Praise for Brilliance & Confusion

Brilliance & Confusion: Saving Children's Vision and Lives with Vitamin A is the best kind of science storytelling: rigorously true, consistently interesting, and filled with the excitement of discovery and unexpected insights into how the human body — and science itself — really works. Prof. Vern Paetkau, himself a renowned biochemist, traces the story of vitamin A from its earliest discovery to current efforts to make vitamin A deficiency a thing of the past. His engaging book leaves readers with a greater appreciation for "the micronutrient that bears the first letter of the vitamin alphabet," and for the many scientists who helped unlock the secrets of its nature and importance along the way.

— Thomas Hayden, Professor of the Practice, Stanford University School of Earth, Energy & Environmental Sciences

Brilliance & Confusion: Saving Children's Vision and Lives with Vitamin A is a wonderful read — indeed, a must-read for anyone interested in vitamins and other essential nutrients, the politics of science, and the misinterpretations, intentional or not, of clinical trials. It is exceptionally comprehensive. Starting with the influential and important studies of Alfred Sommer and his team on vitamin A deficiency in Indonesian children in the late 1970s, it then goes back to the early evidence that there are essential nutrients that must be in one's diet to survive, and the discovery of vitamin A at the beginning of the 20th century as one of those nutrients. It explains the role of vitamin A not only in vision, but for the maintenance of epithelial tissues and in preventing disease and death. The two critical derivatives of vitamin A are described — retinal (vitamin A aldehyde) for vision, and retinoic acid (vitamin A acid) for somatic functions. The book moves on to discuss treating vitamin A deficiency in humans, especially children, and its success in the West and many developing

countries throughout the world, the exception being the rice-dependent Asian countries. A last chapter is devoted to the story of golden rice, which potentially could solve this problem. The resistance over the years to programs designed to eradicate the deficiency in various countries is presented, including the more recent attempts to prevent the development of golden rice. The discussion is not limited just to vitamin A but extends to other vitamins and micronutrients as well. Sprinkled with anecdotes and brief biographies of many of the major players over the years, the book is a pleasure to read, and I learned much from it. I recommend it highly.

— John E. Dowling, Gordon and Llura Gund Research Professor of Neurosciences, Harvard University, pioneer researcher of vitamin A's role in vision and essential cellular functions, and in the neurobiology of vision.

I have been a constant reader of the history of science since encountering *The Structure of Scientific Revolutions* in graduate school. There are many "popular" histories that fail to do justice to the complexities of the science. Other works by scientists are sometimes beyond the comprehension of non-specialists. This fascinating history of the double discovery of vitamin A and its multiple roles in human development does full justice to the science and is an engaging read. *Brilliance & Confusion: Saving Children's Vision and Lives with Vitamin A* not only has roots deep in the beginnings of biomedical science but addresses a vitally important policy issue in today's world.

— Roderick C. Macleod, Professor Emeritus of History and Classics, University of Alberta. Author of *Prairie Fire: The 1885 North West Rebellion and All True Things: A History of the University of Alberta, 1908–2008*.

BRILLIANCE & CONFUSION:

SAVING CHILDREN'S VISION & LIVES WITH VITAMIN A

VERN PAETKAU

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Introduction

This book is about vitamin A, an essential micronutrient for humans. It proposes to take you on an illuminating journey, beginning with an understanding of how we came to discover vitamins and their roles in nutrition. Vitamin A, the "vision vitamin," has an essential role in human well-being and life itself, a fact that was discovered and then rediscovered decades later. This understanding led to an investigation of the effects of vitamin A deficiency in the developing world, which threatens the vision, well-being, and very lives of millions of children. The book describes how this essential micronutrient can be provided in a sustainable way, ending with a detailed look at a controversial effort to use the power of genetic engineering to this end.

