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SYMPOSIUM ON VITAMIN A DEFICIENCY AND XEROPHTHALMIA

PRESENTED IN CONJUNCTION WITH

THE XI INTERNATIONAL CONGRESS ON NUTRITION

RIO DE JANEIRO, BRASIL

SEPTEMBER, 1978

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31 August - 1 September 1978

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FOREWARD

by

Dr. E.M. DeMaeyer
Chairman of the Symposium*

The present Symposium was convened within the framework of the 12th International Congress of Nutrition. The fact that more than half a day in a busy week was spent discussing Vitamin A deficiency is a sign of the growing interest and realization that this is a problem of great importance in public health. It is much more widespread than was believed only a few years ago. Few developing countries are in fact immune: most populacions living in those countries are in a state of hypovitaminosis A leading in some areas to keratomalacia and nutritional blindness. It is estimated that at least one million children develop keratomalacia annually: of this group, 900,000 die; the 100,000 survivors are blind. These figures are probably conservative estimates. This is tragic since keratomalacia is a preventable disease. Those who become blind begin to suffer from this handicap from an early age and in most cases are unable to learn any skills, and become burdens on their families and society. Xerophthalmia must unquestionably be considered as a serious public health problem requiring early attention. This has been recognized by such international organizations as the World Health Organization, UNICEF, and the World Food Council working in the field of health and nutrition.

The means of prevention are well known. The best method is obviously a change in the daily diet resulting in a greater vitamin A intake. One cannot reasonably expect that the intake levels of preformed vitamin A., i.e. retinol, can readily be increased since this would in most cases assume improvements in the socio-economic situation and in the purchasing power. Increases in carotene intake, however, can be readily achieved by family gardening and an increased consumption of green or yellow vegetables, fruits, and some edible tree leaves. It is well known that changes in dietary practices take a long time and that nutrition education is lengthy and tedious. As a shortcut or in emergency situations, the periodical administration of large doses of vitamin A to vulnerable groups of population has been proposed. Such distribution schemes are, in fact, carried out at the present time in several countries. Although it may be premature to conclude that they are completely effective in the prevention of blindness, there is no doubt that they improve the vitamin A status of the beneficiaries. The cost of such distribution schemes and the difficulty of reaching those children who are at greatest risk present major problems, however. An alternative to improved dietary practices is food fortification. Margarine and milk have been fortified for many decades in many industrial countries with excellent results. Sugar is now fortified with vitamin A in several Central American countries and trials are carried out with other food vehicles such as wheat flour and certain spices. Food fortification appears to be an effective measure of control, but it takes a long time before legislation can be passed and a project implemented.

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*Senior Medical Officer, Nutrition Research, World Health Organization, Geneva, Switzerland.

This Symposium, by providing the most recent information on the prevalence and geographic distribution of vitamin A deficiency and xerophthalmia, and on the methods of control and their results, will certainly be of great interest to anyone working in this field. It is hoped, also that publication of the papers and the discussion may help public health administrators and all those interested in the science of nutrition and in the improvement of man's condition to better control the disease by reducing its prevalence to negligible levels.

VITAMIN A DEFICIENCY: THE NATURE AND MAGNITUDE OF THE PROBLEM

by

Donald S. McLaren, M.D., Ph.D.
Reader in Physiology
University Medical School
Edinburgh, Scotland

A paper presented at the XI Congress of Nutrition, Rio de Janeiro, Brazil, August 26 - September 1, 1978

Xerophthalmia due to vitamin A deficiency is one of the major nutritional deficiency disorders affecting mankind at the present time. It is important to consider it at two levels. At the first level, that of the vitamin A deficiency itself, entire populations in many developing countries are affected to a varying degree. At the second level, that of severe deficiency resulting in blindness due to xerophthalmia, we are primarily concerned with the vulnerable groups of very young children, and to a lesser extent, pregnant and lactating women.

Vitamin A deficiency is unique among the major causes of blindness in that it carries a high mortality. Furthermore, it is a tragic and seemingly paradoxical fact that more than half a century after the discovery of the cause, xerophthalmia is still the major cause of blindness in young children throughout the world.

Apart from its blinding effects, very little is known about the damage to other organs caused by vitamin A deficiency in man. Extensive studies in experimental animals, however, have shown that the growth of bone and nervous tissue is impaired, infections, especially of the respiratory and urinary tracts, are very common, and congenital malformations occur in the young deprived of vitamin A in utero.

The economic and social consequences of xerophthalmia in man are enormous. We have no means as yet to estimate the contribution vitamin A deficiency may make to sterility, abortions, malformations at birth, and the problems known to be associated with low birth weight, but it is probably considerable. The young child with vitamin A deficiency is usually suffering from other nutritional deficiencies and various infections. Vitamin A deficiency is known to impair considerably the chances of survival of these already seriously ill children. Survivors from severe xerophthalmia at best have some impairment of vision, only occasionally corrected by corneal grafting, which will limit their ability to profit from education and to contribute in work and leisure to their community and nation. At most, and this is probably true of the majority, they are totally and permanently blind. The more fortunate few of these may be fitted for a limited contribution to society by education in one of the all too few blind schools existing in the developing countries at the present time. Most are to be found at home, where their mere survival is continually hazardous, a constant burden on their families and communities in circumstances where even the physically fit have difficulty in coping with their own problems in the struggle for existence.

