The Vitamin A Story – Lifting the Shadow of Death
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Dedication

For Rita
Preface

My early experience in international health coincided with the fitting of the last piece into the centuries-old vitamin A puzzle. Understanding of these vital food components was only beginning to come into focus when the word in its original form – vitamine – was coined by Polish-American biochemist Casimir Funk in 1912.

As a twenty-five-year-old medical student in 1980, I worked with a Venezuelan medical team treating victims of river blindness (onchocerciasis), a parasitic infection spread among humans by black flies. River blindness was then a leading cause of blindness worldwide, known to afflict nearly 20 million people. Our Venezuelan patients were Yanomami Indians living in the remote headwaters of the Upper Orinoco River. The team was charged with administering intravenous injections of suramin to river blindness victims. (Suramin was developed in pre-War Germany as Bayer 205. It is still in use to treat sleeping sickness.) Suramin can produce nasty adverse reactions, including fever, nausea, rash, and headaches. In extreme cases, a patient can collapse and die during suramin treatment. The team’s nurses were so fearful of causing harm that some inserted the needle in a patient’s vein but then withdrew the syringe without-ever injecting the medication.

The need for a safer river blindness treatment lasted only a few more years. In 1984, while in my residency training in ophthalmology, I joined a scientific team in Liberia studying river blindness at the Uniroyal Rubber Plantation, where the disease afflicted many of the rubber tappers. My colleagues were conducting a clinical trial to see whether ivermectin, a versatile drug with both veterinary and human uses, was effective in treating river blindness. We were pleased to find ivermectin highly effective in both treating the disease and its complications without dangerous side effects. Ivermectin is now the mainstay river blindness treatment and is given community-wide in places wherever river blindness occurs – one tablet, once a year. As a result, this onetime scourge is now under control.

Having participated in the river blindness/ivermectin success, I wanted to tackle another, harder, ophthalmological problem. I was able to do this in 1987, after completing my training at the Wilmer Eye Institute at John Hopkins. With a Physician-Scientist Award from the National Institutes of Health, I decided to work on the particularly persistent problem of vitamin A deficiency, which was known to be
a leading cause of blindness and death among developing countries’ children and a major cause of illness and death in childbearing women. Alfred Sommer, then a professor of ophthalmology and later dean of the Johns Hopkins School of Public Health, encouraged me to join the efforts to understand and control vitamin A deficiency.

It was an exciting moment in public health, with signs of progress on the horizon, but also with frustrating questions still looming. Studies were beginning to suggest that oral doses of vitamin A, when given to young children, could protect them against diarrhea, measles, blindness, and death. Exactly how that worked, however, remained unknown.

I began my first work on vitamin A in Indonesia with Muhilal, a nutritionist (like many Indonesians, Muhilal uses one name only), and Gantira Natadisastra, an ophthalmologist and director of the Cicendo Eye Hospital in Bandung. Our research found that children living on vitamin A-poor diets had weakened immune systems, which went part way toward explaining why they were particularly susceptible to infectious diseases. Looked at the other way, vitamin A was emerging as essential for the proper function of the immune system.

Research groups elsewhere were finding corroborating evidence that vitamin A deficiency weakens immunity. A consensus was growing that vitamin A deficiency is, in fact, an acquired immune deficiency disorder. As such, it can be categorized along with AIDS, but only partly, because its cause is not viral but nutritional. On the one hand, vitamin A deficiency greatly increases susceptibility to infections, many of them potentially fatal such as measles, diarrhea, dysentery, and tuberculosis. On the other hand, once understood, vitamin A deficiency is tractable in ways that AIDS is not. Adequate intake of vitamin A can enable the body to resist – and overcome – these infections. In other words, treatment with vitamin A can cure the conditions that deficiency caused.

These recently determined attributes of vitamin A – that it can both prevent and cure – have placed it at the top of the international public health agenda. Vitamin A supplementation has become part of the basic public health canon of interventions to improve child survival. The other fundamental public health interventions are childhood immunizations against common killers such as tetanus, diphtheria, whooping cough, polio, and measles; iodized salt to prevent goiter and cretinism; oral rehydration to counter the potentially fatal effects of diarrhea; and clean water and sanitation to reduce the spread of dysentery, cholera, and other water-borne illnesses. Vitamin A supplementation alone has saved the lives of an estimated 200,000 pre-school age children a year. Studies have demonstrated that, in the long run, periodic vitamin A supplementation reduces deaths among pre-school age children in developing countries by about 25%. On the recommendation of the World Health Organization and UNICEF, more than one hundred countries worldwide now have implemented programs that give vitamin A to children. More than two million lives have been saved through these programs. With wider implementation and coverage of vitamin
A supplementation, an estimated six hundred thousand or more lives could be saved each year in developing countries.

