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FROM THE LAB TO PUBLIC HEALTH: DOUGLAS VAN ANDEN FROST'S ROLE IN NUTRITION SCIENCE

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ABSTRACT

Douglas Van Anden Frost (1910-1989) was a visionary in nutrition science, leaving an enduring legacy that reshaped the understanding of essential nutrients. From his early work on factor W and the discovery of niacin, which eradicated pellagra, to pioneering investigations into selenium's multifaceted role, Frost's unconventional thinking and meticulous research have significantly impacted human health. Collaborating with biochemist Raymond Shamberger (1934-2022), Frost challenged prevailing notions about selenium's carcinogenic potential, demonstrating its anticarcinogenic properties through groundbreaking research. Beyond the laboratory, Frost's work influences public health policies, emphasizing the interconnectedness of nutrients. This paper explores Frost's trajectory, emphasizing the importance of questioning paradigms, interdisciplinary insights, and dedicated experimentation in advancing nutrition science. Frost's enduring inspiration reminds us of the transformative power of curiosity in unraveling the mysteries of human health.

Keywords: nutrition science; niacin; selenium; anticarcinogenic; nutrients; pellagra.

Introduction

Douglas Van Anden Frost (1910-1989) was a key figure in nutrition science, leaving an indelible mark on understanding essential nutrients and their profound impact on health. He started on a journey that commenced as a graduate student under the mentorship of Conrad Elvehjem (1901-1962) at the University of Wisconsin. Frost's pivotal role in nutritional research began with investigating factor W (1, 2). This water-soluble mixture, crucial for the rapid growth of rats, ultimately led him to the groundbreaking discovery of niacin, which helped to abolish pellagra among the people of the South (2).

Frost's experiments with nicotinic acid, a form of niacin, showcased its transformative effects. A significant moment in his research was the remarkable recovery of a moribund dog administered with nicotinic acid, contributing significantly to the eradication of pellagra (2). Despite his pivotal role, Frost's name did not adorn the seminal paper, underscoring the nuanced dynamics of scientific collaboration and recognition (2, 3).

An unconventional thinker among his peers, Frost was renowned for his well-considered and meticulous approach to research. In his own words, in the 1974-1965 edition of Who's

Who in America, he emphasized the necessity of scrutinizing prejudice through repeatable experiments, aligning with his dedication to serving nature and allowing nature to reciprocate (2).

This paper delves into the contributions of Douglas Van Anden Frost, tracing his trajectory from the discovery of niacin to his pivotal work with selenium and cancer. Focusing on his early investigations and the eradication of pellagra, it explores how Frost's curiosity and dedication laid the groundwork for advancements in nutrition science, shaping the understanding of essential nutrients and their impact on human health.

Selenium Discovery and Animal Nutrition

The mid-20th century witnessed a crucial exploration of essential nutrients for animals, marking a significant chapter in nutritional science. A pivotal moment occurred in 1957 when selenium was identified as a crucial nutrient for animals. This breakthrough, often attributed to independent discoveries by Klaus Schwarz (1914–1978), Calvin M. Foltz (1924-2003), and E. L. Robert Stokstad (1913–1995) (4, 5), reshaped the understanding of nutritional requirements for optimal animal health.

Schwarz, Foltz, and Stokstad made pioneering contributions to recognizing selenium's importance as an essential nutrient (4, 5). Their parallel investigations unveiled the significance of selenium in various physiological processes critical for the well-being of animals. However, it is essential to note that despite the groundbreaking discoveries in 1957, they were not the first to identify selenium's role in nutrition.

In 1941, Alvin L. Moxon (1909–2007) and colleagues had already demonstrated that selenium stimulated the growth of chicks (6, 7), offering an early glimpse into the potential benefits of selenium supplementation in animal diets. However, the true impact of selenium deficiency on animal health and its widespread prevalence in different regions remained largely unnoticed until the late 1950s.

Surprisingly, even with the conclusive evidence Schwarz, Foltz, and Stokstad provided in 1957 (4, 5), the animal industry did not immediately embrace selenium as a vital feed supplement (7). The initial reluctance to adopt selenium supplementation can be attributed to various factors, including a lack of awareness about the severity of selenium deficiency in certain regions.