Children between the ages of 1 and 4 years are most susceptible, and in them, the disease usually takes its most severe form. In highly endemic areas, older and younger children are also affected and occasional cases are seen in pregnant and lactating women and in other persons at special nutritional risk. Chronically undernourished children with repeated infections and those who suffer from the severe form of measles that is common in many developing countries are especially prone to xerophthalmia.

The diet of the mother and her young child is clearly of paramount importance in the pathogenesis of the disease. Animal sources of vitamin A itself are expensive and among lower socio-economic groups, the intake is mainly in the form of carotene precursors from plant sources such as fruit and vegetables, among which those of the dark green leafy varieties such as spinach are especially rich. Red palm oil used for cooking mainly in parts of Agrica is a highly concentrated source. If the dietary intake is low during gestation, the baby will be born with low liver reserves. Normally, the liver contains more than 90 per cent of the vitamin A in the body, which is sufficient to meet the requirements of adults on a vitamin A-poor diet for about two years, although the requirements are relatively greater during the years of rapid growth. Milk is never a rich source of the vitamin and is poorer still if the child is fed by a vitamin A-deficient mother. Growth, infections, and infestations frequently precipitated by artificial feeding increase the nutritional stress. These citcumstances are probably the rule among the poor of developing countries and yet xerophthalmia does not occur in the majority of mainourished children nor is it universally distributed. The crucial factor is undoubtedly the fitamin A content of the supplementary foods that are given. Rice is so satisfying to the child and so easy to prepare that it is frequently regarded as a complete food in itself for babies while other foods are considered optional. The low carotene content of most cereals when consumed in considerable amounts, is usually sufficient to prevent overt deficiency. Rice, although a good food in many other ways, is devoid of carotene. If a strain of rice containing carotene could be found or bred, most of the problems of xerophthalmia would be overcome. Nevertheless, it is important to realise that carotene is far from being absent from the environments in which xerophthalmia prevails. It is a question of poverty in the midst of plenty, for the tropics and sub-tropics are lush with green leaves in myriad form. An adequate nutrition education program would have three objectives: first, to convince parents that a mainly cereal diet for the child is harmful; second, to indicate the sources of the missing vitamin locally available; and third, to provide assistance in the cultivation and preparation of the green leaves.

Formidable obstacles remain in the path of progress on a world wide scale towards controlling xerophthalmia. Notable among these are the difficulties in early detection of both vitamin A deficiency itself and the ocular lesions of xerophthalmia. There is no widely available, simple method of measuring vitamin A concentration in the blood at present, nor is there general agreement on the proportion of values below the normal range that would signal a public health problem in a population. Furthermore, the early non-blinding eye lesions of xerophthalmia are notoriously difficult to identify with precision and accuracy. The sensitivity, specificity, and predictive value of the tests are also suspect. Clearly, there is much need for research in these areas.

The occurrence of xerophthalmia in a community is a very important public health index of its nutritional status. Because vitamin A accumulates in the body well beyond the day to day requirements, large reserves may normally be considered to exist. The occurrence of conjunctival and corneal changes characteristic of vitamin A deficiency thus betokens exhaustion of these reserves, a consequence of severe and usually prolonged malnutrition.

The emergence of xerophthalmia as a new phenomenon in a community thus indicates a serious deterioration in nutritional status. Conversely, the disappearance or amelioration of pre-existing xerophthalmia is a token of definite improvement in nutritional status. It is essential that examination of the eyes and, if possible, plasma retinol levels be included in all monitoring and surveillance programs.

In this connection, it is important to differentiate between the endemic and epidemic occurrence of vitamin A deficiency and xerophthalmia. The problem tends to be endemic among those communities who subsist on diets in which the staple is deficient in pro-vitamin A carotenoids, the prime example being rice. Public health authorities should be alert to the possibility of epidemics, usually characterized by night blindness, occurring in emergency situations like crop failures and other natural disasters and sometimes associated with the epidemic occurrence of measles.

Our understanding of the magnitude of the problem or xerophthalmia and vitamin A deficiency has not only increased considerably in recent years, but the nature of the data upon which it has been based has changed. In this regard, one may discern three historic periods. The first, extending up to about 1960, was characterized by isolated reports of the occurrence of xerophthalmia based mainly on hospital case reports. This was followed in the early 1960's by the world-wide survey of xerophthalmia sponsored by WHO in which there was a coordinated effort to coolect a wide variety of data relating both to vitamin A status and xerophthalmia from many countries. The third period since then has been characterized by a more scientific approach in epidemiologic methodology. A number of country-wide, point-prevalence surveys have been carried out. There is increasing use of the WHO classification of xerophthalmia (Table 1) and its criteria for diagnosis of a public health problem (Table 2) (WHO 1976 Vitamin A Deficiency and Xerophthalmia, Technical Report Series 590, WHO, Geneva), and monitoring and surveillance programs are being introduced in some countries.

