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# Vitamin A Deficiency and Clinical Disease: An Historical Overview[1,2]

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## Abstract

Vitamin A deficiency has a plethora of clinical manifestations, ranging from xerophthalmia (practically pathognomonic) to disturbances in growth and susceptibility to severe infection (far more protean). Like other classical vitamin deficiency states (scurvy, rickets), some of the signs and symptoms of xerophthalmia were recognized long ago. Reports related to vitamin A and/or manifestations of deficiency might conveniently be divided into ''ancient'' accounts; eighteenth to nineteenth century clinical descriptions (and their purported etiologic associations); early twentieth century laboratory animal experiments and clinical and epidemiologic observations that identified the existence of this unique nutrient and manifestations of its deficiency; and, most recently, a flowering of carefully conducted clinical studies and field-based randomized trials that documented the full extent and impact of deficiency among the poor of low- and middle-income countries, which in turn changed global health policy. J. Nutr. 138: 1835–1839, 2008.

## Xerophthalmia

Xerophthalmia is the quintessential expression of vitamin A deficiency (1,2). Under conditions of gradually worsening vitamin A status, the eye undergoes a series of changes, beginning with night blindness (the inability to see under low levels of illumination). This reflects the essential role retinol plays in the formation of rhodopsin, the visual pigment essential to the retinal receptors responsible for dark adaptation (3,4).

The Eber's Papyrus describes night blindness in ancient Egypt. Physicians treated the condition by squeezing the "juices" of a grilled lamb's liver into the eyes of afflicted patients. In 1971, George Wolff speculated that these topically applied "drops," rich in retinol, probably drained into the lachrymal sac, where they were absorbed into the systemic circulation and thereby reached the retinal cells (5). Perhaps that was the case, but I observed the treatment of a young boy in rural Indonesia that was described in exactly the same fashion, but provided a more direct explanation for the way in which "liver juices," applied topically, could reach the back of the eye. At the conclusion of the ceremony, after juice from a goat liver had been squeezed onto the boy's eyes, the traditional healer fed the child the remaining liver! The healer did not consider eating the liver part of the treatment; he fed the child the liver so as not to waste precious food (6).

## 18th and 19th centuries

Cases of xerophthalmia were described throughout the 18th and 19th centuries. "Night blindness" was apparently common and a variety of cures recommended. These ranged from incarcerating the sufferer for 1 mo or more in a darkened room to the administration of cod liver oil (7). Hubbenet and his colleague, Bitot (8,9), independently recorded the association between night blindness and small foamy white spots on the outer aspects of the conjunctiva. Although Hubbenet published first, these classical lesions became known as "Bitot's spots." They represent keratinizing metaplasia of the conjunctiva, a piling up of dead, keratinized squamous epithelial cells, and an overgrowth of gram negative rods (so-called xerosis bacilli) (1,10). Vitamin A, it would subsequently be discovered, is essential for the differentiation of mucous-secreting epithelium.

More severe forms of vitamin A deficiency, xerosis of the cornea, corneal ulceration, and "keratomalacia" (a full-thickness melting of the cornea that progresses rapidly to loss of the eye), tend to occur in tandem with protein-energy malnutrition. Children suffering these maladies are often near death from severe malnutrition, diarrhea, and pneumonia by the time they receive treatment in a clinic or hospital (2). Most cases of xerophthalmia occurred in neglected children receiving poor diets, whether European orphans, peasants during the Lenten fast, or slaves from the north of Brazil (2).

The nature of the specific nutritional deficiency causing xerophthalmia began to emerge in the 19th century. As early as 1816, Magendie (11) caused "starvation" and corneal ulceration in dogs by restricting their diet to sugar and water.

## Early 20th century

It was not until the first 2 decades of the 20th century that systematic research on laboratory animals began to identify essential dietary components, which came to be called "vital

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amines" (subsequently "vitamins"). Hopkins, McCullum, and Osborne and Mendel (12–16) found that animals (and their even more deficient offspring) fed only fats, protein, starch, and inorganic salts failed to grow normally, became susceptible to infection, and often died of overwhelming sepsis. Only those animals that survived the longest developed ocular inflammation and corneal ulceration (17). Administration of accessory factors present in dairy products and cod liver oil prevented these conditions. McCollum termed this critical factor fat soluble A (14).

