Functions and Actions of Retinoids and Carotenoids: Building on the Vision of James Allen Olson

Vitamin A Deficiency Disorders: International Efforts to Control A Preventable “Pox”

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ABSTRACT

Visual symptoms (night blindness) of vitamin A deficiency (VAD) were among the earliest diet-related deficiencies documented. Knowledge of vitamin A chemistry, metabolism and deficiency consequences accrued rapidly during the first eight decades of the 20th century. A series of disorders were described in animals, including impaired growth, reproduction, epithelial integrity, and disease resistance that were relieved by consumption of both animal and plant sources of the vitamin. Identification of the intestinal beta-carotene cleavage enzyme in the laboratory of James Allen Olson was seminal to understanding the mechanism for formation of vitamin A from ingested carotenoids. WHO’s 1990 estimate of about 40 million children annually with clinical eye signs of VAD was revised upward to 140–250 million at risk of vitamin A deficiency disorders (VADD) when epidemiological and clinical trials demonstrated morbidity and mortality risk even in the absence of ocular signs. Alternative methods for VAD status assessment and more reliable analytical techniques were developed, several in Dr. Olson’s laboratory. The last decade has seen global progress in VADD control by expanding distribution of medicinal supplements, fortification of foods and dietary diversification through horticulture and education programs. Experience shows that achievements gained through narrowly focused interventions are fragile and vulnerable to national political and economic instability. Contextually relevant, community-centered strategies that improve household food and nutrition security and self-reliance are critical to sustaining international efforts to control the VADD “pox.” J. Nutr. 134: 231S–236S, 2004.

KEY WORDS: • history vitamin A deficiency • vitamin A • vitamin A deficiency disorders • intervention programs • IVACG

Pre20th century efforts

Micronutrient deficiencies were unlikely features of human-kind’s early existence. As a hunter-gatherer the primary food sources were flesh foods, wild fruits and vegetables that provided a quality-rich diet. Most likely deficiency problems emerged as lifestyles gradually changed toward more stationary living and dependence on subsistence agriculture. Cultivated cereals, fruits and vegetables significantly replaced flesh foods, which almost certainly introduced bioavailability problems for several micronutrients, including provitamin A carotenoids from plant sources.

Written evidence for micronutrient deficiencies appear in ancient writings, including those that describe night blindness symptoms relieved by certain animal foods. For example, physician-followers of Hypocrates and others through the centuries associate cure with animal liver ingested or its juice placed on the eye. Wolf (1,2) provides an insightful historical record from early times to the present of anecdotal accountings of this association. Early in the 19th century, Sepoys in India ascribed night blindness to a bad diet and insufficient food (3). Not until the latter half of the 19th century, however, did investigations become more systematic. Credit is given to Eduard Schwarz for conducting an early experiment in nutrition during an around the world scientific exploration from 1857 to 1859 (2). Night blindness (often in conjunction with scurvy) frequently was reported during long sea voyages. Physician colleagues of Schwarz were said to have requested him to test the administration of boiled ox liver against night blindness symptoms. Schwartz records a miraculous permanent cure occurred and this confirmation of old folk medicine firmly established night blindness as a nutritional disease. By the turn of the 19th century, reports from dissimilar parts of the world had clearly linked diet and eye health in both man and large animals. These findings set the stage for the exciting early years of the 20th century and the birth of the scientific
underpinning of knowledge about vitamin A and its public health consequences.

20th century efforts

Animal studies. There are many historical accountings of the exciting first three to four decades of the 20th century when scientists systematically disassembled animal and plant foods to isolate, characterize and synthesize their chemical constituents with curative activity. Rapid progress, led by McCollum (4) and Osborne and Mendel (5), was made possible after McCollum first convinced peers of the validity of using rats, rather than large animal models for nutritional investigations (6). Early pioneers were then able to feed purified diets and systematically add back individual foods or isolates from them to evaluate impact and to begin exploring biochemical functioning of vitamin A. By mid-century, vitamins A and pro-vitamin A carotenoids had been chemically characterized and synthesized (7). Additions to the diets were evaluated for effectiveness in preventing elevated cerebrospinal fluid pressure, eye signs and growth faltering, and in maintaining epithelial tissue integrity, supporting reproduction and extending survival. Comparisons were made to human conditions and links established to dietary improvements and outcomes, mainly ocular and epithelial tissue health (8).