At the Second Session of the Committee on Food Aid Policies and Programs held in Rome, November 1976, WHO presented a tentative list of 74 countries and territories where vitamin A deficiency is considered to be a public health problem. They are shown in the map (Fig. 1). The highest endemicity and also the vast majority of the total cases of xerophthalmia are found in those countries where most of the classical clinical and epidemiological accounts of the disease come from what might be termed the 'home' of xerophthalmia. These are the rice-dependent areas of south and east Asia, most notably central and southern India, Bangladesh, and Indonesia.

Although the advent of a more scientific and systematic approach to the delineation of the problem of vitamin A deficiency is to be welcomed and pursued wherever possible, it must be recognized that this will not be practicable in many developing countries in the near future. In these situations, there is

still great merit in the careful collection and compilation of data on a hospital basis, an exercise that has been carried out widely in such countries as India and Indonesia. The reporting of data from district hospitals as shown in Table 3 would provide much needed information at both national and international levels.

As a rough guide, it may be stated that the occurrence of xerophthalmia in more than 10 per cent of malnourished hospitalized children strongly suggests the existence of a public health problem. Figures as high as 70 to 75 per cent have been reported in the past, for example, from Indonesia.

WHO has accepted an approximation of 100,000 cases of xerophthalmia occurring annually throughout the world. The mortality rate appears to be usually 20 to 40 percent among survivors and about 25 per cent remain totally blind, about 50 to 60 per cent partially blind, and only 15 to 25 per cent escape with unimpaired sight.

At the World Health Assembly in 1977, WHO passed a resolution to eradicate the severe clinical forms of malnutrition by the year 2000. The control of xerophthalmia is a major part of this objective and calls for the concerted efforts of all concerned.

TABLE 1 WHO Xerophthalmia Classification

Classification	Signs - primary
X1A	Conjunctival xerosis
X1B	Bitot's spots with conjunctival xerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
X3B	Keratomalacia
	Signs - secondary
XN	Night blindness
XF	Xerophthalmia fundus
XS	Corneal scars

TABLE 2

WHO Suggested Criteria for Community Diagnosis of Xerophthalmia and Vitamin A Deficiency

Clinical

1. X1B in more than 2.0 of the population at risk
2. X2 & X3A & X3B in more than 0.01% of the population at risk
3. XS (attributable to vitamin A deficiency) in more than 0.1% of the population at risk

Biochemical

4. Plasma vitamin A level of less than 10 μg/100 ml in more than 5.0% of the population at risk

TABLE 3

Hospital Data on Xerophthalmia

1. Total number of PEM cases
2. Percentage with xerophthalmia
3. Seasonal distribution
4. Sex distribution
5. Age distribution
6. Eye Lesions by WHO Xerophthalmia Classification
7. Mortality
8. Survivors - Totally blind
   - Partially blind
   - Full vision

Abstract

Strategies for the Prevention of Vitamin A Deficiency

by

Barbara A. Underwood
Associate Professor Nutrition
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Vitamin A deficiency remains a public health problem of varied severity and magnitude in many developing countries. Substantial improvement in the rate and level of development and the distribution of benefits would contribute substantially to reducing the problem. Progress however is too slow, and specific strategies are needed to attack directly hypovitaminosis A. No one strategy is universally applicable. The appropriate national strategy usually will include more than one alternative to be adapted to local conditions and resources. The strategy selected must have specifically stated objectives and be formulated within the context of overall health, nutrition, agriculture and development goals.

Strategies for the Prevention of Vitamin A Deficiency

Paper prepared for

XI International Congress of Nutrition

Symposium on Vitamin A Deficiency

by

Barbara A. Underwood
Associate Professor Nutrition
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Each year thousands of young children go blind or develop impaired vision because of vitamin A deficiency. Frequently the permanently blinding form of hypovitaminosis A is superimposed on acute protein, and sometimes calorie, deficiency, and often on an infectious disease such as measles. Countless thousands more young children and adults may have their health compromised in ways difficult to prove by subclinical hypovitaminosis A that results from an inadequate dietary intake of vitamin A-active foods. Hence, vitamin A deficiency continues to be a public health problem in many parts of the world, the serious, irreversible forms primarily affecting young children, and the more subtly debilitating form affecting older children and adults as well.

This problem can be prevented and controlled in its public health dimensions by appropriate policies and programs implemented both nationally and at the community level. But

there is no one universally applicable strategy for prevention. Rather, the most effective strategy must be determined from an evaluation of conditions prevailing and contributing to the etiology locally and of the resources available for prevention where the problem exists through local, national, or international channels.

Alternative Strategies

There are two basic approaches to prevention. The first is to provide directly for an increased dietary intake of vitamin A, and the second is to attack those factors in the environment that decrease the availability of the vitamin from foods and/or increase the requirement. The two approaches are not mutually exclusive, and where possible should be the combined objective of any strategy for prevention and control of hypovitaminosis A. For the purposes of this presentation, the two approaches and examples of programs that fall into each category will be discussed separately.