Bloch (18–20), studying the growth and development of children in a Danish orphanage, found that those children fed generous portions of butterfat and whole milk grew better than their less fortunate colleagues, were less susceptible to infections (of the urinary and respiratory tracts and middle ear), and were less likely to develop xerophthalmia. He and McCollum independently recognized that the laboratory animals, and the affected children, were suffering from the same constellation of symptoms, brought on by deficiency of vitamin A.

By 1928, Green and Mellanby (21) had declared vitamin A an antiinfective factor. A series of trials were mounted to treat (and occasionally prevent) a wide variety of infections with vitamin A (2,22–24). In one of the most important studies, Ellison (25) administered daily vitamin A to one-half of the cases of measles admitted to the Grove Fever Hospital outside London. Those given vitamin A had only one-half the case-fatality rate of those restricted to standard therapy.

Thus, by the early 1930s, the cause of vitamin A deficiency and its clinical manifestations, including impaired growth and reduced resistance to (some) microbial infections, had been worked out. Vitamin A was finally crystallized in 1937 (26).

At this point in time, further investigations on (and advocacy for) the administration of vitamin A to treat and prevent infections virtually stopped. It is likely that a number of issues accounted for this loss of interest in the prevention of vitamin A deficiency and its associated clinical manifestations.

Although investigators claimed vitamin A could treat or prevent a variety of infections from puerperal sepsis to the common cold, the poor quality of many of the trials and the lack of appreciation for the context in which they were conducted (the nutritional status of the study subjects, the nature of the infectious agent, etc.) resulted in seemingly conflicting results (23,24). Sulfa-based antimicrobials that became available before World War II, and antibiotics afterwards, were dramatically more effective for the treatment of acute infections than vitamin A had been. Finally, improvements in the nutritional status of wealthy nations caused clinical vitamin A deficiency (particularly xerophthalmia) to virtually disappear; from then on, most clinical interest and reports emanated from "the colonies," eliciting little interest on the part of mainstream medical investigators. McLaren, a central figure in human nutrition research, claimed that in 1980, "it was generally assumed [...] each vitamin served one particular function; [for] vitamin A, [it was] the eye" (27).

## Late 20th century

Although nutrition and infectious disease experts occasionally called attention to the potential antiinfectious properties of vitamin A (28), interest in the 1960s–1980s was primarily focused on elucidating the biochemical pathways governing vitamin A absorption, storage, distribution, and action (29–31). The existence and properties of cellular and nuclear receptors, the conversion of carotenes to retinol, and the role that vitamin A plays in regulating gene function remain topics of continuing discovery and interest.

When nutritionists and physicians turned again to the clinical importance of vitamin A deficiency, as they did at an international meeting in 1974 convened by WHO and the U.S. Agency for International Development, they noted the increased mortality associated with xerophthalmia but stressed the public health importance of blinding xerophthalmia in the developing world (32).

Interest in the systemic consequences of vitamin A deficiency increased following the observation that Indonesian children with "mild" xerophthalmia (night blindness, Bitot's spots) died at far higher rates than their nonxerophthalmic peers. We estimated that preventing all xerophthalmia (and its associated vitamin A deficiency) would reduce the mortality of young Indonesian children by 16%. In addition, the monotonic relationship between mortality rates and the severity of xerophthalmia suggested that even "subclinical" deficiency (unaccompanied by ocular changes) might be associated with increased mortality as well. If so, then the reduction in overall mortality that might accompany prevention of all significant vitamin A deficiency might be much greater (33). This article was virtually ignored.

The first large-scale randomized field trial of the impact of 200,000 IU vitamin A (60 g) supplementation every 6 mo on subsequent child mortality in Aceh, Indonesia, was published in 1986 (34). Although the results, a 34% reduction in mortality among children 1–5 y of age, received considerable scrutiny and skepticism, it sparked interest in replicating the trial in other populations, using other schemes for improving children's vitamin A status (fortification of monosodium glutamate, dosing children with an appropriately sized supplement once every week or every 4 mo) (2).