From 1930 to about 1975 vitamin A-related research focused on clarifying the pathology of deficiency both in ocular and nonocular tissues, interactions with other nutrients and disease conditions, and the teratogenic effects resulting from too little or too much vitamin A. Although others had worked extensively on defining components related to vision, the superb work of Wald, his colleague Dowling and their students first documented the specific biochemical pathway linking retinol to opsins and the formation and breakdown of rhodopsin in the visual cycle (9). That seminal work, the first to tie a biochemical function to a fat-soluble nutrient, has stood the test of time, although refined in detail in subsequent years (10).

This remarkable achievement provided the scientific explanation for the age-old symptom of night blindness and its association with nutrition, but it did not explain the nonocular molecular functioning of vitamin A. It was clear from Dowling and Wald’s subsequent work (11), as well as many others (12) that nearly all of the nonocular roles, including survival—excepting those associated with reproduction—were carried out by retinoic acid. Dr. Olson and colleagues in Thailand during the 1970s provided a methodology for clarifying the sequence of appearance of deficiency signs and symptoms using dietary retinoid acid for draining body stores of retinyl esters and retinol while maintaining survival even into adult life. Vitamin A-deficient rats were maintained until their growth stopped or began to decline. Nonstorable dietary retinoid acid was provided for 18 d to stimulate stalled growth followed by withdrawal for 10 d to drain residual vitamin A stores (13). The rats after repeated cycling became blind and could not reproduce but otherwise appeared healthy. Synchronized deficiency permitted study of mature deficient animals, as well as those still growing, and thereby to clarify the sequential pathology of vitamin A deficiency in rats (14).

Notwithstanding the work of Dr. Olson and many others that elucidated mechanisms of absorption and metabolism of retinol and showed the efficacy of retinoic acid in fulfilling most nonocular functions, a molecular explanation awaited the seminal reports of Chambon and colleagues (15) and Evans and colleagues (16). Their revelation of a pivotal nuclear role for retinoic acid that modulates genetic expression of many proteins has invigorated retinoid studies by basic scientists in the last decade.

Human studies

The synthesis of vitamin A around 1930 permitted fortification of foods and availability of medicinal supplements in the US and other developed countries that virtually eliminated ocular forms of vitamin A deficiency (VAD) as a public health problem six decades into the 20th century. However, there are some populations of children in the US whose vitamin A status is not optimal even today as shown using a modified dose-response methodology developed by Dr. Olson and colleagues (17). Cross-sectional serum distribution of vitamin A from the National Health and Nutrition Examination Survey (NHANES) III survey (18) also suggests suboptimal status among some children 4–8 y (younger children were not studied) and some minority groups, but few (around 1%) had values to suggest clinical risk, i.e., <0.7 μmol/L. Indeed, today, there is little evidence that VAD is of public health significance in most developed countries although status could be improved for some by increased intake to Recommended Dietary Allowance (RDA) levels of vitamin A from food sources or supplements. Regrettably, the early programmatic success with food fortification (19) and medicinal supplements in the developed world were not transferred even today to many developing countries where the “pox” of VAD continues to take a toll on the sight and life of children.

How large is the problem in the developing world?

WHO-sponsored the first systematic attempt to quantify the magnitude and public health dimensions of VAD in the early 1960s. Based on clinic records, anecdotal observations and personal interviews, 20,000 to 100,000 children were projected to be affected (20). This “guestimate” was shown to underestimate the problem upon completion of the first carefully conducted national representative survey in Indonesia. From this survey about 60,000 corneal and 1.3 million noncorneal cases of xerophthalmia were calculated to occur annually in this one country (21), and 500,000 corneal and 4–8 million noncorneal xerophthalmia cases annually in four South and East Asia countries (India, Bangladesh, Philippines and Indonesia). Further, globally 13 million children were estimated to be overtly deficient (xerophthalmic) with another 40–80 million at risk of subclinical deficiency (22).

Recognizing that health consequences occurred before clinical eye signs, WHO in 1995 redefined VAD to include tissue depletion below which functional impairment was likely. The prevalence of low serum levels (≤0.7 μmol/L) of vitamin A was used as a population-based indicator of health risks (23). By the end of the decade, 140–250 million preschool age children were estimated to be at risk of vitamin A deficiency disorders (VADD, clinically deficient and subclinically at risk), including 3 million who annually have clinical signs (24). Progress in implementing broad coverage interventions—primarily high-dose vitamin A supplements—in the last two decades undoubtedly has reduced the magnitude of VADD, but documentation awaits postintervention surveys of serum distribution levels that show impact.

