Perspectives in Nutrition

Xerophthalmia

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It is hoped that Perspectives in Nutrition will review the literature selectively, interpret it moderately and present a spectrum of ideas that will serve as a continual stimulation to nutritional research applied to medical problems.

Known in antiquity, its association with defective diet recognized for more than one hundred years and specific treatment in the form of synthetic vitamin A readily available during the past two decades, xerophthalmia today, in certain parts of the world, takes a greater toll of sight and life in infants than ever before.

The medical nutritionist today may rightly be proud of the scientific knowledge at his disposal, but his miserable failure to eradicate nutritional deficiency disease makes him an inadequate artist. Because of the attention lavished upon kwashiorkor (protein malnutrition of infants) in recent years, interest in other deficiency diseases has suffered an eclipse; this has been particularly true of xerophthalmia. Following are two instances of this general attitude. Throughout the Fifth International Congress on Nutrition in 1960 no mention was made of xerophthalmia although one of the plenary sessions purported to cover the worldwide problems in human nutrition. Even more disheartening was the failure to give nutritional blindness any place at all in the accounts appearing in the medical and lay press of the world to mark the World Health Day theme for 1962 "Prevention of Blindness." The fact that WHO is currently engaged in a three-year program aimed at the prevention of xerophthalmia adds poignancy to the feelings of frustration of those who are trying to make the facts known.

In North America and Europe only occasionally is a case encountered nowadays, usually as the result of mismanagement of a problem of infant feeding, although xerophthalmia was not uncommon up until the time of the first world war. The virtual disappearance of xerophthalmia from these countries and the knowledge that there is a cure seem to have led to a complacent attitude with regard to what is happening elsewhere in the world. In areas in which the disease continues to be commonplace there is also widespread apathy, but for quite a different reason. The frequency with which the eyesight has already been irrevocably destroyed by the time the child is brought to a hospital engenders a fatalistic attitude in physicians and parents alike.

GLOBAL DISTRIBUTION

The map (Fig. 1) indicates the parts of the world in which infant xerophthalmia constitutes a problem of public health significance. In certain "black spots" this may mean that as high a proportion as 1 per cent of all infants born have some residual corneal damage which may interfere with vision—if it does not cause actual blindness.[1,2] In these same areas about 25 per cent of the children affected in this way fail to survive.[3,4] Lesser degrees of vitamin A

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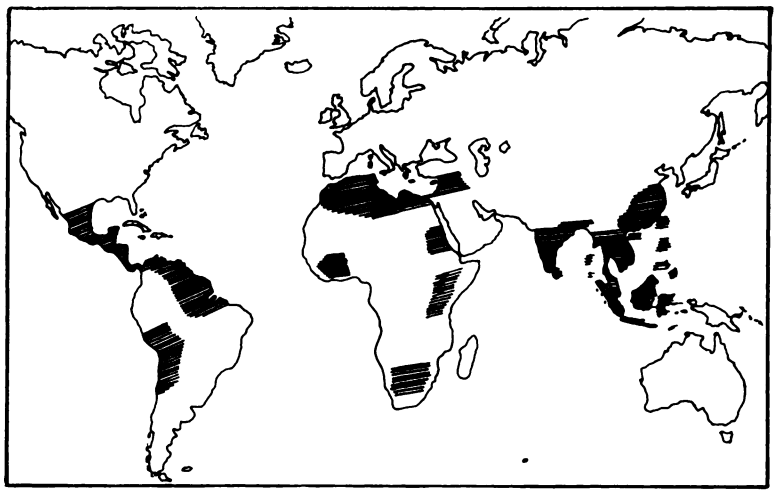

FIG. 1

deficiency in the remainder play an ill-defined, although undoubtedly important, role in producing susceptibility to infectious disease. For example, previously unpublished data from this department show that in thirty consecutive cases of gastroenteritis in Lebanese infants the mean serum vitamin A level was only 7.7 μg. per cent. The lower limit of normal is approximately 20 μg. per cent. Only one of these infants had xerophthalmia, but all were clearly suffering from vitamin A deficiency.