Vitamin A public health efforts are generally seen as a success, but they have sometimes been stopped short by insurmountable obstacles – politics, cultural conflicts, bogus science, and commercial agendas. I detail many of these in this book. Vitamin A is not the only public health effort to have faced obstruction. In 2002, for example, religious clerics in northern Nigeria effectively opposed delivery of oral polio vaccine. The holy men saw the vaccination program as a plot to harm children. No surprise, large outbreaks of paralytic polio followed the halt of the program in 2003.

Nor are such impediments to improving wellbeing through public health programs limited to the developing world. Despite definitive evidence that fluoridation of water promotes oral health and reduces cavities in the general population, the Board of County Commissioners of Pinellas County, Florida, gave in to critics of so-called Big Brother government and voted in 2011 to end fluoridation of the water supply.

The incidence of whooping cough, which was common through World War II, was largely arrested thanks to the routine administration of three-pronged DPT (diphtheria, pertussis, tetanus) vaccinations – until recently, that is. Whooping cough is currently in resurgence in the United States, in part because of parents’ refusal to have their children immunized.

This book could not have been written two decades ago. Only in the last twenty years has it been possible to define vitamin A deficiency as a nutritionally acquired immune deficiency syndrome. The new scientific certainties about vitamin A make possible a new historical interpretation. Whereas as recently as the early 1980s, a pediatrician might have said, ‘This child is about to die from measles’ or another infection, today we can correctly assign blame to an underlying culprit and take action against it. Likewise, an obstetrician might have closed the books on a lost patient, saying, ‘Died of puerperal sepsis (childbed fever).’ Adequate intake of vitamin A, either before the onset of disease or once the patient was sick, may have ruled out both scenarios.

I began research for this book the year after my initiation in public health fieldwork, with questions about the seminal clinical observations of vitamin A deficiency made during the nineteenth century in such places as Paris, Bordeaux, and Lisbon. Army and navy medical records attest to the pervasive problem of vitamin A deficiency among soldiers and sailors. People by the millions, young and old, perished as a result of vitamin A deficiency. It took nearly two hundred years to understand what vitamin A was, that it could prevent or cure many diverse and deadly diseases, and how it did so.

There was no ‘eureka!’ moment of discovery in the quest to understand vitamin A. Nor was there one towering genius to could lay claim to understanding vitamin A and its biochemical powers. In this book, I attempt to reconstruct the twisted, broken path toward understanding vitamin A and toward introducing the men and women who, together, lifted the dark shadow that condemned to death the victims of vitamin A deficiency.
The preparation of this book was greatly facilitated by the superb assistance and expertise of the staff of the National Library of Medicine, especially Stephen Greenberg, Elizabeth Tunis, Kenneth Niles, Crystal Smith, and Khoi Le. I thank the staff of the Bibliothèque Nationale de France, the Österreichische Nationalbibliothek, the Caird Library at the National Maritime Museum in Greenwich, the National Archives at Kew, the Bibliothèque de l’Académie Nationale de Médecine, the University of Cambridge Library, the Bodleian Library at the University of Oxford, the Forbes Mellon Library at Clare College, the Library of the Royal College of Surgeons of England, the Rugby School Museum, the St. George’s Medical School Library, the Kenneth Spencer Research Library, University of Kansas Libraries, the Wellcome Institute for the History of Medicine, Contemporary Medical Archives Centre, the Yale University Library, Manuscripts and Archives, and the Archives départementales de la Gironde in Bordeaux. I also owe appreciation to Jean François Girardot of the Bibliothèque de Médecine, Université Henri Poincaré, Nancy, France, Florence Greffe of the Archives of the Académie des sciences – Institut de France, David Null at the Steenbock Library, University of Wisconsin – Madison Archives, John Hessler of the Geography and Map Division, Library of Congress, and Vickie Bomba-Lewandoski of the Connecticut Agricultural Experiment Station. Joanne Katz kindly shared her wealth of material from the Albay Child Health Project. I thank Kate Burns, Alfred Sommer, Omar Dary, Steve LeClerq, and Keith West Jr. for sharing their perspectives on vitamin A research and programs. My colleagues Martin Bloem, Klaus Kraemer, and Saskia de Pee provided valuable insight during the early formulation of the book. Kai Sun conducted the data analyses of Corry Mann’s milk studies in children and of night blindness and infectious diseases in white and black troops during the US Civil War.

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Richard D. Semba
Glossary

Many terms used in this book occur only in a scientific/medical context; the brief definitions given here may be useful to the reader. Certain words that are familiar in nonscientific usage acquire distinct, specific meanings when used in a scientific/medical context (e.g. control, describe, synthesis, wasting). Their scientific/medical meanings are given here, along with many other frequently used scientific/medical terms.