In Chapter 1, I relate the rediscovery in the 1980s of the life-essential properties of vitamin A, some 55 years after this had been previously documented but which had then been largely forgotten. The next chapter outlines the history of vitamin discovery more generally and explains how the realization that dietary deficiency can cause disease profoundly changed the way we view human health. In Chapter 3, I describe the structure and functions of the various forms of vitamin A and how the vitamin's two unrelated biological activities are responsible for maintaining vision, on the one hand, and life itself, on the other. Chapter 4 explains the effects of vitamin A on human health. Chapter 5 describes some strategies for overcoming vitamin A deficiency and also the limits on those strategies, which may not be feasible, or robust, for some segments of the world's population. Chapter 6 then presents and explores a controversial solution

to the problem of vitamin A deficiency for the three billion people of the world who depend on rice for their well-being. Finally, I close with a consideration of future directions and advocate for an evidence-based, collaborative approach to globally eradicate the devastating effects of vitamin A deficiency.

CHAPTER 1

Vitamin A, Essential for Vision and Life

An epiphany in Baltimore

It was Christmas week of 1982, a quiet time away from clinical duties, research, and teaching, when Dr. Alfred Sommer, professor of ophthalmology at Johns Hopkins University, decided to take another look at the results of a large public health study he had been involved in. The fieldwork for that study had taken place between March 1977 and December 1978, in rural West Java, Indonesia. The government of that country wanted to understand the degree of vitamin A deficiency among children in rural areas and the associated risk factors. Vitamin A was known to be important for sight — one form of the vitamin is part of the visual pigment of the eye — and without enough vitamin A in the diet, a child will start to lose vision. Vitamin A deficiency results in a condition called xerophthalmia, a series of steps of deterioration of the eyes that begins with an inability to see in low light, or "nightblindness." If the vitamin deficiency continues, the damage becomes worse, leading ultimately to complete blindness and the destruction of eye tissue. The government of Indonesia wanted to know whether there were factors in the lives of children that made vitamin A deficiency, and the resulting problems with their vision, more likely. Many children in rural Indonesia suffered from nightblindness, although they often soon recovered. But carrying out a field study in those areas was challenging. It required a multifaceted team of investigators and careful assessment of the study's conditions and goals. In response to

a request from the Indonesian government, Sommer had put together a team uniquely qualified to answer those questions.

Sommer had earned his medical degree at Harvard in 1967 and already had a hankering — which he shared with his wife — to serve in the Peace Corps. But Congress passed legislation the following year that essentially guaranteed he would be drafted out of the Peace Corps and sent to Vietnam. The fighting there was heavy, and doctors were badly needed. So instead, he enrolled with the Center for Disease Control, in Atlanta, Georgia. He found the pace at this government institution a bit slow, and when he became aware of a chance to go to East Pakistan to join a group trying to contain a cholera outbreak, he jumped at the opportunity. He served in East Pakistan from 1969 to 1972. This was his first experience living and working in a hot, uncomfortable, challenging, developing-world environment, and he loved it. It was a time of political upheaval, as East Pakistan was breaking away from its larger West Pakistan overlords to become Bangladesh, a development in which Sommer had a small but non-trivial part, as described in his entertaining account of that time (1).

At that point, Sommer had yet to undergo any specialist training, but what interested him was epidemiology, the study of disease patterns in populations, and ophthalmology, the treatment of eye diseases. This combination of specialties was, and remains, uncommon. Upon his return to the United States from Bangladesh, he undertook the necessary further training in those sub-disciplines while retaining a strong interest in working in developing countries. Sommer obtained a degree in epidemiology in 1973 and immediately enrolled in the residency program in ophthalmology at Johns Hopkins University. During this time, he met a woman named Susan Pettis, who was the Director of Blindness Prevention for the American Foundation for Overseas Blind, now known as Helen Keller International. Because of his experience in East Pakistan, Sommer was able to help that organization, and Pettis became something of a mentor to him. In 1974, Sommer had a chance to go to Indonesia with her to attend the first international conference to address blindness caused by nutritional deficiencies, "nutritional blindness," of which vitamin A deficiency is a prime example. The conference was organized by the World

Health Organization (WHO), and Sommer considered himself lucky to be able to attend, given his junior status.

