism and the presence of other components that may be concomitantly ingested or available at the time of administration or ingestion. The stepwise reduction of nitrate to nitrite and NO may

account for the now well described clinical benefits, while pathways leading to nitrosation of low-molecular-weight amines or amides may account for the health risks of nitrite and nitrate exposure. Understanding and affecting those pathways will certainly help in mitigating the risks. The early concerns about nitric oxide reactivity and the propensity to undergo unwanted nitrosation reactions also are invariably related to nitrite and nitrate biochemistry. We know from previous chapters that these reactions can occur, but there are also very effective inhibitors of nitrosation reactions including vitamins C and E, as well as polyphenols that are present in many foods that contain nitrite and nitrate, particularly vegetables.

The first pathway to be discovered for the endogenous production of NO was that involving L-arginine. For years scientists and physicians have investigated L-arginine supplementation as a means to enhance NO production. This strategy has been shown to work effectively in young healthy individuals with functional endothelium or in older patients with high levels of asymmetric dimethyl L-arginine [2] where the supplemental L-arginine can outcompete this natural inhibitor of NO production. Patients with endothelial dysfunction, however, by definition, are unable to convert L-arginine to NO due to a dysfunctional nitric oxide synthase (NOS) enzyme and, therefore, this strategy has not proven effective consistently in clinical trials. In fact, L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial published in the *JAMA* in 2006, concluded that L-arginine, when added to standard postinfarction therapies, did not improve vascular stiffness measurements or ejection fraction and was associated with higher postinfarction mortality [3]. L-arginine should not be recommended following acute myocardial infarction (MI). Similarly, long term L-arginine supplementation in patients with peripheral artery disease (PAD) did not provide any clinical benefit and, in fact, many patients did worse [4]. However, there are also a number of studies showing benefit to healthy patients taking L-arginine and just as many showing no benefit, no harm. Collectively, the literature suggests that strategies to enhance NO production through L-arginine supplementation are equivocal at best.

NOS and Nitrite: A Concert in NO Homeostasis

The nitrate–nitrite–nitric oxide pathway may be a redundant system for overcoming the body's inability to make NO from L-arginine. The emerging literature suggests such and the information included in this book presents a strong case for such. It appears we have at least two systems for affecting NO production/homeostasis. The first is through the classical L-arginine–NO pathway. As we know from Chap. 13, this is a complex and complicated pathway, and if any of the cofactors become limiting, then NO production from NOS shuts down, and in many cases, NOS then produces superoxide instead. The enzymatic production of NO is, indeed, a very complex and coordinated effort that normally proceeds very efficiently. However, in diseases characterized by oxidative stress where essential NOS cofactors become oxidized, NOS uncoupling, or conditions of hypoxia where oxygen is limiting, this process can no longer maintain NO production. Therefore, one can argue saliently that there has to be an alternate route for NO production. It is highly unlikely that Nature devised such a sophisticated mechanism of NO production as a sole source of a critical molecule. After all, there is enormous redundancy in physiology.

This alternate route involves the provision of nitrate and nitrite reductively recycled to NO. The two-electron reduction of nitrate to nitrite requires oral commensal nitrate reducing bacteria since humans lack a functional nitrate reductase gene. Nitrite reduction to NO can occur in a much simpler mechanism than nitrate. The one-electron reduction of nitrite can occur by ferrous heme proteins (or any redox active metal) through the following reaction:

$$NO_2^- + Fe^{(II)} + H^+ \leftrightarrow NO + Fe^{(III)} + OH^-$$

This is the same biologically active NO as that produced by NOS, with nitrite rather than L-arginine as the precursor but it is a relatively inefficient process [5]. Therefore, for this reaction to occur, the tissues or biological compartment must have a sufficient pool of nitrite stored. Since plasma nitrite is a direct measure of NOS activity [6], a compromised NOS system can also affect downstream nitrite production and metabolism, which can perhaps exacerbate any condition associated with decreased NO bioavailability. Replenishing nitrate and nitrite through dietary means may then act as a protective measure to compensate for insufficient NOS activity under conditions of hypoxia or in a number of conditions characterized by NO insufficiency. It is very likely that exogenous nitrite contributes to whole body NO production and homeostasis. Considerable published data now support this redundant pathway: NO produced from nitrite in the upper intestine is up to 10,000 times the concentrations that occur in tissues from enzymatic synthesis [7], nitrite can act as a circulating NO donor [8], and nitrite can itself perform many actions previously attributable to NO [9] without the intermediacy of NO [10].