Xerophthalmia is most common in the countries of South and East Asia. The only exception is Japan where rapid industrialization and economic advance throughout the country have led to the disappearance of what was the major cause of blindness half a century ago. The best information comes from India, Malaya and Indonesia. On the island of Java, with an estimated population of about 65 million, in one eye hospital alone as many as 11,000 cases of xerophthalmia and keratomalacia were seen in the twenty years before 1954.

Xerophthalmia was widespread in pre-Communist China. The greatly increased population coupled with the problems of food shortage in recent years would suggest that there has been no improvement in the situation there. The densely populated parts of Central America and some of the less favored and less developed areas of South America have an infant xerophthalmia problem comparable in nature and magnitude with that of the Asian countries.

In the dry cultivation steppe areas of Africa, south of the Sahara—especially Central Tanganyika, Sudan, Northern Nigeria and Basutoland—and in most of the North African littoral and countries of the Middle East xerophthalmia is common. Sources of vitamin A are not readily available and in any case tend to be omitted from the infant's diet. It frequently accompanies the marasmus precipitated by measles and the gastroenteritis of "summer diarrhea." The high incidence of trachoma and purulent conjunctivitis in these parts obscures the role of malnutrition in causing blindness.

Excluding Communist China, because data are not available, it has been computed that approximately 20,000 infants go blind every year from xerophthalmia.[5]

EPIDEMIOLOGY

Environmental Factors

The various adverse influences in the environment operating at different age levels are shown in Table 1. The basic and constant element is the inadequate dietary intake of vitamin A either as the vitamin itself or as the provitamin. The situation giving rise to this, which is common to all parts of the world in

TABLE I
The Age Spectrum of Vitamin A Deficiency

Stage	Pathogenic Factors	Manifestations
Pregnancy	Basic diet low in vitamin A (mostly carotene) Increased requirements Food taboos Strain of repeated pregnancies Urbanization = lack of green foods	Low plasma vitamin A Low liver stores Bitot's spots, occasional Xerophthalmia, rare
Fetus		Low liver stores Xerophthalmia, rare ? abortion ? congenital malformations
1st year of life	Breast milk, low concentration Breast milk, diminished volume Artificial feeding Dyspepsia Maternal neglect Infections	Lowered plasma vitamin A Depletion of liver stores Xerophthalmia and keratomalacia, relatively common Xerosis conjunctivae and Bitot's spot, rare
2–5 years	Prolonged breast feeding Supplementation with foods low in vitamin A Deposed child situation Infections Dyspepsia	Peak incidence of xerophthalmia and keratomalacia Xerosis conjunctivae and Bitot's spot, not uncommon Fundus changes
School age	Diet low in vitamin A (mostly carotene), fat and protein Infections	Xerosis conjunctivae and Bitot's spot predominate Night blindness Fundus changes
Adult	As above plus special privation (famine, prison)	Night blindness predominates Bitot's spot, occasional Keratomalacia, rare

which the problem exists, is lack of knowledge of correct infant feeding practices exemplified by the use of rice or other cereals deficient in carotene as a supplementary food for infants. In areas in which population pressure is greatest, i.e., Asia, Latin America, and the large conurbations in parts of Africa and the Middle East caused by detribalizing influences and the flocking to the towns of unskilled laborers, the factor of "landless poverty" is super-added. This concept pictures the displaced family, growing rapidly in size despite the high infant mortality and morbidity, surviving precariously on income from the casual labor of its older members, often including the mother. It has no land on which to grow its own food and therefore will tend to subsist on the satiety-producing cereals to the neglect of vitamin-containing vegetables and fruits. The increasing attraction of consumer goods and proprietory foods aggravates the problem. The tragedy is that many of these places are among the greenest on earth, but the natural nutrients are not generally available—poverty in the midst of plenty.