Abbreviations used: IVACG, International Vitamin A Consultative Group; NHANES, National Health and Nutrition Examination Survey; RDA, Recommended Dietary Allowance; RDR, relative dose response; USAID, United States Agency for International Development; VAD, vitamin A deficiency; VADD, vitamin A deficiency disorders.
What accounted for accelerated efforts to purge the “pox”?

**Committed scientists.** Before 1974, there was little coordinated global commitment toward elimination of the vitamin A "pox" that had plagued society since ancient times. A few committed clinicians, nutritional biochemists and public health workers, even several WHO World Health Assembly Resolutions, were unsuccessful in attracting substantial attention and resources for actions to rid societies of VAD. In 1974 a joint WHO/United States Agency for International Development (USAID) meeting to consider priorities for research and action programs to combat vitamin A deficiency and xerophthalmia brought together concerned nutritionists, pediatricians, ophthalmologists, UN agencies, nongovernmental organizations and private industry (25). Dr. Olson at this time had completed his time at Mahidol University in Thailand with the Rockefeller Foundations and was in Brazil continuing work for the Foundation. He was among the small number of nutritional biochemists invited to the Jakarta meeting in recognition of his biochemical expertise in vitamin A nutrition, experiences with assessment methodology in rats and humans, and exposure to human deficiency problems in Southeast Asia. The Jakarta gathering was a stormy meeting with strongly expressed opposing views between biochemists, ophthalmologists and clinicians. Program implementers sat in shock that there were such dissimilar points of view among scientists. At issue were criteria for classifying xerophthalmia (e.g., was night blindness a primary or secondary indicator under field-survey conditions); prevalence of cut-off values for each ocular sign as indicative of a public health problem; validity of ocular and biochemical assessment indicators; nonocular health consequences of inadequate vitamin A status; and effectiveness/efficacy of different interventions strategies. WHO did produce a meeting report (25) that included a summary of current knowledge on chemistry and metabolism, available assessment methodologies, epidemiology of the problem and available intervention programs. Research priorities were also set forth to resolve outstanding controversies prominent in the meeting that were limiting progress in eliminating the VADD "pox."

The following year (1975) USAID formally established the International Vitamin A Consultative Group (IVACG) to provide a forum for information exchange across professions and programs and to produce task force reports on issues relevant to moving forward in controlling VADD. Dr. Olson was a charter member and very active in preparing many of the early reports (26). He continued his contributions to IVACG publications, including the 1999 review entitled "The Bioavailability of Dietary Carotenoids: Current Concepts." In addition, Dr. Olson missed few IVACG meetings and was called upon frequently for an update on biochemical advances relative to the continuing global public health problem. He was preparing a background paper for the 25th anniversary meeting of IVACG celebrated in Hanoi, February 2001 when his untimely death occurred.

Following the 1974 seminal meeting in Jakarta and the formation of IVACG, researchers from 1975 to the early 1990s went to their bench and field laboratories to implement carefully designed studies aimed at resolving controversial issues. The 1975 national survey in Indonesia improved knowledge of the regional magnitude of the problem, and epidemiological studies that followed over the next several years showed associations with morbidity and mortality (21). However, Sommer (an ophthalmologist/epidemiologist) and colleagues shocked the scientific world with their public announcement published in 1986 of a 34% reduction in child mortality in Aceh, Indonesia by giving 200,000 IU vitamin A concentrate at 6 mo intervals (27). (In the 1974 meeting the ophthalmologists generally viewed vitamin A deficiency as an ocular problem with little or no nonocular health consequences!) Some biochemists (myself among them), based on VAD animal studies, firmly believed in nonocular health consequences of VAD, but disbelieved that a single nutrient “magic bullet” could have such a profound effect in the midst of unrelenting chronic undernutrition, poverty and social deprivation. The Aceh report stimulated vitamin A researchers to design replication trials in other settings. Many of us were certain we would validate our skepticism, but later had to reevaluate positions as earlier anecdotal observations in human populations were replaced by findings from well-designed randomized controlled community intervention trials.

**Mortality reduction.** Early in 1990, randomized intervention studies using vitamin A supplements and evaluating morbidity and/or mortality impacts had been completed. Variable results were reported. Beaton et al (28) summarized sixteen studies and determined that seven, in addition to the Aceh study, were appropriate for a meta-analysis to determine if reduced childhood mortality could be expected by restoring adequate vitamin A status to deficient children. The analysis concluded that on average a 23% reduction could be expected, but that variation based on program area context could be considerable. Further, the analysis related the positive effect to restoring vitamin A status in amounts approaching the RDA either by daily or weekly low doses or by periodic medicinal high doses. This finding opened doors to a variety of intervention strategies that could be adapted to the community setting according to the context and available resources, e.g., food-based approaches through fortification and/or increasing intake of natural food sources. Similar meta-analyses corroborated the conclusions (29,30). Mortality reduction was real though variable in magnitude!