There are known strategies that will affect both pathways positively. Exercise has been shown to enhance endothelial production of L-arginine and improve endothelial function. Since the burden of exposure of nitrite and nitrate comes from the diet, eating a diet rich in green leafy vegetables or other NO_x-rich foods can fuel the second pathway. We believe that both systems complement one another. When we are young and healthy, the endothelial production of NO through L-arginine is efficient and sufficient to produce NO; however, as we age we lose our ability to synthesize endothelial derived NO. Taddei et al. [11] have shown that there is a gradual decline in endothelial function due to aging with greater than 50 % loss in endothelial function in the oldest age group tested as measured by forearm blood flow assays. Egashira et al. [12] reported more dramatic findings in the coronary circulation of aging adults whereby there was a loss of 75 % of endothelium-derived nitric oxide in 70–80-year-old patients compared to young, healthy 20-year olds. Vita and colleagues [13] demonstrated that increasing age was one predictor of abnormal endothelium-dependent vasodilation in atherosclerotic human epicardial coronary arteries. Gerhard et al. [14] concluded from their 1996 study that age was the most significant predictor of endothelium-dependent vasodilator responses by multiple stepwise regression analysis. Collectively, these important findings illustrate that endothelium NO-dependent vasodilation in resistance vessels declines progressively with increasing age. This abnormality is present in healthy adults who have no other cardiovascular risk factors, such as diabetes, hypertension, or hypercholesterolemia. Most of these studies found that impairment of endothelium-dependent vasodilation was clearly evident by the fourth decade. In contrast, endothelium-independent vasodilation does not change significantly with aging, demonstrating that the responsiveness to NO did not change, only the ability to generate it did. These observations enable us to conclude that reduced availability of endothelium-derived nitric oxide occurs as we age and to speculate that this abnormality may create an environment that is conducive to atherogenesis and other vascular disorders. It is that early event, the inability to produce sufficient NO under the right preclinical conditions that enhances the risk for a number of diseases that plague the older population. If true, then there exist an opportunity to intervene early during this process, implement strategies to restore NO homeostasis, and, perhaps, delay or prevent the onset and progression of certain diseases. This gradual loss of NO activity with age can be sped up or slowed down based on individual lifestyle and diet. This idea is illustrated in the hypothetical graphical representation in Fig. 22.2. Adopting healthy habits such as a good diet and exercise can prolong the precipitous drop in NO production with age. To the contrary, a poor diet along with physical inactivity can accelerate the process and lead to a faster decline in NO production at a younger age. Therapeutic strategies directed at improving endothelial function and/or providing an alternative source of NO should be the primary focus because they may reduce the incidence of atherosclerosis or other diseases that occur with aging, even perhaps Alzheimer's disease or at the very least vascular dementia.

Exercise training has been shown, in many animal and human studies, to augment endothelial, NO-dependent vasodilatation in both large and small vessels (reviewed in [15, 16]); however, the response to exercise is diminished in patients with age-dependent endothelial dysfunction [17, 18].

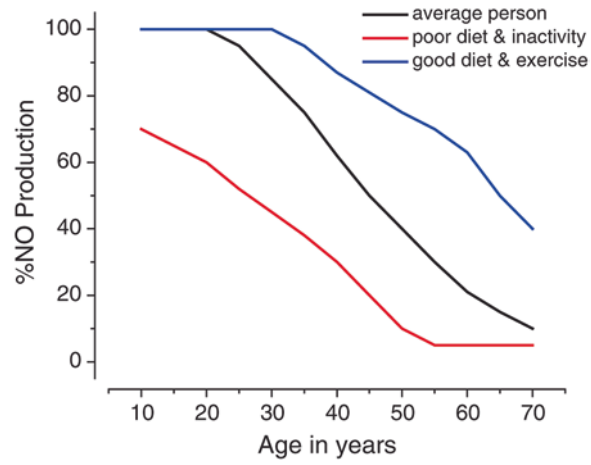

Fig. 22.2 Hypothetical representation of NO production based on diet and lifestyle