Increased Intake

Locally available foods. Nutrition and health education of mothers is a fundamental long-range approach toward solving the problems of both an inadequate intake of the vitamin and of increased requirement. In most, though not all, localities where hypovitaminosis A occurs, food sources of provitamin A

are available but underutilized in the diets of the "at risk" groups. Ignorance of the fact that green leaves and vegetables are needed in the diet and about how they can be appropriately incorporated into the foods of young children is largely responsible for underutilization. Taboos, cultural or religious constraints against the utilization of these foods are seldom the primary constraint to consumption, although acquired association with a "prestige" value may be a factor. For example, a readily available cheap source of leaves sometimes bears the label of a "poor man's" or "animal's" food. Educational programs implemented by community workers, e.g., agricultural extensionists, community development agents, family planning implementors, health aides, etc., using very simple messages combined with demonstration and follow-through programs can effectively increase the intake of locally available, inexpensive vitamin A-containing foods. These educational approaches should incorporate equally simple instructions on the sanitary preparation and feeding of these foods. Studies have shown that as little as 15-20 grams -- a handful -- of carotene-rich leaves in a child's daily diet can maintain adequate blood levels and prevent xerophthalmia.

There are some geographic areas where hypovitaminosis A exists because there is no available source of vitamin A-containing foods. This may be due to inappropriate agricultural planning or to the lack of the necessary environmental conditions to produce

such foods. Although theoretically this situation could be most efficiently altered by an increased supply of the preformed vitamin found in animal products, it is unlikely, for economic reasons, that this approach would improve the intake of those most "at risk" of deficiency. As an alternative, increased availability of the usually less expensive plant sources of precursor vitamin A (carotenes) is more apt to improve the intake when combined with educational programs to assure utilization by those most "at risk." Horticultural improvement programs may take the form of intercropping carotene-rich foods with the more traditional staple crops on the farm land; for example, tomatoes or sweet potato (the stem tips as well as leaves are edible) intercropped with corn. Community or school gardens with priority utilization of products in local infant and child feeding programs, and backyard garden production for family use are other possibilities. Some have calculated that as little as one square yard of land could provide sufficient carotene over a six-month harvest period to provide the vitamin A needs of two young children.

There are, of course, situations in which horticultural approaches at any of the three levels of production are not feasible because of the lack of water, fertilizers, or seeds. In such cases these constraints could be removed by appropriate agricultural subsidy programs or community development projects.

This emphasizes the need for integration of nutrition and health concerns into overall agriculture and development policies and their adaptation to local situations.

For some, particularly the low-income rural and urban dwellers who depend on the market for food, the cost of food sources of vitamin A is prohibitive when weighed against the need for calorie-dense foods. Studies in some areas show that providing incidental income-generating activities for women is the most effective way to improve the diet of young children. Women from these economically marginal families usually are occupied in assisting husbands in agricultural activities as well as in home and child care. Often, however, they can find some time to enter into barter activities for minimal monetary return, and they are more likely to use this extra money to provide food for their children. Hence, a development policy that includes a strategy for an increased income, including that of women, and again, combined with an educational approach to increase awareness of good child feeding, can improve the vitamin A intake from locally available food resources.

Fortification of a food vehicle. Vitamin A fortification of foods or other dietary products, such as condiments and beverages consumed widely by the vulnerable population, can effectively improve the intake of vitamin A at a comparatively low cost. This has been demonstrated by programs currently under way in some countries and will be discussed in detail by others

participating in the symposium. At times, a narrow view toward fortification of a single food item on a national scale had limited the options considered because an appropriate single food centrally processed and consumed by children as well as adults could not be identified. Before abandoning this alternative, thought should be given to regionalization in the search for a variety of alternatives, and to the feasibility of a decentralized community-level fortification program. Such a program does complicate the logistics, including those of monitoring, to assure that the quantity supplied is sufficient but not excessive so that there is minimal risk of toxicity from over consumption.

Direct vitamin supplements. This approach toward augmenting the dietary intake of vitamin A has been tested in several countries. There is no doubt about its effectiveness in reducing the prevalence of xerophthalmia in those who receive periodic concentrated dosing, but there is uncertainty about how long the interval between dosings should be to assure efficacy and affordability. There is also the question of whether this approach alone is adequate to prevent keratomalacia when acute protein-energy malnutrition occurs concurrently. Evidence is amassing to indicate that the acute dietary protein deficit must be corrected concomitantly with vitamin A deficiency to assure the physiological availability of the vitamin to deficient tissues. The evidence to date is not convincing that mild

or moderate PEM is critically limiting vitamin A utilization. As a public health measure to reduce the prevalence of xerophthalmia and subclinical vitamin A deficiency, periodic dosing with concentrated supplements can be effective, but to prevent keratomalacia, programs may need to be targeted to the acutely protein-energy malnourished child who is then provided protein as well as the vitamin.

A six-month dosing with 200,000 IU of vitamin A in capsules also containing 40 IU vitamin E has been the most common approach. This schedule has resulted in the least number of adverse side effects. However, this direct provider-recipient delivery program is costly and difficult to sustain over a long period. The cost component for a minimally focused distribution program in terms of use of scarce personnel and monetary resources from local budgets is prohibitive for most countries where serious forms of deficiency are prevalent. In addition, these broadly based programs are limited in their effectiveness because they do not always reach those most at risk of irreversible health consequences, and are decreasingly effective in coverage with each subsequent delivery period.