Unlike laboratory studies, large-scale field trials are sensitive to political disturbances. The first replication trial was launched in the Philippines. Although it survived the overthrow of the Marcos regime, hostilities between the central government and local leftist insurgents forced the study from the field. It was moved to Nepal (35). Similarly, the principal investigator of a trial in the Sudan was blocked from visiting the country during data collection.

All but 2 of the 8 major trials generally cited demonstrated a clinically and statistically significant reduction in all-cause mortality among children 6 mo to 5 y of age (2,36) (**Fig. 1**). In the 5 (of 6) Asian trials, the level of impact was surprisingly similar: a reduction in mortality of 29–54%. Most of the deaths

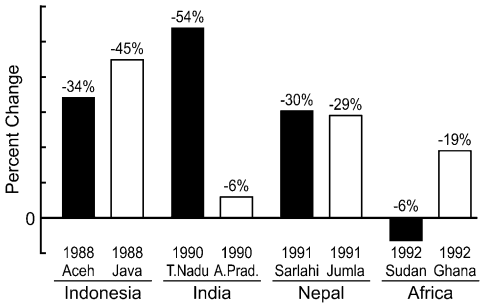


**FIGURE 1** Impact of vitamin A on mortality. Relative mortality among children 6 mo–5 y of age randomized to receive periodic large-dose vitamin A supplementation. Eight major randomized clinical trials, 6 in Asia and 2 in Africa, randomized rural children to receive periodic vitamin A supplements at regular intervals. Six of the trials observed clinically and statistically significant reductions in mortality, 19–54%, compared with controls. Reproduced with permission (2).

prevented were associated with measles and diarrheal disease, not because the incidence of measles or diarrheal disease was reduced but because the clinical manifestations among those receiving vitamin A supplements were less severe (2,37–39).

Presumably, vitamin A supplementation increased resistance to (the severity of) infection by reducing the functional degree of vitamin A deficiency. Indeed, the studies with the lowest impact (including Aceh, at 34%) dosed the children least frequently. Previous work demonstrated that only 50% of a large oral dose of retinyl palmitate was retained and serum retinol levels returned to baseline after 12–14 wk (2,40). The greatest reduction in mortality was observed in an Indonesian study that employed monosodium glutamate fortification (thereby providing subjects with daily, small doses of vitamin A) and an Indian study in which the children received a small dose once a week (reductions in mortality of 45 and 54%, respectively) (41,42). Relatively small doses of vitamin A (a recommended daily allowance every day or 7 recommended daily allowance weekly) are almost entirely absorbed and retained and therefore more likely to result in a sustained increase in vitamin A status and serum retinol. Nonetheless, periodic dosing with a large dose [100,000–200,000 IU (30–60 mg) once every 4–6 mo] does reduce childhood mortality and the incidence of new cases of xerophthalmia throughout the postdosing interval (43). Clearly, the duration of benefit of periodic vitamin A supplements persists (although not necessarily to the same degree) longer than might be expected from its impact on the serum level of retinol.

Following the Aceh study, a parallel question was addressed: was vitamin A deficiency responsible in part for the large number of measles deaths (and corneal destruction) observed in African children and might treatment with vitamin A reduce measles case fatality? Studies in several countries, particularly Tanzania and South Africa, showed that it could, by roughly the same 50% that Ellison (2,44,45) had observed in London. Embarrassingly, when we published the first of these trials (44) in the *British Medical Journal*, we were unaware of Ellison's earlier work, which had been published in the same journal 50 years before!

Soon after the vitamin A treatment trials were published, the United Nations Children's Fund (UNICEF) and WHO recommended the use of vitamin A supplements for the routine treatment of measles in populations in which vitamin A deficiency was likely (46).

By 1992, most large-scale mortality prevention trials and at least 3 measles treatment trials were completed. A meeting convened at the Rockefeller retreat in Bellagio reached consensus that vitamin A deficiency increased overall mortality, particularly from measles; improving vitamin A status would reduce overall mortality; and treating children already ill with measles with high-dose vitamin A was an effective means of reducing their risk of complications and death (47). This "Bellagio Brief," published widely, helped draw attention to the importance of vitamin A. UNICEF, USAID, and the Canadian government must be credited with moving vitamin A onto the global health agenda. National programs of varying effectiveness have been launched in over 70 countries and vitamin A "coverage" is now one of the core health indicators published annually in the State of the World's Children. By UNICEF's estimate, over one-half a billion vitamin A capsules are distributed every year, preventing 350,000 childhood deaths annually. Better coverage would prevent more deaths. The World Bank lists vitamin A supplementation as one of the most cost-effective of all medical interventions (48).