In fact, plasma nitrite has been shown to predict exercise capacity [19] and further demonstrates that endothelial production of NO declines with age and increasing risk factor burden [20]. More recent data reveal that dietary supplementation with nitrate reduces oxygen costs of low intensity exercise and enhances tolerance to high intensity exercise [21–23]. This effect is due to an increase in plasma nitrite. These data support the notion that one can compensate through dietary nitrite and nitrate for the endothelial production of NO during exercise. This dietary pathway may also extend beyond exercise. Dietary supplementation of nitrite and nitrate in animals has been shown to reverse endothelial dysfunction, suppress microvascular inflammation, and reduce levels of C-reactive protein in mice subjected to a high cholesterol diet [24] and to protect from ischemia–reperfusion injury [25–27]. This proof-of-concept in animals has now been translated and corroborated in humans. Low-dose nitrite supplementation (80–160 mg/day) has shown to improve endothelial function by 45–60 % without changes in body mass or blood lipids. Measures of carotid artery elasticity improved without changes in brachial or carotid artery blood pressure. Nitrite-induced changes in vascular measures were significantly related to 11 plasma metabolites identified by untargeted analysis [28]. In another study, nitrite supplementation improves aspects of motor and cognitive function in healthy middle aged and older adults, and that these improvements are associated with, and predicted by, the plasma metabolome [29]. Studies using a patented formulation (US patents 8,303,995, 8,298,589, 8,435,570, 8,962,038, 9,119,823 and 9,241,999) using 15–20 mg of sodium nitrite in the form of an orally disintegrating tablet found that it could modify cardiovascular risk factors in patients over the age of 40, significantly reduce triglycerides, and reduce blood pressure [30]. This same lozenge was used in a pediatric patient with argininosuccinic aciduria and significantly reduced his blood pressure when prescription medications were ineffective [31]. A more recent clinical trial using the nitrite lozenge reveals that a single lozenge can significantly reduce blood pressure, dilate blood vessels, improve endothelial function and arterial compliance in hypertensive patients [32]. Furthermore in a study of pre-hypertensive patients (BP >120/80 < 139/89), administration of one lozenge twice daily leads to a significant reduction in blood pressure (12 mmHg systolic and 6 mmHg diastolic) after 30 days [33]. The same lozenge was used in an exercise study and was found to lead to a significant improvement in exercise performance [34]. These studies provide evidence that sodium nitrite supplementation is well-tolerated, increases plasma nitrite concentrations, improves endothelial function, and lessens carotid artery stiffening in middle-aged and older adults, perhaps by altering multiple metabolic pathways, thereby warranting larger long-term clinical trials.

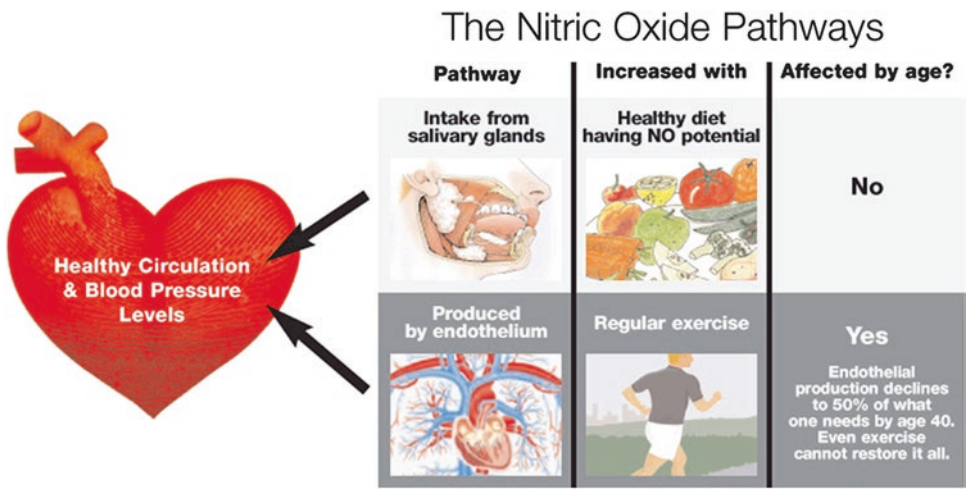

Fig. 22.3 The two pathways for NO production; one from the reduction of the nitrate and nitrite from the foods we eat and the other from the oxidation of L-arginine