Despite his youth, Sommer took an active part in the meeting proceedings. On the last day, he was sitting on one side of Susan Pettis, and a high-ranking official of the Indonesian Ministry of Health was sitting on the other. The government of Indonesia was interested in the problem of nutritional blindness and wanted to learn more about its epidemiology before starting a program of vitamin A capsule distribution to combat it. Sommer remarked to Pettis that Indonesia would be a wonderful country in which to investigate nutritional blindness. The Indonesian official overheard the remark and, as recalled by Sommer more than twenty years later, whispered to her, "Is there any way that we can get Dr. Sommer to come here for a few years and work with us?" Recalled Sommer further, "And she's sitting in the center and smiling to herself, and saying, 'I think I can make a deal here.'" As a result, Sommer found himself invited to start such a study, which he put off for a few years while he finished his residency in ophthalmology at Johns Hopkins.

In 1976, Sommer had completed his residency. His talents had been noticed, and his future looked bright, with a faculty appointment at Johns Hopkins a real possibility. He was given friendly advice that undertaking an epidemiological study in a far-off, developing country might harm his career — people back in the USA would forget him, and he could be damaging his chances of an academic medical position. Sommer disregarded that conventional wisdom and began to organize funding and people to look at the problem of vitamin A deficiency in Indonesia. With those in place, he gathered up his wife and two young children and left the United States for four years.

When the study in rural Indonesia began, it was already known that children there had a high rate of mild xerophthalmia, mainly characterized by nightblindness, but that most of the affected children spontaneously regained normal vision. The children being studied were from poor, rural backgrounds, and their high incidence of nightblindness was presumed to result from diets deficient in certain critical nutrients, particularly vitamin A. Fluctuations in the diet probably accounted for the

transient nature of their nightblindness. One of the goals of the study was to see whether any other circumstances contributed to nightblindness.

The group put together by Sommer included a paediatrician, an ophthalmologist, a nutritionist, two nurses, and six local field workers. Close to 4,600 children were enrolled in the study. The presence of the field workers allowed the doctors to obtain extensive histories from their patients, including the mothers' recollections about their children's health. Blood samples were taken, and objective clinical tests for nightblindness were performed. Of those children with nightblindness, most got better spontaneously, as expected. Children showing signs of more serious eye damage due to progressive xerophthalmia were given vitamin A to help them recover.

The children were seen every three months over a period of a year and a half. The doctors often found themselves relying on the mothers' memories, as told to a local fieldworker — memories that almost always turned out to be correct, as seen by clinical examination. A mother might recall that her child had recently undergone a period of nightblindness, during which the child could not see at dusk or dawn, could not find their food, would huddle in a corner of the hut, and would not walk about in the village during periods of low light.

The doctors determined that the incidence of mild xerophthalmia increased until about age three. As predicted, children with xerophthalmia had low levels of vitamin A in their blood. Children whose diet was low in foods that provide vitamin A, such as dark green leafy vegetables and orange or yellow vegetables or fruits, were more likely to be vitamin A deficient. So were children with respiratory diseases or diarrhoea, which draw down vitamin A levels. And vitamin A deficiency was associated with nightblindness. All of this made sense and wasn't unexpected.

Sommer believed that after so much effort and expense, it was important to analyze the results of such studies intensively and repeatedly, to obtain every morsel of understanding the data could provide beyond the initial answers to the leading questions. That's what he was doing during Christmas week four years after the fieldwork had ended. As he repeatedly reviewed the data from the Indonesian study, something nagged at him.

In studies of this type, it's important to retain the study subjects; if too many drop out, the results may be biased and conclusions can be compromised. A point of pride in this particular study was that by diligent effort, most of the children enrolled could be followed to the end of it. But retention is never 100%; some people move away, or sometimes they are busy working in the fields when it comes time for the next visit to the clinic. So, there was a decrease in the number of children seen as the study progressed. This was expected. But what suddenly caught Sommer's attention was that these losses were disproportionately from the group of children who at one point or another had experienced nightblindness or other symptoms of early, mild xerophthalmia. Why? An examination of additional data provided the answer: they had died. Children with the very mildest, early stages of xerophthalmia, nightblindness, were dying at three times the rate of those not showing such symptoms, even though they usually recovered their vision. Children with a more severe condition, with more progressive xerophthalmia, died at six times the rate of healthy children. Children with advanced xerophthalmia, but still not near total blindness, died at nine times the rate of children with no symptoms. Not only were the children losing their vision, they were losing their lives. Mild xerophthalmia, a condition that usually reverses spontaneously, was associated with an increased risk of death. At the time, this was completely unexpected.