In the arid rural areas of Africa, the Middle East and South America (notably north east Brazil), the same end result is produced by a combination of incorrect infant feeding practice and sheer lack of carotene sources in the environment for most of the year. Here improvement in agricultural methods would make a notable contribution but, as elsewhere, infant feeding remains crucial.

Age

In both man and animals vitamin A deficiency has its greatest effect on the young. Table I shows the age spectrum of the disease in man and it will be seen how, except under exceptional circumstances, all the serious complications occur early in life. For all practical purposes, the problem of xerophthalmia is confined to the infant, closely resembling kwashiorkor in this respect.

Sex

In general the male is more susceptible than the female. For xerophthalmia there appear to be two quite distinct attack rates by sex, a low one for the preschool child (1.4 male:1.0 female) and a much higher one after about ten years of age (6.0 male:1.0 female).[2] The larger sex difference applying to the older age groups is also true for night blindness. Bitot's spots are two or three times as common in males as in females.

The occurrence of keratomalacia during the first two years of life, however, affects the sexes equally. The fact that the sexes tend to start extrauterine life with equal levels of the vitamin in the serum may be significant.

PHYSIOLOGY

Vitamin A is an essential nutrient for all vertebrates, as far as is known, but requirements may also be met, with the known exception of the cat, by ingestion of various carotenes

of which beta carotene is the most efficient. Conversion takes place in the intestinal wall. Infections impair absorption, and "summer diarrhea" of multiple etiology has already been mentioned as a potent precipitating factor in the development of infant malnutrition of which xerophthalmia is a not infrequent feature.

The vitamin is absorbed in the form of higher fatty acid ester through the lymphatic system and is carried in the low density S_f 10–100 lipoproteins to be deposited in the liver. Nearly all the circulating vitamin A in the plasma is in the form of the alcohol. In severe cases of kwashiorkor the depression of serum protein, in particular the albumin or closely related fraction, may lead to immobilization of liver stores and impaired utilization of the vitamin given therapeutically. Consequently, as deficiency of protein and vitamin A so frequently coexist, treatment should be aimed at their simultaneous correction.

The well known vitamin A-sparing effect of vitamin E may be of considerable importance, especially as vitamin E serum levels tend to be low even in healthy infants.

CLINICAL FEATURES

The eye is the organ most characteristically involved in vitamin A deficiency. The retina is first affected and impairment of scotopic vision, as revealed by rod scotometry and dark adaptometry, is the earliest evidence. Reversible structural damage to the retina, accompanying changes in the anterior segment, has also been described.[6] Only when blood levels of the vitamin approach zero and liver stores have been exhausted is the anterior segment of the eye affected—first the conjunctiva and then the cornea. The conjunctiva of the bulb becomes progressively dry or xerotic, thickened and wrinkled, sometimes with deposition of pigment and heaping up of foamy patches of keratinized epithelial cells (Bitot's spots) in the interpalpebral fissure. None of these signs alone should be regarded as indicative of vitamin A deficiency,[7] but the presence of them all—true xerosis conjunctivae—is highly suggestive.

Xerosis corneae consists of the drying up of the precorneal film, keratinization of the corneal epithelium and infiltration of the stroma, giving the cornea a dry and hazy appearance. Together xerosis conjunctivae et corneae constitute xerophthalmia, with no deformity of the cornea, and respond dramatically to therapy with large doses of vitamin A. At this stage ulceration is common and if it extends into Bowman's membrane scarring will result. In the untreated case it is not long, perhaps only a matter of hours, before the cornea becomes deformed as the result of a distinctive softening process that has been called colliquative necrosis. When this has occurred, the final stage—keratomalacia—has been reached and even with prompt and adequate therapy, there will be at least some scarring and deformity of the cornea. Much more likely, the damage will be greater with total loss of sight from panophthalmitis with such complications as incarceration of the iris, extrusion of the lens, loss of vitreous, leading eventually to phthisis bulbi.