Dietary nitrate has also been shown to reduce blood pressure [35–37], inhibit platelet aggregation [37], and restore endothelial function [37] in humans. What is clearly emerging is that there are two pathways for NO production, one through endothelial production via the L-arginine pathway and one through dietary sources of nitrite, nitrate, and antioxidants. This overview is illustrated in Fig. 22.3. The L-arginine pathway becomes dysfunctional with age, and we, therefore, need a backup system to compensate. Eating a diet rich in NO potential, i.e., sufficient nitrite and nitrate along with antioxidants to facilitate reduction to NO, can appear to overcome an insufficiency in endothelium-derived NO. This dietary pathway does not appear to be affected by age. However, overuse of antibiotics or antiseptic mouthwashes can affect this pathway by eliminating the commensal bacteria that are essential for the first step of nitrate reduction to nitrite. Furthermore, use of proton pump inhibitors can decrease the acid secretion in the stomach, thereby affecting the acidic disproportionation of nitrite to NO (pKa nitrite = 3.4). This dietary pathway is reliant upon recognizing foods that are rich in NO potential. The inherent NO bioactivity of certain foods or diets is a delicate balance between nitrite and nitrate content as well as antioxidant capacity to facilitate reduction to NO and to inhibit any unwanted nitrosation reactions. Antioxidant status can be generically estimated by the Oxygen Radical Absorbance Capacity or ORAC. An antioxidant's strength reflects its ability to eliminate oxygen-free radicals to prevent scavenging of nitric oxide as well as provide the reductive capacity to activate dietary nitrate and nitrite to NO. Foods with a high ORAC score are thought to protect cells and their components from oxidative damage. The ORAC score combined with the inherent nitrite and nitrate content of certain foods may provide a novel scoring system for NO potential or NO index. The Bryan lab has created a nitric oxide index below by applying an algorithm considering the average nitrite/nitrate content of foods as well as their reported ORAC values. We define the NO index below:

Table 22.1 Nitric oxide index of select foods

	Nitrite + nitrate (mg/100 g)	ORAC (μmol/100 g)	NO index
High			
Kale	1950	3500	**6825**
Swiss chard	822	2500	**2055**
Arugula	612	2373	**1452**
Spinach	741	1515	**1123**
Chicory	625	1500	**938**
Wild radish	465	1750	**814**
Bok choy	310	2500	**775**
Collard greens	317	2200	**697**
Beets	174	3632	**632**
Chinese cabbage	161	3100	**499**
Lettuce	268	1447	**388**
Cabbage	125	2496	**312**
Mustard greens	116	1946	**226**
Cauliflower, raw	202	829	**167**
Parsley	115	1301	**150**
Kohlrabi	177	769	**136**
Carrot	190	666	**127**
Broccoli	39.5	3083	**122**
Medium			
Cole slaw	55.9	1500	**84**
Asparagus	50	1644	**82**
Celery	160	497	**80**
Watercress	33	2200	**73**
Artichoke	9.6	6552	**63**
Eggplant	42	933	**39**
Strawberry	9.4	3577	**34**
Potato	20	1300	**26**
Garlic	3.4	5708	**19**
Tomato	39.2	367	**14**
Vegetable soup	20.9	500	**10**
Cereal	4.9	2000	**10**
Melons	68	142	**10**
Low			
String beans	30	300	**9**
Cured, dried sausage	78.8	100	**8**
Figs	2	3383	**7**
Prunes	1	5770	**6**
Sweet potato, raw, uncooked	5.4	902	**5**
Blackberries	1	5347	**5**
Raspberries	1	4882	**5**
Raisins	1.2	3037	**4**
Banana	4.5	879	**4**
Cherries	1	3365	**3**
Cucumber	14	214	**3**
Onions	3.2	1034	**3**
Bean sprouts	1	1510	**2**
Hot dog	9	100	**1**
Kiwi	1	882	**1**
Cucumber	9.3	100	**1**