Scientists really do have revelatory experiences, although they don't usually shout, "Eureka!" That moment when a scientist realizes that he or she has seen something that nobody else has seen, when the understanding of a scientific story changes, even to a small degree, is golden and often shapes the rest of his or her life. A single observation cannot establish the validity of a dramatic new result — it requires corroboration — but the path by which the new finding can be tested and either accepted or rejected is now clear.[1] A flash of insight has illuminated something that had not been seen previously, and interrogating the natural world to determine

1 Further testing of a new finding to prove its veracity is of course required, but at some point in a working scientist's life there may be an event that carries an aura of inevitability about it at its first observation. Or at least, that's how we remember it.

whether that insight reflects reality is what scientists are trained to do. Alfred Sommer thought he was seeing something new and important, linking mild xerophthalmia, a condition thought to be benign and easily reversible, to an increased risk of death. In interviews, he refers to this revelation as his "holy cow" moment, although in his memoir of the time he admits that "cow" wasn't actually the word he used (1).

The initial study by Sommer and his colleagues was an observational investigation that suggested a link between vitamin A deficiency, mild xerophthalmia, and childhood death. A logical conclusion would have been that vitamin A deficiency causes nightblindness, which in turn can lead to death. But correlation isn't proof of causality. The critical next step would have to be a study that specifically asked: Does vitamin A supplementation in a large group of nutritionally challenged children prevent nightblindness and early childhood death? At the moment of Sommer's epiphany, he was busy setting up another, larger study in Indonesia, which would extend the findings of the first one. By modifying this study, the researchers could directly test the hypothesis that vitamin A supplementation prevents childhood deaths. Over the next years, the work of the Johns Hopkins team and others confirmed Sommer's initial suspicion, but reaction to and repercussions from those studies still engage medical science and health policy today. Discoveries about the importance of vitamin A in the diet have led to beneficial intervention on a global scale by non-governmental agencies. But there have also been ideological and nationalistic reactions to those interventions. The issue of vitamin A deficiency has taken medical science to the leading edge of biological research, through the creation of genetically engineered crops that may be an answer to vitamin A deficiency. There also has been profound opposition to that approach.

At the heart of these issues is the health of millions of children in the developing world. For as the first observational study suggested, their very lives, as well as their vision, depend on their ability to obtain the micronutrient that bears the first letter of the vitamin alphabet. It is a micronutrient essential for life. This book is the story of how that vitamin was identified during a golden age of vitamin discovery, what it does in

the human body, how it affects our health, and how it presently is — and in the future can be — provided to those who do not currently get enough of it.

What is vitamin A?

"Vitamin A" is a generic term for a small group of related, fat-soluble compounds. Retinol and two closely related chemical forms called retinal and retinoic acid constitute the vitamin A found in animals' bodies, where they carry out a number of essential functions. They are referred to as "preformed" vitamin A, whose structures and functions will be described in detail in Chapter 3. Retinol is stored in animals' livers and is present in dairy products, eggs, and a number of other animal-derived foods.

Vitamin A is also present in many food plants in "provitamin" forms called carotenoids. That name suggests carrots, and in fact, carrots are a good source of these provitamins, as are some other yellow or orange vegetables, such as sweet potatoes, as well as dark green leafy vegetables, such as spinach. Beta-carotene, the most common provitamin A, is split by cells in the human gut into two molecules of functional vitamin A; these are absorbed into the blood and either used immediately or stored in the liver for later use. Only animal tissues contain "preformed" vitamin A. Plants contain only provitamin A forms such as beta-carotene and other carotenoids.