While the ocular lesions of vitamin A deficiency are the best-defined and most serious, it must not be forgotten that the body as a whole is affected, as evidenced by retardation of growth, marked marasmus and high mortality. Many epithelial tissues besides those of the eye undergo keratinization, but the importance of vitamin A deficiency in such conditions as hyperfollicular keratosis, urinary lithiasis and respiratory and pancreatic disease is uncertain.

PATHOLOGY

The characteristic change, keratinizing metaplasia, affecting not only conjunctiva and cornea but also the respiratory, alimentary and genitourinary tracts, consists of atrophy of the epithelium followed by proliferation by the basal cells of layers of keratinized cells. All affected epithelia, irrespective of their type or origin, tend to resemble that of the skin. Only the basal cells remain normal; therefore, when the vitamin is given they are able to begin producing normal cells again and eventually the pristine character of the epithelium is restored.

The cornea differs from all other tissues

affected, possibly because it is avascular under normal conditions, in that in the advanced stage of deficiency it virtually melts away when the little-understood process of colliquative necrosis supervenes. This liquefaction and dissolution of corneal tissue may possibly result from the removal of the protein-stabilizing influence that vitamin A appears to have[8] in a structure particularly susceptible to injury, inflammatory reaction and disturbances of metabolism because of its precarious nutrient supply. In the germ-free rat, corneal changes were minimal,[9] suggesting that secondary infection plays a part in the later stages of the human condition.

TREATMENT

Any degree of corneal haziness implies the possibility of permanent visual impairment and necessitates the institution of the maximum therapy with vitamin A. The potential danger of inducing the symptoms of hypervitaminosis A by administering massive doses to patients virtually devoid of the vitamin is negligible and must indeed be disregarded in the face of the disastrous alternative of blindness.

In general the administration of 100,000 I.U. of vitamin A daily for three days will initiate recovery in any true case of xerophthalmia. In practice, it is wise to divide the dose equally between intramuscular and oral routes; although the latter utilization is superior, only by the former can the physician be sure that the full dose has been administered. The vitamin is usually given as acetate or palmitate by injection and a potent concentrate from halibut or similar marine fish liver for oral use. Absorption is better with watery than with oily solutions. Carotene, obtained from red palm oil or any other rich natural source, will initiate cure despite statements to the contrary, but because of the possibility of impaired conversion and absorption it should only be used in mild cases or when the vitamin is not available. The practice still followed in some parts of the world of instilling cod liver oil directly into the eye must be condemned as unphysiologic and therapeutically totally inadequate.

In the absence of evidence of structural changes in cornea and retina less energetic therapy consisting of up to about 1 ounce of cod liver oil or its equivalent providing about 30,000 I.U. daily should be instituted. This is also satisfactory for maintenance treatment after the first three days in those severely affected.

In view of the frequent association of xerophthalmia with kwashiorkor in some areas, and because of the marasmus which accompanies nearly all the severe cases, special attention must also be paid to the diet to ensure adequate intake of protein, calories and fat.

PREVENTION

In considering the epidemiology of infant xerophthalmia the major problems of lack of knowledge of proper infant feeding and lack of vitamin A-rich sources in the environment and diet have been discussed. The explosive dimensions of the increase in world population going on at the present time and the rapid breakdown of long-established ways of life in the parts of the world in which infant malnutrition is most prevalent indicate that the situation is likely to go from bad to worse. Improvement in food production, greater literacy and better social services and other mitigating factors are unlikely to check this. The question that needs to be asked is "How long is it going to take parents throughout the developing countries to become actively desirous of incorporating foods into the diets of their infants which they have hitherto regarded as unnecessary or positively harmful?" On the other hand, is there any other approach than the conventional one possible? Certain special features about the present problem indicate that there may be.