(continued)

Table 22.1 (continued)

	Nitrite + nitrate (mg/100 g)	ORAC (μmol/100 g)	NO index
Bacon	5.5	100	**1**
Apricot	1	1115	**1**
Papaya	1	500	**1**
Chickpeas	1	847	**1**
Bacon, nitrite-free	3	100	**0**
French fries	2	150	**0**
Juices	(mg/100 mL)		
Beet root	279	1727	**482**
Vegetables juice	20	548	**11**
Carrot	6.8	195	**1**
Pomegranate	1.3	2681	**3**
Cranberry	1		**0**
Red wine	1	3000	**3**
Green tea	0.02	1253	**0**
Acai	0.06	1767	**0**

$$\left[\left(\text{Nitrite} + \text{nitrate}\left(\text{mg}/100\,\text{g}\right) \times \text{ORAC}\left(\mu\text{mol}/100\,\text{g}\right)\right)\right]/1000 = \text{Nitric}\mathbf{O}\text{xide}\,\text{Index}$$

Similar to the glycemic index for diabetics, the nitric oxide index may be a useful tool for people with vascular disease or any conditions associated with NO insufficiency. A list of the NO index of select foods is included in Table 22.1. We suspect the context of a Nitric oxide Index whereby nitrite and nitrate along with antioxidants will help define the health benefits of certain foods or diets. However, the difficulty is the fact that there are highly variable differences in nitrite and nitrate of the same vegetable based on different farming practices in different geographical locations [38]. In fact, there can be more than a 100-fold difference in the nitrate content of a single vegetable depending on where it is consumed and how it was grown. Therefore, this NO index can only be used when quantities of nitrite and nitrate are quantified and known for any given vegetable. We can use averages from historical database for proof of principle but we cannot be certain that any given vegetable in the table will contain the amount of nitrite and nitrate reported.

Although dietary nitrite and nitrate have been shown to replenish blood and tissue stores of NO, it is still not clear how this pathway is regulated or controlled. The production of NO through the NOS enzymes is a precise, spatially and temporally regulated, controlled event that generates NO in a local environment upon need or specific stimulus. Gladwin and colleagues have proposed that nitrite reduction to NO is allosterically linked to oxygen saturation of hemoglobin [39, 40], thereby providing a sensing mechanism for production of NO from nitrite during hypoxic vasodilation. Myoglobin has also been implicated in serving such a function in the heart [41]. More work is needed to determine if nitrite alone is necessary and sufficient to elicit specific cellular events as has been well described for NOS-derived NO. Although it may be argued that nitrite is simply a storage pool that can be reduced to NO under appropriate conditions, we consider this an unlikely role for nitrite in normal physiology, i.e., the normoxic and neutral pH conditions under which nitrite is supposedly stable. Alternatively, nitrite acts as an important molecule in its own right but which has regulatory effects on the NO pathway. It may be that both hypoxic reduction of nitrite to NO and normoxic metabolism of nitrite represent an advantageous oxygen sensing system, which is a vestige of denitrifying microorganisms that existed long before the advent of aerobic respiration and the emergence of an NO synthase system [42]. The fact that both systems still exist today highlight the importance of nitrite in all cellular processes throughout the entire physiological oxygen gradient [9]. More research is needed in order

to completely delineate the precise and regulated cell signaling aspects of nitrite, both from endogenous sources as well as from dietary sources.