**Assessment indicators.** An early IVACG task force, on which Dr. Olson participated, clearly advocated use of serum retinol distribution curves for evaluation of program effectiveness, while recognizing the inadequacy of serum levels for individual assessment of vitamin A status (31). Other assessment tools clearly were needed. Liver reserves of vitamin A were recognized as the best indicator of status but of course, not ethical or feasible to obtain for living population assessment. Postmortem liver analyses were suggested as a surrogate for identifying areas and population groups at risk. Dr. Olson provided assessments of this type from Thailand (32,33), Brazil (34) and the US (35) but there were problems in acceptance and routine use of this assessment approach.

To overcome deterrents to direct liver analyses, a more feasible indirect indicator of liver reserves was proposed based on early studies from DeWitt, Gourley’s laboratory and mine. The RDR test, which we called the relative dose response (RDR) test, was developed in rats from a series of observations of factors influencing homeostatic control over blood levels of vitamin A (37–39). The RDR as an indirect measure of critically depleted liver stores was evaluated among Brazilian preschool age children suspected to be subclinically deficient before receiving a vitamin A supplement and periodically for six months after supplementation (40); to evaluate the affect of an unexpected infection on depletion of vitamin A stores (41); and in repeated surveys to determine how many rounds of six monthly distributions of high-dose capsules were needed to restore population distribution curves to that of apparently nondeficient populations (42). Dr. Olson, with colleagues at Iowa, validated the RDR test in human surgical patients from whom liver biopsies also were analyzed (43,44).
Although the RDR test proved valid, logistical limitations were encountered in field studies because it required two blood samplings with an intervening five-hour wait. It is challenging to keep young children and their mothers under surveillance and entertained for five hours. The group in Iowa modified the RDR procedure to provide a fasting tracer dose of a naturally occurring vitamin A derivative, i.e., didehydroretinol (Vitamin A₂), in the home, thus eliminating a baseline blood drawing and limiting to sampling only once after five hours (45). This modification was more field-friendly for use with children, although technically more laborious and costly for obtaining the tracer, and it required sophisticated analytical instrumentation (HPLC). Other assessment procedures also emanated from Dr. Olson’s laboratory, including isotope dilution and glucuronide metabolite excretion, both of which hold promise as reliable indicators for evaluating vitamin A status and biological impact and are discussed by others.

From the studies cited and many more not reviewed, it is obvious that from 1974 to 1990 a committed scientific community had removed many gaps in knowledge on researchable issues hindering progress in eliminating the “pox” through public health interventions. More advocacy was needed, however, to mobilize the global community’s resources toward large-scale public health actions.

Committed politicians

Political clout was needed to mobilize international and national resolve and resources. James Grant, Director of UNICEF in 1990 and a strong advocate for child health, was briefed on micronutrient control issues and the exciting data available from the vitamin A mortality and morbidity field trials. Micronutrients were placed on the agenda for the politically high level (ministerial and heads of state) Summit for Children hosted by UNICEF in NY, September 1990. At last the attention of politicians was captured and commitments were made at the Summit for virtual elimination of VADD by the end of the decade. Important to successfully recruiting Mr. Grant as advocate for political commitment to reducing vitamin A deficiency was the convincing scientific-based evidence for magnitude, public health consequences and available cost-effective interventions to support his call for action. Subsequent international policy-setting meetings in 1991, 1992 and 1996 reinforced the micronutrient deficiency reduction goals, and resources began to flow into global intervention strategies (46).

Committed program implementers

High-level international and national commitments and policies must become relevant actions at country level for impact on child health and survival to occur. Affordable efficacious interventions were known in 1990 and awaited implementation for short and longer term curative and control programs (47).

Periodic supplementation. To rapidly respond, many countries accepted external donor pressures to distribute high-dose vitamin A capsules periodically. Donors were willing to subsidize purchase of capsules and national governments were agreeable to their health workers providing support for distribution. Coverage rates, low and inconsistent in the early days, reached levels up to 90% when a link was made to the campaign approach of the WHO expanded program of immunization (48). Fortunately for the successful polio eradication campaign, these annual immunization days are scheduled to stop in the near future. However, this leaves countries to find alternative affordable approaches for twice-yearly delivery of capsules sustaining the coverage levels reached earlier. Some countries already have met the challenge by establishing twice-yearly micronutrient days or finding ways to integrate the activity into routine health programs.