(1) *Storage.* In the liver vitamin A is stored in healthy subjects in amounts that would in some cases meet the normal requirements over a period of several years. These stores are only slowly drawn upon when the diet is deficient and have to be completely exhausted before the destructive lesions of the eye supervene. While adequate vitamin A therapy restores blood and tissue levels to

normal in a matter of days, it has taken many months of deprivation both before and long after birth to give rise to the gross deficiency state.

(2) *Period of Susceptibility*. This extends from soon after birth until the third or fourth year. Almost all the cases of xerophthalmia and keratomalacia fall within this period. Thereafter, xerosis conjunctivae and night blindness are the usual manifestations.

(3) *Availability*. Vitamin A is readily available in concentrated form and is cheap.

(4) *Areas Affected*. Xerophthalmia as a serious public health problem is limited to a few areas.

With these factors in mind there would seem to be a distinct possibility that a large single dose of the vitamin of the order of several hundred thousand units given at birth, or shortly afterward, would be capable of raising stores to such a level that they would not be completely exhausted by the end of the susceptible period even though the dietary intake was low throughout. This is based on the assumption that the administration of repeated doses would be impracticable for all infants and if carried out through existing Maternal and Child Health Centers would reach only a small percentage.

A birth in a community, however, is an event of interest and importance and is usually noised abroad soon after it occurs. It ought not to be beyond the realms of practicability for someone in each community to be supplied with vitamin A capsules and to be responsible for seeing that each infant received these within a few days of birth. This person would require no special training, would best be someone in the confidence of the local headman and supervised by the local doctor, midwife or medical assistant. This presupposes an awareness of nutritional problems among these medical workers which, at present, does not usually exist. Training of personnel and implementation of a program against xerophthalmia must be part of an over-all attack on malnutrition from clinical and preventive points of view. In four areas of the world, geographically and ethnically distinct, in which malnutrition problems are most pressing—Southeastern Asia, Middle East, Africa South of the Sahara and Latin America—nutrition programs now in operation are capable of meeting these needs in each area.

At the present time the United Nations agencies distribute millions of capsules annually containing vitamin A. Mainly these go to pregnant women and school children—presumably because they can be easily reached, not because they are in special need. Close cooperation of these agencies with local nutrition programs in training and research would bring a breath of reality to this and many of their other activities.

FUTURE RESEARCH

Of prime importance is the need to develop preventive programs along the lines indicated herein during which we should (1) develop an accurate, readily reproducible, micromethod for the determination of vitamin A; (2) devise a simple field test to detect impairment of vision in the susceptible age group—the preschool child who is too young to cooperate in ordinary dark adaptation tests—the electroretinogram requires the administration of a general anesthetic for children, but the newly devised electrooculogram, or the opticokinetic reflex, offers possibilities; (3) the optimum form, medium and route for administering the vitamin to infants in need of it; (4) establish a safe and effective dose of vitamin A which, when given at birth, will protect against the grosser lesions of the eye throughout the susceptible period; (5) determine the role of infectious disease and, in particular, measles in precipitating xerophthalmia (it has recently been shown[10] that there is a constant, characteristic and minimal keratitis of measles and this reaction might become exaggerated in the cornea of the malnourished subject); (6) investigate the precise nature of colliquative necrosis and the part played by infection; (7) establish the characteristics of retinal changes and investigate the suggestion that vitamin A deficiency may be partly responsible for changes in the posterior segment in onchocerciasis; and (8) reinvestigate the pathologic changes in human vitamin A deficiency with modern technics.

The solutions to the first five are an integral

part of the onslaught on the disease. One would like to hope that we might never need to know the answers to the remaining three.

CONCLUSIONS

The road ahead leading to the eradication of xerophthalmia is a long and difficult one. The medical profession at large as well as the agencies and individuals with a concern for human welfare are barely aware that the problem exists and quite ignorant of its magnitude. The occurrence of the disease will have to be more precisely described and the corporate conscience stirred before government concern can be aroused.

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