It took some time before the realization that severe selenium deficiency in animals was widespread in some parts of the world, such as New Zealand, the United States, Norway, Sweden, and Finland (2, 8, 9). This deficiency affected various species, including chicks, sheep, and pigs, leading to significant health issues. One notable problem was the impairment of the immune system, resulting in lethal coccidiosis in chicks (10) and other conditions, such as lethal heart disease in various species (8, 9).

Severe Selenium Deficiency in Animals

Recognition of severe selenium deficiency in animals unfolded gradually, with a delayed realization of its prevalence worldwide. Despite groundbreaking discoveries in 1957 regarding selenium's essential role (4, 5), the full extent of deficiency and its impact on animal health took time to emerge. In regions with widespread selenium deficiency, it became apparent only after meticulous investigations (2, 8, 9). This deficiency led to severe health implications in animals that were initially overlooked.

A significant consequence of insufficient selenium was its association with lethal coccidiosis in chicks (10). The compromised immune system in selenium-deficient chicks heightened their vulnerability to this deadly disease, emphasizing the critical role that selenium plays in maintaining animal well-being. Moreover, inadequate selenium levels were identified as contributing to lethal heart disease in various species (8, 9), extending beyond specific species and emphasizing the universality of health consequences associated with insufficient selenium.

Insights gleaned from veterinary nutrition science played a pivotal role in unraveling the intricate interactions between selenium, vitamin E, and polyunsaturated fatty acids (PUFAs). Recognizing the close relationship among these nutrients, veterinarians documented that their deficiency could significantly impact animal health outcomes (11, 12), turning this three-way interplay into a focal point of study within veterinary nutrition science.

The realization that a high intake of polyunsaturated fatty acids amplifies the nutritional requirement for vitamin E led veterinarians to understand that this complex interaction was driven by the susceptibility of PUFAs to peroxidation. Peroxidation is a process in which free radicals damage cellular structures, and the antioxidant properties of vitamin E and selenium could mitigate this oxidative stress. These revelations laid the foundation for a deeper comprehension of nutritional requirements in animals, subsequently influencing the understanding of human nutrition.

In 1973, a crucial breakthrough in understanding the antioxidant role of selenium occurred with the discovery by John T. Rotruck and collaborators that glutathione peroxidase is a selenium-dependent enzyme (13). Subsequent research unveiled various selenium-dependent antioxidative enzymes, prominently featuring a subclass known as selenoproteins (14, 15). Within the context of selenium dependency, these antioxidative enzymes play a crucial role in safeguarding against reactive oxygen species. Notably, the identification of several non-enzymatic selenoproteins (16) expanded the spectrum of selenium's involvement in cellular defense mechanisms.

The insights gained from veterinary nutrition science revolutionized the understanding of animal nutrition and laid a solid foundation for comprehending the role of selenium in human nutrition. The interaction among selenium, vitamin E, and PUFAs, coupled with the discovery of selenium-dependent antioxidative enzymes, served as a critical paradigm for exploring the broader implications of selenium in preventing oxidative stress and maintaining overall health.

Neglect in Human Nutrition Science

The transition from veterinary nutrition science to its integration into human nutrition faced considerable delays and oversights, with lasting consequences for public health. This negligence, particularly in recognizing the importance of selenium and understanding the nuanced effects of specific nutrients on cardiovascular health, highlights the need for interdisciplinary insights in broader public health discourse.

An illustrative example of this neglect is evident in the report by the Nicolaysen Committee in 1963 (17). Despite the committee's findings and recommendations, the crucial role of selenium, especially concerning cardiovascular health, was largely overlooked. The committee emphasized increased intake of saturated fat and PUFAs without acknowledging the synergistic interactions elucidated by veterinary nutrition science, highlighting selenium's critical role.

In the 1960s, another stark illustration is the lack of awareness regarding the contrasting effects of oleic acid and industrially produced trans-fatty acids in Norway and other countries. These fatty acid types were erroneously considered neutral concerning coronary heart disease, primarily due to their perceived impact on total cholesterol concentration in blood plasma. It was not until much later that the harm of industrially produced trans-fatty acids became evident, while oleic acid proved beneficial (18, 19).