A simple, if important, practical problem was solved in 1980 when a tightly controlled hospital-based, randomized trial demonstrated that orally administered large dose oil-miscible vitamin A worked as rapidly, and effectively, in healing severe xerophthalmia and boosting serum levels of physiologically active retinol (holo-retinol binding protein) as an i.m. injection of a water-miscible preparation (49). It took over a decade before WHO recommendations fully reflected this simpler, more practical approach to the treatment and prevention of vitamin A deficiency.

Although vitamin A has finally taken its place as a major health intervention, we still do not precisely know how it increases resistance to infection, although there is ample clinical and laboratory evidence that it does.

Recent attention to other core issues, such as the efficiency of conversion of $\beta$-carotene to vitamin A, has enormous implications for combating deficiency. Ever since the 1974 WHO/USAID conference reignited global interest in the problem, there has been sharp disagreement about whether it can (and should) be solved solely through changes in the consumption of $\beta$-carotene–containing foods or requires some form of nondietary vitamin A supplementation (in the form of periodic dosing or fortification). For practical purposes of immediacy, most countries have embarked on supplementation programs. Increasingly, evidence suggests these will be required in the long term. Even wealthy populations that consume foods rich in preformed vitamin A (eggs, dairy products, liver) achieve their full vitamin A requirements with the help of supplements (50). Children who live in low-income countries rely almost entirely on the conversion of $\beta$-carotene in fruits and vegetables for their vitamin A. Recently, the Food and Nutrition Board acknowledged that the conversion of $\beta$-carotene to vitamin A was less efficient than had previously been thought: it requires not 6 but 12 molecules of $\beta$-carotene in the diet to make 1 molecule of vitamin A (51). As Blegvad (52) wrote over 80 y ago, "There are indications that human beings, in contrast to herbivorous animals, may not assimilate much fat-soluble A derived from plants."

Recent studies in the developing world suggest the rate of conversion is even less efficient, requiring 21 molecules of $\beta$-carotene from mixed fruit and vegetable diets to get 1 molecule of vitamin A (53). The implications of this discovery have not been fully appreciated. At these lower rates, Africa appears to produce only one-half the vitamin A it requires and Asia only one-third (**Fig. 2**). Before health officials can even begin to consider solving the problem of vitamin A deficiency through a change in

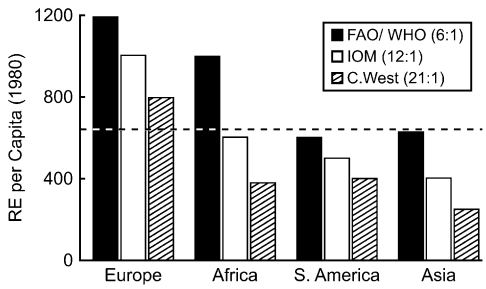


**FIGURE 2** Vitamin A in food supply. Adequacy of vitamin A in regional food supplies. Availability of vitamin A in the food supply is highly dependent upon the assumed rate of bioconversion of $\beta$-carotene. At the conversion level applied by the FAO (6:1), average per capita availability is adequate in all regions. At the conversion rate recommended by the Institute of Medicine (12:1), Asia and Africa are deficient in vitamin A. At conversion rates estimated from recent field studies (21:1), supplies in Asia, Africa, and South America are seriously deficient. Reproduced with permission (53).

diet, most of the world will have to drastically change its agricultural practices and priorities.

Interest in vitamin A, at both the molecular and clinical level, continues, with potentially important implications for global health policy. Recent studies, for example, have suggested that dosing expectant mothers in populations where deficiency is common and maternal mortality high can dramatically reduce the maternal mortality ratio (54) and dosing newborn infants with 50,000 IU (15 mg) vitamin A within 2 d of birth, can significantly reduce neonatal mortality (55–57).

Although vitamin A was one of the first "accessory" factors to be identified by nutritional research, our understanding of its role in human health is still evolving.

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