The role of diet in the prevention and control of morbidity and premature mortality due to non-communicable diseases has been well established by vast population-based epidemiological studies carried out during the last decade [43]. Nothing affects our health more than what we choose to eat. Nitric oxide is essential for maintaining normal blood pressure, preventing adhesion of blood cells to the endothelium, and preventing platelet aggregation; it may, therefore, be argued that this single abnormality, the inability to generate NO, puts us at risk for diseases that plague us later in life, such as atherosclerosis, myocardial infarction, stroke, Alzheimer's, and peripheral vascular disease. Therefore, developing strategies and new technologies designed to restore NO availability is essential for inhibiting the progression of certain common chronic diseases. The provision of dietary nitrate and nitrite may allow for such a strategy. The information presented throughout this text illustrates that the beneficial effects of nitrite and nitrate are seen at doses and levels that are easily achievable by eating certain foods enriched in nitrite and nitrate, particularly green leafy vegetables. The fact that exposure to nitrite and nitrate from certain foods or diets exceeds the World Health Organizations limit for Acceptable Daily Intake (ADI) calls into question the current regulatory limits.

Hord and Bryan have shown that people following the Dietary Approaches to Stop Hypertension [44] diet exceed the ADI for nitrate by greater than 500 % [45] and infants consuming human breast milk and some formulas can also exceed the regulatory limits [46]. The DASH diet was developed by the US National Institutes of Health to lower blood pressure without medication. The DASH diet is based on the research studies and has been proven to lower blood pressure, reduce cholesterol, and improve insulin sensitivity [47]. The DASH diet provides more than just the traditional low salt or low sodium diet plans to help lower blood pressure. It is based on an eating plan proven to lower blood pressure, a plan rich in fruits, vegetables, and low-fat or nonfat dairy. DASH diet is recommended by The National Heart, Lung, and Blood Institute (one of the National Institutes of Health, of the US Department of Health and Human Services), The American Heart Association, The Dietary Guidelines for Americans, US guidelines for treatment of high blood pressure, and, the DASH diet formed the basis for the USDA MyPyramid. So how can such a diet exceed regulatory limits for the molecule that may be responsible for its blood pressure lowering effects? The same argument can be made for breast milk [46]. Human breast milk is recommended to serve as the exclusive food for the first 6 months of life and continue, along with safe, nutritious complementary foods, up to 2 years [48, 49]. Breast milk is nature's most perfect food. In fact, the U.S. Centers for Disease Controls in 2010 acknowledged, "Breast milk is widely acknowledged as the most complete form of nutrition for infants, with a range of benefits for infants' health, growth, immunity and development." Breast milk is a unique nutritional source for infants that cannot adequately be replaced by any other food, including infant formula. It remains superior to infant formula from the perspective of the overall health of both mother and child. Human milk is known to confer significant nutritional and immunological benefits for the infant [50–52]. And yet, human breast milk and colostrum is enriched in nitrite and nitrate [46, 53–55]. It may be time to reconsider new regulatory guidelines for dietary sources of nitrite and nitrate given the last two decades of research showing remarkable health benefits at levels that do not pose any significant risk.

We hope this work on nitrite and nitrate in human health and disease will provide the reader with a comprehensive body of knowledge on these molecules. The last 25 years of research has drastically altered the landscape of how we think about nitrite and nitrate. The discovery of the nitric oxide pathway revealed that these two anions are naturally produced within our bodies and are not simply synthetic food additives. Prior to this discovery, much of the scientific research focused on the toxic properties due to exposure in both industrial settings and from cured and processed foods. Surprisingly, the context for nitrite and nitrate in human health and disease has not been adequately addressed since. We feel privileged to be able to communicate this information for the Nutrition Series. Nutrition can play a key and cost-effective role in decreasing the risks of different chronic diseases. Hippocrates himself said, "let

food be thy medicine and medicine be thy food." Identifying the key components of food and nutrition that may be responsible for the medicinal effects will help in refining dietary guidelines and designing optimal preventive nutrition regimens for specific disease. Future clinical studies will determine if nitrite and nitrate can provide a nutritional approach to prevention and/or treatment of specific diseases and if such positive effects will outweigh any negative health effects traditionally attributed to these anions. Nutritionists, physiologists, physicians, toxicologists, and dieticians need to converge and establish nutrient guidelines for nitrite and nitrate similar to other well recognized nutrients. The data and facts are now available for such an initiative and the ground is now fertile for such studies.

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