Perhaps the best use of direct vitamin supplementation programs is delivering these through medical institutions, the health network, and community channels that reach not only the high risk, acutely ill, but also those such as pregnant and lactating mothers and young children, all of whom have elevated requirements. This means making the vitamin supplement available through hospitals and health centers and through community health aides

trained to recognize the conditions and signs associated with deficiency, and who have frequent direct contact with mothers and their children. A prevention strategy would have to include training this type of personnel to identify problems and to provide various solutions.

Safeguards are needed, especially in programs that rely on auxiliary or paramedical personnel for delivery. For these workers, dosages in the range of 25,000 to 50,000 IU would be safe and appropriate, as they see the "at risk" individuals on a more frequent schedule and can give the supplement more often. The effectiveness of a targeted approach will be determined by the provider's recognizing both the ecologic and physiologic factors generally associated with a high risk of deficiency, and the clinical ocular evidence of a deficiency state.

Decreased Requirements

Improved efficiency of absorption. Efficient fat absorption is important for adequate absorption of preformed vitamin A and especially of carotenes. This assumes that there is sufficient fat in the diet and that it is effectively hydrolyzed in the gut to facilitate the formation of water-miscible mixed lipid micelles that act as solubilizers and carriers of the water-insoluble vitamin. Dietary fat requirements are not known, but some studies suggest diets containing less than 5 grams daily are associated with a reduced absorption of carotenes. The diets of many preschool aged children contain this low level of fat, and

furthermore, these children often rely almost exclusively on a limited dietary supply of carotenes to meet their vitamin A needs. Whereas dietary fat may not be limiting to the absorption of preformed vitamin A given either in the diet or as capsule supplements, it may become limiting in diets marginal in carotenes. In these situations a strategy to improve the consumption of fat by the at-risk children may be appropriate to improved carotene absorption. This would have the added benefit of an increase in the caloric density of the diet as well.

Dietary protein also facilitates absorption of carotenoids by assuring sufficient precursors for the synthesis of digestive enzymes and the mucosal carotene dioxygenase, as well as for maintenance of a healthy mucosal surface.

Control of infections through public health interventions. Public health interventions offer several advantages because most improve the general quality of life in the community. Those aimed at control of enteric and systemic infections through improved sanitation and immunization will not bring about the immediate impressive changes in the vitamin A status of a population offered by a direct increased intake of vitamin A through a supplementation program. But public health measures will lead to an incremental improvement, and where possible, should be part of any long-range strategy for prevention.

Furthermore, there is some evidence that local or generalized infection may directly or indirectly be one of the factors along with acute protein deficiency causing keratomalaria in a vitamin A deficient subject.

Selection of a Strategy for Prevention of Hypovitaminosis A

Several possible approaches toward prevention have been mentioned, some of which will be discussed in greater detail by other participants in this symposium. The strategy selected and the specific programs of which it is composed will depend upon the seriousness and magnitude of the problem, its relationship to other health needs, and the role of objectives for prevention within national health, food, nutrition, and development goals. It is essential that the objectives and goals for a vitamin A prevention strategy be agreed upon at the highest levels of national planning. Program success will depend not only upon the effectiveness of implementation within and by communities, but also on the political commitment to support such programs with scarce resources for which there are usually many competing needs.

The strategy selected should be influenced by the severity and magnitude of the problem. Where clinical signs of xerophthalmia are prevalent at rates near or above the level that WHO suggests is a public problem, the immediate objective might be: 1) to control xerophthalmia and eliminate related blindness as a public health problem, or 2) to improve the vitamin A status of populations at "high risk" of developing xerophthalmia. While both objectives require an immediate increased intake of vitamin A, the target population and numbers to be treated varies. For example, objective 1 calls for a program

targeted to young children, especially those with clinical PEM and associated acute infections. Objective 2 would include this same population as well as under-privileged but not acutely ill children, and pregnant and lactating women.

A third objective for a national program where clinical signs are less prevalent might be to improve the level of vitamin A nutrition of the population as a whole. This is an appropriate objective on which to base programs even where the prevalence of xerophthalmia is not high, but where there is evidence of inadequate vitamin A intakes. From parallels in animal models we can assume that there are non-visual health consequences of hypovitaminosis A. The decision to initiate an intervention strategy based on this objective, however, is largely a political one. Although a large segment of an underprivileged population might be in a preclinical state of hypovitaminosis A as well as of other nutrient deficits, it will be difficult to document just how their health might be benefited from improved vitamin A nutrition alone.

Conclusions

The long-term goal of a strategy to prevent vitamin A deficiency is, broadly defined, to provide all people with a diet adequate in the vitamin and other nutrients that interact in vitamin A metabolism. WHO has compiled a list of 73 countries whose populations are likely to have an inadequate level of vitamin A to a degree worthy of immediate public health attention. Obviously, a general upgrading of the level of

development in these countries and a more equitable distribution of the benefits of development, including income, would substantially reduce the magnitude of the problem. We cannot wait for this to occur while the irreversible consequences of acute deficiency of vitamin A accrue. Hypovitaminosis A is amenable to solution through public programs that need not await overall development. Where the serious irreversible forms of visual impairment are prevalent, appropriate programs should be instituted immediately. Where milder forms exist, and where resources are available, earnest consideration should be given to improving vitamin A nutrition for the general population as well. A global political commitment is needed for the eradication of hypovitaminosis A as a public health nutrition problem.