**Accessory food factors** – an early twentieth-century term for the essential food components that became known, first, as ‘vitamines’ and, then, as ‘vitamins’.

**Adequate Intake (AI)** – as determined by the Food and Nutrition Board of the Institute of Medicine (US), a recommended average daily nutrient intake level based on observations or estimates of apparently healthy people. AI is used when an RDA cannot be determined.

**Albumin** – a simple form of water-soluble protein such as that present in egg white, milk, and blood serum.

**Amine** – a group of organic compounds that are derivatives of ammonia.

**Amino acid** – a compound that contains carbon, oxygen, hydrogen, and nitrogen and is a ‘building block’ or basic unit that joins with other amino acids to form proteins.

**Atropine** – a substance that will dilate the pupils if instilled into the eyes.

**Belladonna** – an atropine-containing drug prepared from the deadly nightshade plant.

**Basal** – a diet that contains the caloric content to meet basic needs.

**Beriberi** – a nutritional deficiency caused by lack of thiamin and characterized by an array of clinical findings including loss of sensation in the extremities, paralysis of wrists and feet, burning sensation in the legs or toes, muscle atrophy and weakness, enlargement of the heart, and heart failure.

**Bitot’s spot** – named for French physician Pierre Bitot (1822–1888), a raised, foamy or pearly-appearing patch of abnormal tissue arising on the surface of the conjunctiva and considered specific to the diagnosis of vitamin A deficiency.

**Bran** – the outer coats of cereal grains that are rich in B complex vitamins such as thiamin.
Calorie – a unit of heat energy mostly used to define the amount of energy in foods.

Carbohydrate – a group of organic compounds that includes starches, sugars, celluloses, and gums.

Carbonic acid – a weak acid present in solutions of carbon dioxide dissolved in water.

Butterfat – the natural fat in milk from which butter is made; butterfat is a rich source of vitamin A.

Buttermilk – the liquid remaining after butter has been separated from milk or cream; buttermilk is devoid of vitamin A.

Carotene – an orange-yellow to red pigment present in carrots, mangoes, papaya, and dark green leafy vegetables and a dietary precursor to vitamin A.

Carotenoids – a class of yellow to red pigments present in plants and animals.

Casein – the main protein in milk and cheese.

Case-fatality rate – the ratio of the number of deaths to the number of people with a given condition, for example, the case fatality rate of measles was 8% or 80 deaths per 1,000 children with measles.

Cod liver oil – an oil extracted from the liver of the cod fish; cod liver oil is a rich source of vitamin A.

Conjunctiva – the mucous membrane that lines the inner surfaces of the eyelids and the exposed surface of the eyeball.

Cornea – the transparent dome-shaped tissue that forms the front of the eye.

Contagious – of infectious diseases, spread person-to-person by direct or indirect contact.

Crystallize – to cause the formation of crystals.

Deficiency – a lack or shortage, for example, vitamin D deficiency.

Diarrhea, diarrheal disease – a condition characterized by frequent, loose, watery stools. Among infants and children, it is usually caused by harmful viruses or microorganisms; it is also especially severe in persons with underlying vitamin A deficiency.

Describe – in science, to identify.

Dementia – a deterioration of mental abilities such as memory, concentration, and judgment.

Dermatitis – inflammation of the skin; a skin rash.

Diet – the kinds of food that are regularly consumed.

Dysentery – an especially severe infectious form of diarrhea that is accompanied by blood and mucus in the stool.

Fat – compounds composed of glycerol and fatty acids that constitute the body’s main energy storage.

Fibrin – an insoluble protein that forms during the clotting of blood.

Epidemic – the widespread occurrence of a disease or condition in a community or group at the same time.
**Epidemiology** – a branch of medicine that deals with the patterns, causes, and control of disease in populations.

**Estimated Average Requirement (EAR)** – as determined by Food and Nutrition Board of the Institute of Medicine (US), the average daily nutrient intake level required to maintain good health in about half of healthy people.

**Gelatin** – a colorless and odorless substance obtained by boiling the skin, bones, and tendons of animals in water.

**Germ/germ theory** – micro-organisms; the germ theory states that microorganisms are the cause of many diseases.

**Hemeralopia** – a term used to describe the impaired ability to see at night, i.e., night blindness.

**Infectious** – caused by a harmful micro-organism and transmitted through the environment.

**Iris** – the colored ring-shaped membrane of the eye that is located between the cornea and the lens of the eye.

**Keratomalacia** – a softening or melting of the cornea that occurs in the most advanced stage of vitamin A deficiency and usually results in blindness.