People have been indirectly aware of the existence of vitamin A for thousands of years, well before we knew what it is. Today, those of us fortunate enough to enjoy a balanced and nutritious diet don't need to be concerned about vitamin A deficiency; it's present in many of our foods, including whole milk (and skim milk, to which it is added after the fat has been skimmed off), other dairy-based foods, eggs, meats, and several kinds of vegetables. But in parts of the world where diets are not well rounded, such as large areas of sub-Saharan Africa, India, Asia, and parts of Central America, vitamin A deficiency threatens the health and the lives of millions, particularly children. The results of the early studies of Sommer and his colleagues reflected that threat. The WHO concluded

in 2009 that between 190 and 250 million people worldwide, including 19 million pregnant women, are vitamin A deficient (2). Estimates of the number of children globally whose very lives are at risk run to the hundreds of thousands *a year*.[2] To have such numbers of people at risk is unacceptable, especially as solutions for the problem exist. The question is, which solutions are effective, sustainable, and acceptable?

Just over a hundred years ago, nutritional scientists in the United States showed that there was a fat-soluble, trace nutrient in animal liver, dairy products, the dark green leaves of many plants, and a number of yellow or orange foods that was necessary for health and for life itself. They gave it the name "fat-soluble A" because it was the first identified fat-soluble essential trace nutrient. Within a few years, its name was changed to "vitamin A." The term "vitamin" was a revision of "vital amines," the first general descriptor for the vitamins as a class of micronutrients. Over time, several other fat-soluble vitamins were discovered. The water-soluble vitamins, several of whose essential roles in nutrition had been identified even before "fat-soluble A," were mostly grouped as "B vitamins." The B vitamins were later separated into seven different chemical entities, whose individual functions cover a wide spectrum of essential metabolic activities. Another water-soluble vitamin, C, was one of the earliest essential micronutrients to have its effects identified.

We live in a time of high demand for dietary news. As coverage has grown ever more extensive in the area of lifestyle and the many food-related issues that surround us, interrogating Google for articles on "nutrition" will apparently produce 419 million articles in 0.34 seconds. This number includes articles in sources that we wouldn't expect to have much interest in dietary news, and they range from the commonsensical (*The New Republic*: "Many doctors dismiss nutritional therapies as quack medicine. But many patients disagree, and they're taking matters into their own hands — sometimes to the detriment of their health."), to the satisfying (*The Economist*: "Chocolate is blamed for causing cavities and making people fat, but in modest quantities it is actually a healthy treat."), to the

2 For reasons that I will explore later, it is difficult to know how many children die each year of vitamin A deficiency. The WHO estimates 125,000; most other estimates are higher.

unsubstantiated ("Dr. Oz's Three-Day Detox Cleanse"). Other than enriching a few entrepreneurs, almost none of this "news" will have much of an effect on anyone, beyond perhaps a brief period of weight loss or of anecdotal well-being, or ill health, almost always followed by a return to a previous state of mind and body. But there is a large, important nutrition-related story just beyond our everyday experience, and it is one seldom commented on. It concerns the profound health effects of vitamin A deficiency. That deficiency can be quantitatively demonstrated — blood levels of vitamin A in those affected are low to non-existent, they have insufficient vitamin A stored in their livers, and they suffer exactly the symptoms of incipient blindness, failure to thrive, and consequent death that have been known to accompany vitamin A deficiency in studies on animals and clinical trials in humans.

There are multiple reasons why the problems of vitamin A deficiency are not generally better known in the developed world and why effective solutions have not been developed. In the first place, we tend to see it as a "third-world" problem, well removed from most first-world eyes. It's a depressing and apparently unsolvable problem from a Western point of view — poor or insufficient nutrition is still widespread, and despite progress in increasing the quantity of food produced in the developing world, we have yet to adequately solve issues of nutritional quality. Vitamin A deficiency is directly connected to poverty, and even when solutions exist, those affected often can't afford them and depend on donors, who may grow fatigued in their efforts. Progress in solving the problem has been slow, and sometimes it stalls for irrational reasons. Against all of this, it is clearly the case that solutions already exist, that newer solutions are available for testing, and that none of these solutions costs very much on a global scale. There are people with a strong concept of how to overcome the damaging effects of vitamin A deficiency, but the enabling plans are sometimes blocked by interfering priorities and interests, as I will describe.