Factors Affecting the Bioavailability and Metabolism of Vitamin A and Its Precursors*

by

Dr. James Allen Olson
Professor of Biochemistry and Biophysics
Iowa State University
Ames, Iowa 50011 (U.S.A.)

An invited paper for the "Symposium on Vitamin A Deficiency"
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In dealing with the problem of vitamin A deficiency in preschool children, the dietary intake required to satisfy the needs of a child for growth and the prevention of clinical symptoms of vitamin A deficiency should obviously be defined. At first glance, we are seeking a specific number, which appears to be a simple, easily resolvable task. In actuality, it is not a simple task at all, because the number keeps changing as a result of five major factors: 1) the bioavailability of vitamin A and its precursors in the diet, 2) nutrient interaction, 3) the presence, length, and severity of disease, 4) metabolic parameters--and in particular storage efficiency, the turnover of reserves, and recycling efficiency, and 5) statistical considerations. I wish first to consider each of these major factors, and then to suggest a new approach to vitamin A nutriture which might allow simplification of many of the complexities involved in assessing their importance.

The amount of carotenoids and vitamin A in the diet can be fairly well estimated under two major conditions: 1) when essentially no vitamin A is present, e.g., on a post-weaning diet primarily composed of sticky rice or of cassava gruel and molasses, or 2) when abundant amounts of vitamin A or provitamins are ingested, such as liver, red palm oil, papaya, amaranth, or indeed vitamin A supplements. Accurate dietary information becomes most difficult to obtain among children who receive marginal amounts (100-300 μg) of vitamin A or its equivalent. Information obtained by dietary recall is only semiquantitative, even under the best of conditions; local fruits and vegetables often contain quite different concentrations of provitamin A than those indicated in standard dietary tables, the state of maturity and mode of preparation of fruits and vegetables can drastically affect the percentage of provitamins present among total carotenoids, the direct chemical analysis of food together with the professional monitoring of intake over a significant period is both costly and time consuming, and seasonal changes in the diet can be considerable. The general utility of dietary information in assessing many aspects of nutritional status is not in question; knowing what children eat is an essential part of baseline information on which nutritional programs should be based. The actual intake of carotenoids and vitamin A however, is particularly difficult to assess among that large group of children who are receiving marginal levels of many nutrients, including vitamin A and carotenoids.

The conversion of carotenoid intake into retinol equivalents, even when the carotenoid intake is accurately known, poses additional problems. The generally recognized equivalencies are 1 μg retinol = 6 μg β-carotene = 12 μg mixed dietary carotenoids. In India 1 μg retinol is equated with 4 μg β-carotene, and in recent controlled studies with adult American males, 2 μg β-carotene, given as a pure substance in oil, gave the same response as 1 μg retinol. The redefinition of the retinol equivalent of carotenoids is not necessary, however; indeed, it may still be the best overall value to use. The value is not necessarily reliable under a given set of conditions, however, and consequently, estimates of vitamin A intake become even more uncertain.

Quite apart from the problem of estimating the amount of vitamin A and biologically-active carotenoids in the diet, the absorption efficiency must be considered. Happily, vitamin A is very well absorbed under normal conditions, i.e., about 80% or more of the dose, and the absorption efficiency falls only slightly with increasing dosage. Thus, a 200,000 I.U. dose of retinyl palmitate, which has been extensively used in massive dosing programs, is >60% absorbed. Carotene is different; first, more fastidious requirements exist for the formation of a suitable micelle for carotenoids; second, the absorption rate is much slower than for vitamin A; and third, the absorption efficiency falls rapidly with increasing dosage. Thus, under ideal conditions, about 60% of a dose of β-carotene is absorbed, but it can be much lower.

The interaction of other nutrients with vitamin A also must be considered. Nutrients affect each other in many ways, and vitamin A is no exception to this rule. Predominant among nutrient factors which are associated with acute vitamin A deficiency is severe protein energy malnutrition. Although corneal disease due to vitamin A deficiency may occur in moderately well-nourished children, extensive corneal involvement and keratomalacia seem to be mainly, if not invariably, associated with severe PEM. In a biochemical sense, many enzymes and proteins involved in vitamin A metabolism which are impaired in PEM can be cited; carotene cleavage in the intestinal mucosa, the synthesis and release of plasma retinol binding protein, the formation of the storage lipoglycoprotein of liver, the formation and release of lipolytic and proteolytic enzymes of the gastrointestinal tract, and many more. Thus in PEM, vitamin A and carotenoids are less well absorbed, less well stored as retinyl ester in the liver, and less well transported to peripheral tissues as a RBP-retinol complex.