**Lesion** – a localized area of disease in a tissue.

**Lactose** – a sugar that is present in milk.

**Lipid** – a large group of organic compounds that are insoluble in water, oily in consistency, and includes fats, oils, waxes, sterols, and triglycerides.

**Malnutrition** – a condition that occurs when the body does not get the right amount of vitamins, minerals, or nutrients for optimal health.

**Mineral** – an inorganic element such as iron, calcium, potassium, sodium, or zinc that is essential to human, animal, and plant nutrition.

**Niacin** – a B complex vitamin found in meat, wheat germ (see Bran, above), and dairy products and is essential for nerve and digestive function.

**Night blindness** – impaired or no ability to see at night that, today, serves as a clinical indicator of vitamin A deficiency. Also referred to as hemeralopia or nyctalopia. (q.v.)

**Nitrogen, nitrogenous** – the nonmetallic element nitrogen that makes up nearly four-fifths of air and is also contained in proteins; compounds containing nitrogen.

**Nyctalopia** – a term used to describe the impaired ability to see at night, i.e., night blindness.

**Nutritive** – nutritious or nourishing.

**Ophthalmia** – an inflammation of the eye.

**Ophthalmoscope** – an instrument for viewing the interior of the eye, especially the retina.

**Pasteurization** – partial sterilization (killing of micro-organisms) of food by heating.

**Pellagra** – a nutritional deficiency caused by lack of niacin and characterized by dermatitis, diarrhea, and mental disturbances.
Polyneuritis – a term used to describe experimental beriberi induced in birds by a diet lacking in thiamin.

Protein – a large group of organic compounds that are essential constituents of living cells and consist of long chains of amino acids.

Pupil – the constricting/dilating opening at the center of the iris of the eye through which light passes to the retina.

Recommended Dietary Allowance (RDA) – as determined by Food and Nutrition Board of the Institute of Medicine (US), the daily amount of a specific nutrient that is required to maintain good health in practically all healthy people.

Retina – the light-sensitive membrane that lines the inside posterior wall of the eyeball and receives visual images, which are transmitted to the brain via the optic nerve.

Retinol – a chemical term for vitamin A.

Retinol Activity Equivalent (RAE) – as determined by Food and Nutrition Board of the Institute of Medicine (US), 1 microgram RAE is equivalent to 1 microgram of all-trans retinol, 2 micrograms of supplemental all-trans-beta-carotene, 12 micrograms of dietary all-trans-beta-carotene, or 24 micrograms of other dietary provitamin A carotenoids.

Rods and cones – the light-detecting cells in the retina that allow night and day vision, respectively.

Rickets – a nutritional deficiency in children caused by lack of vitamin D and characterized by weak, soft bones and impaired growth.

Rhodopsin – a light-sensitive pigment in the rods of the retina that converts light energy into a nerve signal.

Scurvy – a nutritional deficiency caused by lack of vitamin C and characterized by spongy, bleeding gums; a blotchy pattern of bleeding under the skin; weakness, and joint pain.

Spanish fly – a preparation made from dried, crushed blister beetles that causes blistering when applied to the skin.

Starch – a carbohydrate that is the main source of energy in plants, of which the most familiar sources in are rice, potatoes, and wheat.

Stunting – a condition of shortened stature caused by chronic malnutrition in children.

Syndrome – a group of signs and symptoms that together characterize a disease or abnormal condition.

Synthesize – in chemistry, to combine different chemical constituents to make a specific compound.

Thiamin – a B complex vitamin that is found in nuts, legumes, and whole grains and is essential for nerve function and metabolism.

Tryptophan – an amino acid that is essential in the diet because it cannot be synthesized by the body.

Ulcer, ulceration – an open sore on an external or internal surface of the body.
**Vesicatory** – a substance that causes blistering when applied to the skin.

**Vitamin A** – a fat-soluble vitamin found in liver, egg yolk, butter, and whole milk that is essential for normal growth, immunity, and vision.

**Vitamin B** – see niacin, thiamin

**Vitamin C** – a water-soluble vitamin, also known as ascorbic acid, that is found in fruit and vegetables and is essential for maintaining bones, teeth, and blood.

**Vitamin D** – a fat-soluble vitamin found in milk, fish, and eggs (also generated in the skin through direct sunlight exposure) that is essential for normal growth and development.

**Wasting** – a condition of abnormal thinness that is often associated with acute starvation or severe disease.

**Xerophthalmia** – a term that describes any one or more of the clinical findings of the eye with vitamin A deficiency: night blindness, Bitot’s spots, corneal xerosis, corneal ulceration, keratomalacia, or corneal scarring.

**Xerosis** – a condition affecting the cornea in which the epithelium is altered with vitamin A deficiency and takes on a dry, glazed, whitish appearance.