Progress dependent primarily on supplement distribution, however, can be fragile. For example, Indonesia had made significant progress declaring itself xerophthalmia free and assumed full financial responsibility for integration into the national health program (49). The recent economic decline and even more recent civil unrest, however, interrupted programs and led to a reappearance of xerophthalmia. This country experience illustrates that consistent periodic capsule distribution can control VADD, but sustained control is fragile when not underpinned by other measures that concurrently address underlying constraints to achieving adequate diets, reducing frequent infections and combating socio-economic underdevelopment (47).

Food fortification. Attention of external agencies and donors recently has turned toward expanding access to fortified foods. As noted earlier, this has been a successful sustainable strategy in industrialized countries (19) and some countries in mid-level development status. An often-cited model for VADD control is progress in control of iodine deficiency by iodized salt universally mandated. Iodized salt has reached even remote areas in less developed countries (24). Comparable condiments or single foods with the characteristics necessary for mandatory fortification are more difficult to identify for vitamin A. Guatemala is exemplary as a country with over three decades of experience with a mandated vitamin A sugar fortification program documented to be effective in raising vitamin A status of the population (50). The mandated program in Guatemala, however, has experienced a rocky political road. It was disrupted for a few years for economic and political reasons, reinstated around 1990 and even today continues to struggle to remain a government-mandated program. Stoppage of the program was soon followed by a decline in vitamin A status throughout the country that was reversed when the program was reinstated. It is too early to predict the sustainability and impact of newly created fortification programs in less developed countries that lack an established infrastructure for monitoring, quality control and enforcement.

Dietary quality and diversity. Most give lip service to food-based programs linked to production and consumption of vitamin A-dense foods in a varied diet as the most sustainable intervention with wide-ranging benefits for health. Food-based interventions, however, have received inadequate attention and resources, in part because of the widely held view that they require difficult to change eating behaviors too labor intensive and too costly for mass scale application. The strategy also involves linking agriculture to nutrition and health education, and with gender considerations, which are particularly important in developing countries (51). There have been successful experiences that claim biological impact and have been sustained for at least ten years of follow-up (52), but most food-centered programs are criticized for not being rigorously evaluated. Evaluation of a community food-based approach is costly and difficult due to multiple potential co-founders in free-living communities that defy rigorous control. Among communities deriving most vitamin A activity from plants, some question whether VAD can be controlled due to limited bioavailability from green leafy vegetables (53). Notwithstanding such variability, recent studies demonstrate that body stores of vitamin A are retained, though not substantially increased, in children consuming predominately mixed vegetable diets, including green leafy vegetables (54,55).
At IVACG meetings, as well as at Experimental Biology, Dr. Olson strongly supported the benefits associated with carotenoid-rich diets. He lamented the fact that the IVACG meetings in recent years downplayed food-based interventions and he organized breakout groups to provide a forum for information exchange among those with similar interests. These sessions were well attended, participants always feeling they had learned from Dr. Olson’s excellent leadership of sessions. Unfortunately, his absence from the most recent IVACG meeting was evident by the absence of such a forum, in part due to a change in meeting format that only allowed breakout groups to meet over dinner at a local restaurant—hardly a milieu conducive to substantive information exchange. Interestingly, the participants’ call from the meeting floor was for future IVACG meetings to give greater emphasis to food-based interventions.

Scientific evidence is accumulating to substantiate earlier anecdotal and experiential reports that food-based approaches are effective, sustainable and worthy of their share of donor-agency support. The UN General Assembly Special Session on Children was held in New York City May 2002. The session report is titled “A World Fit for Children.” Paragraph 22 of the draft action plan provided a timely opportunity to reframe the call for the virtual elimination of VADD using a combined approach of dietary diversification, food fortification and supplementation, while recognizing also the importance of disease control and poverty reduction to sustained elimination of the “pox” by 2010.

**CONCLUSION**

Slow progress in overcoming the VADD “pox” that plagued humankind through millenniums to the 1990s has yielded to accelerated progress in the last decade. Renewed international political commitment occurred at the UN General Assembly Special Session on Children May 2002. With continued commitment by all the players, scientists, politicians and program implementers, and with allocation of necessary resources, “A World Fit for Children” free of the VADD “pox” is possible. James Allen Olson’s contributions toward this goal will long be remembered through his scientific work and that of the students and colleagues, including me, for whom he served as role model and mentor.

**LITERATURE CITED**