But just as PEM markedly affects vitamin A utilization, so also does vitamin A deficiency impair protein utilization. Of particular note are the abnormal plasma amino acid patterns, the negative nitrogen balance, and the loss of appetite observed in acute vitamin A deficiency in experimental animals. Thus, vitamin A deficiency and PEM exacerbate the imbalances caused by each other, thereby setting in motion a tragic, vicious circle of rapid debilitation. The close epidemiological relationship among deficiencies of these nutrients, therefore, is in full accord with biochemical and physiological observations.

Vitamin E and vitamin A also have been linked nutritionally. In vitamin E deficient experimental animals, vitamin A is less well absorbed and stored and is more rapidly depleted from the liver. Interestingly these effects seem to be relatively specific, in that other anti-oxidants do not replace α-tocopherol. The existence of frank vitamin E deficiency in children is still uncertain, although severely malnourished children must certainly be marginal in vitamin E nutriture if not acutely deficient. The addition of vitamin E to a vitamin A preparation given to malnourished children, however, did not significantly

enhance vitamin A absorption and storage. Nonetheless, in view of its anti-oxidant properties, its low cost and its possible effectiveness in severe cases, the inclusion of vitamin E in vitamin A preparations is certainly well-warranted.

Other nutrient interrelationships with vitamin A are less well defined. Anemia due to iron deficiency has been correlated with vitamin A deficiency epidemiologically, but the existence of a specific molecular interaction is yet undertain. Similarly, zinc deficiency and vitamin A deficiency produce some similar clinical signs, such as growth depression and epithelial keratinization. Although plasma vitamin A levels are depressed in zinc deficiency and are restored upon supplementation with zinc, zinc deficiency seems to act indirectly on vitamin A metabolism by reducing tissue requirements for vitamin A as a result of a reduced growth rate. Undoubtedly, other interactions exist; calcium excretion increases in vitamin A deficient animals, for example, although vitamin A status and urinary calcium excretion have not been correlated in malnourished children. But as a general principle, we might expect that any stress--whether nutritional imbalance, infection, harsh climate, or the like--which impairs the capability of an organism to function optimally will inevitably increase the need for any specific nutrient.

Disease is a good case in point since it may disrupt the processes of vitamin A absorption, transport, storage, or metabolism. In chronic lipid malabsorption syndromes, such as pancreatitis, biliary cirrhosis, sprue, chronic diarrhea and cystic fibrosis, one or several aspects of the absorption process is defective, and consequently, vitamin A together with most lipids is poorly absorbed. Interestingly, a significant part of a massive dose of vitamin A is still taken up in such patients, although the efficiency is of course low. The absorption of β-carotene and other carotenoids, which have more fastidious requirements for micelle formation and are normally absorbed at a much slower rate than vitamin A, is particularly affected by malabsorption syndromes.

Diseases such as hyperthyroidism or those associated with febrile conditions increase the rate of tissue metabolism and consequently increase the needs for vitamin A. Other energy-draining stresses, such as chronic exposure to cold, have similar effects both on the metabolism of vitamin A and on its required intake.

Because of the importance of the liver and kidney in the storage of vitamin A and in the transport and metabolism of retinol binding protein, diseases of these two organs will naturally affect vitamin A nutriture in a marked way. Parenchymal cell disease, such as hepatitis, will depress the synthesis of apo-RBP, prealbumin and storage lipoglycoprotein, and will therefore influence both the storage of vitamin A and its transport in the plasma. The kidneys are involved both in holo-RBP absorption from the tubules and in the catabolism of apo-RBP. In tubular dysfunction, therefore, much RBP is lost in the urine, and in renal diseases which depress glomerular filtration, holo-RBP levels in the plasma rise dramatically.

Since the physiological role of vitamin A is expressed within cells, the ultimate objective of nutrition is the provision of an optimal amount of a biologically active molecule at its active site within cells at the proper time. Outside of vision, where 11-cis retinal is involved as the chromophore of visual pigments in rod and cone cells, we do not know precisely what the physiological site is for the somatic functions of vitamin A. Nonetheless, a phospherylated form of vitamin A can serve a function in glycoprotein synthesis, and a protein-bound form may influence the expression of the genome. But whatever its precise function, the presence of vitamin A within target cells requires suitable intracellular transport, recognition of RBP by cells, uptake of vitamin A by cells, transport in the plasma and controlled release from the liver.

To maintain a proper steady-state, vitamin A must also be oxidized, cleaved and excreted. Indeed, the major protection against hypervitaminosis A when large doses of vitamin A are ingested are these same flexible catabolic systems. Finally, conservation mechanisms exist; vitamin A released in the form of glucuronides in the bile is partially reabsorbed in the intestine and recycled back to the liver. Similarly, retinol released as a complex with retinol binding protein is recycled to a significant extent from peripheral tissues, probably as retinyl ester, back to the liver.

Each of these interrelated processes is under subtle metabolic controls about which we still know very little. But in a nutritional sense, the disruption of any one of them can either precipitate a state of deficiency or increase substantially the requirements of vitamin A.