The delayed recognition of the disparate effects of oleic acid and trans-fatty acids on cholesterol levels exemplifies the negligence in considering the nuanced roles of specific nutrients. Trans-fatty acids were found to enhance LDL-cholesterol and decrease HDL-cholesterol, contributing to adverse cardiovascular outcomes. In contrast, oleic acid displayed a protective effect by decreasing LDL-cholesterol and enhancing HDL-cholesterol, underscoring the importance of distinguishing between different types of fatty acids for cardiovascular health.

Additionally, it was only in the late 1970s that the disparities between omega-3 and omega-6 PUFAs were unveiled, thanks to the studies of Jørn Dyerberg and collaborators on platelet function among Inuits in Greenland (19). This revelation marked a turning point in understanding the specific impacts of different PUFAs on cardiovascular diseases.

The neglect of these critical nuances in human nutrition science during the mid-20th century emphasizes the necessity of incorporating interdisciplinary insights, such as those from veterinary nutrition science, into broader public health discourse. This negligence impacted the understanding of selenium and hindered progress in recognizing the intricate roles of specific nutrients, contributing to long-term implications for public health.

Early Interest of Douglas Van Anden Frost in Selenium

Douglas Van Anden Frost's foray into selenium research marked a groundbreaking effort that impacted the trajectory of nutritional science. As an unconventional thinker and meticulous researcher, Frost demonstrated a profound interest in uncovering the potential health benefits of selenium (2, 20, 21).

Frost's inquisitiveness sparked a collaboration with biochemist Raymond Shamberger (1934-2022), initiating animal experiments to unravel selenium's potential anticarcinogenic effects (22). In an era when early experiments erroneously labeled selenium as carcinogenic, Frost, unwavering in his belief in its contrary potential as an anticarcinogen, laid the foundation for understanding selenium's multifaceted roles in health and disease. Frost's early recognition of selenium's protective potential against cancer and Shamberger's biochemical insights and epidemiological evidence were pivotal in redirecting attention to selenium in human nutrition and disease prevention (22-25).

Geographic epidemiological studies led by Shamberger unveiled an inverse correlation between total cancer deaths and average selenium intake across different states in the US. Further research by Shamberger highlighted the enhancement of peroxidation in carcinogenesis (26) and the mutagenic nature of malondialdehyde, a secondary lipid peroxidation product (27). Moreover, a similar geographic association was found between cardiovascular death rates and selenium intake in states in the US (28, 29).

Building on this legacy, collaborating with fellow researchers, we reviewed selenium's role in cancer in 2018 (30). Our findings revealed an inverse relationship between selenium intake and cancer mortality in epidemiological studies across 27 countries in Europe, the United States, and Japan. Furthermore, a recent review with other co-authors (31) delved into selenium's anti-aging effects, underscoring that inadequate selenium status may accelerate aging and increase vulnerability to disorders such as immune dysfunction and cancer. Ongoing research extends Frost's pioneering vision and reaffirms the enduring significance of selenium in human health.

Concluding remarks

Douglas Van Anden Frost is a pivotal figure whose contributions have indelibly shaped the landscape of nutrition science. From discovering niacin to exploring selenium's multifaceted role in animal and human nutrition, Frost's scientific journey reflects a remarkable trajectory of inquiry and discovery.

Frost's early work on factor W and the subsequent discovery of niacin eradicated pellagra and laid the foundation for unraveling the complexities of essential nutrients. His unconventional thinking and meticulous approach position him as a visionary in nutrition science.

The profound impact of Frost's research extended to selenium, where his collaboration with biochemist Raymond Shamberger challenged prevailing notions about selenium's potential carcinogenic effects. Their work paved the way for groundbreaking experiments demonstrating selenium's anticarcinogenic properties, underscoring the significance of selenium intake in influencing cancer death rates.

Frost's contributions resonate beyond the laboratory, emphasizing the interconnectedness of nutrients and their profound impact on health. His work has reshaped the understanding of nutrition and influenced public health policies and dietary recommendations.

In the broader context of human nutrition, Frost's legacy is a testament to the importance of questioning prevailing paradigms, embracing interdisciplinary insights, and meticulously conducting experiments that illuminate the intricate relationships between nutrients and health outcomes. When navigating the complexities of nutrition science, the pioneering spirit of Douglas Van Anden Frost remains an enduring inspiration, reminding us of the transformative power of curiosity, collaboration, and dedication to unraveling the mysteries of human health.

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