Vitamin deficiencies have been known, by various names, for thousands of years. Nightblindness due to vitamin A deficiency was apparent to ancient Egyptians, as was its solution — eating ox liver (which works). Vitamin C deficiency was an impediment to Britain's efforts at global

domination through its naval might; sailors were dying, suddenly and inexplicably, when they spent more than a few weeks away from land. And as peasant farmers moved from the land to jobs in smoke-beclouded cities during the industrial revolution, their children began to suffer from the crippling effects of vitamin D deficiency due to a lack of solar ultraviolet light. Their bones were ill-formed, and their lives often ended prematurely.

The problem of scurvy, caused by a lack of vitamin C, was solved in the early nineteenth century, but most vitamin discovery began only toward the end of that century. At that time, even as research indicated that certain trace nutrients are essential for health and for life itself, the hypothesis that a deficiency in a trace nutrient could cause disease was denigrated by many scientists and doctors, who were wedded to two valid but incomplete paradigms: that diseases are caused by infectious microorganisms (many are, but some very important ones, like cancer, heart disease, and vitamin deficiencies, usually are not), and that what matters in nutrition is quantity — eat enough food and you will be healthy. The latter idea derived from the metaphor that your body is an engine, and you need to provide it with enough fuel or it will fail. But gradually, increasing levels of scientific rigour, which demanded that claims be backed up by verifiable, reproducible evidence, led thoughtful people to the ineluctable conclusion that some micronutrients are indeed essential for animal, including human, well-being, and that deficiencies in these can cause dangerous illness and even death. Eventually, humans were found to need 13 vitamins in all, one after another of which was identified between about 1880 and 1945. The structure of each was determined in due course, and its role in human biology was mapped.

As this classical phase of vitamin discovery was winding down, it was assumed that we understood almost everything we needed to know about the vitamins. Like Lord Kelvin's pronouncement in 1900 that there was nothing new to be discovered in physics, the notion that our understanding of vitamins was now complete was not correct, even in 1945. And nowhere did that inadequacy become more evident than in the biology of vitamin A, the most complex of all the vitamins in its actions

and activities. In retrospect, we should have recognized its significant and complex effects on human health because of research in the 1920s and 1930s. But we failed to grasp the full meaning of that work, until suddenly the evidence that vitamin A deficiency was the key element in a large global health problem was overwhelming.

The late Arthur Kornberg, discoverer of the enzyme system that duplicates genomic DNA, described himself and many of the biological scientists of the 1940s and 1950s as "enzyme hunters." Enzymes are the biological catalysts that carry out all of the chemical reactions in living cells, from breaking down sugar for energy to expressing genes, and the search for these proteins was particularly intense during that time, although it had begun earlier and continues today. Kornberg described the progress of biomedical research as a succession of periods. The "microbe hunters" described by the popular science writer Paul de Kruif occupied the spotlight in the first two decades of the 20th century, as they discovered one microbe after another responsible for human diseases. The next 20 years featured the "vitamin hunters," followed by the "enzyme hunters" and then the "gene hunters." Kornberg noted that each age, "with its particularly bountiful quarry, was seen as golden" (3). Be that as it may, the early decades of the 20th century did indeed see tremendous progress in the discovery of various organic trace nutrients, or micronutrients, that came to be identified as the vitamins essential for our well-being. The hunt for vitamins was facilitated by the fact that laboratory animals also need most of the same vitamins as humans do and hence can be used to identify and characterize them.

This is more than a story about a branch of human nutrition; there are serious current issues of life and death related to vitamin A that go well beyond the science and medicine. To properly deal with these issues requires a cool-headed and logical approach, together with a will to help those who cannot help themselves. There are contentious issues and competing visions in play when we consider what is to be done. What makes the matter especially urgent is that very young children are most at risk. The obvious risk is to their eyesight, but as the experience of Sommer and his research team indicated, there is a profound risk to their broader

well-being and their very lives. The effects of vitamin A on their health are a reflection of the biological roles of this most complex of the vitamins. Its name reflects that it was one of the first to be discovered, but its complexities continue to be revealed to this day.