Statistical considerations are of great significance in vitamin A nutriture, and in nutrition generally. Ideally, all members of a society should be well nourished and happy. Unfortunately, such Utopian dreams help us little in dealing practically with current problems of malnutrition. In approaching this issue, current Recommended Dietary Allowances are defined as "the levels of intake of essential nutrients considered.....to be adequate to meet the known nutritional needs of practically all healthy persons." With the exception of energy, which is expressed as an average requirement, the R.D.A.'s for most nutrients purport to satisfy the requirement for 97.5% of a given group, i.e., two standard deviations from the mean. Unless the distribution curve is well-defined with respect to a given indicator, however, no way exists of estimating the degree of sufficiency of any given intake or the mean requirement.

The R.D.A. for vitamin A for children 0.5-4 years of age is 400 μg retinol equivalents per day. Although this value is rather an arbitrary one, no child receiving that amount of vitamin A, to my knowledge, has suffered any impairment of growth or any sign of deficiency. On the other hand, we know little of the distribution curve for vitamin A intake with respect to any given indicator, and hence, can make no meaningful estimate of the mean requirement, or of a minimal requirement to prevent

corneal disease. Perhaps the effects of nutrient interaction, disease, differences in growth rate, and variations in the metabolic balance of children would make such estimates either impossible or useless. But this matter should probably be probed a bit further, at least to the extent of relating vitamin A intake, insofar as possible, to clinical signs of deficiency.

A new approach, which avoids most of the difficulties cited above, might be taken to the problem of assessing vitamin A status; namely, to define the vitamin A intake needed to maintain the total body stores of vitamin A at a satisfactory steady state level. In infants and small children, a satisfactory level might be set at 20 μg retinol/g liver, or about 10 mg retinol for a 15 Kg child. The replacement rate might then be calculated both with respect to liver turnover and to RBP synthesis. By using an estimated half life of 50 days for liver retinol, the fractional metabolic rate would be 0.014 of the total body pool per day, or 140 μg. If the efficiency of storage is 50%, the child should ingest 280 μg retinol per day to maintain the total body pool at 10 mg. At a plasma RBP concentration of 20 μg/ml, the total plasma RBP pool would amount to 11.1 mg, which would bind 150 μg retinol. If replaced 2.7 times daily, retinol used daily for holo-RBP synthesis would be 410 μg. A significant portion of that retinol, perhaps 70%, would be recycled back to the liver. Thus, with 30% excretion and 50% absorption, 246 μg retinol would be required in the diet daily. However, if no recycling takes place and the storage efficiency is 50%, 820 μg retinol should be ingested daily to maintain the steady state. These calculated dietary intake values of 280, 246, and 810 μg retinol agree remarkably well with the empirically set R.D.A. of 400 μg retinol for 0.5-4 year old children.

Determination of the total body stores of vitamin A by the use of deuterated vitamin A has been accomplished in experimental animals and has been applied to humans in a few cases. Further refinement of this method, as well as other non-invasive techniques, might allow this more kinetic approach to the nutrition of vitamin A to be fruitfully applied.

The above calculation is not intended as a definitive expression of the required intake of vitamin A for young children, but rather as an example of a different approach to the definition of vitamin A needs. The example also points out the need to obtain more information about the turnover of vitamin A in the liver and of RBP in the plasma as a function of age and stress, and to define the extent of recycling under various conditions. The fact that calculated values based on the concept agree reasonably well with those obtained empirically bodes well for the use of these procedures in the future.

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CHARACTERIZATION OF VITAMIN A DEFICIENCY AND DESIGN OF INTERVENTION PROGRAM

Ignatius Tarwotjo, Ignatius Joko Susanto,

and Alfred Sommer

From the Nutritional Blindness Prevention Project
Bandung, Indonesia

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ABSTRACT

CHARACTERIZATION OF VITAMIN A DEFICIENCY AND DESIGN OF INTERVENTION PROGRAM

A large scale nutritional blindness research project is nearing completion in Indonesia. In this paper we discuss the more practical aspects relating to determination of the magnitude and geographical distribution of the problem, and choice of intervention program. Thirty-five thousand pre-school age children were examined in 250 sample sites throughout the country by three survey teams each consisting of an ophthalmologist, a nutritionist, a nurse and five enumerators.

Preliminary analysis indicates 40-80,000 children develop potentially blinding corneal involvement and over one million noncorneal xerophthalmia each year. Fortification of either wheat, mono-sodium-glutamate or refined sugar with vitamin A should eliminate 50-70 per cent of the problem. A variety of other programs needed to reach the remaining 30-50 per cent of xerophthalmic children is discussed.

INTRODUCTION

To design an effective xerophthalmia prevention and control program one must first determine the magnitude and distribution of the problem, and second elucidate those factors that might be manipulated to improve the vitamin A status of the population at risk. On the basis of anecdotal and hospital reports, xerophthalmia was long felt to be one of the major nutrition problems in Indonesia. These reports, however, depended upon the interest of the observers and clinic and hospital usage patterns. They were, therefore inadequate to determine the magnitude and epidemiologic basis of the disease. For this reason a large nationwide nutritional and xerophthalmia prevalence survey was undertaken by the Government of Indonesia with substantial support from Helen Keller International.

DESCRIPTION OF THE SURVEY

The country was stratified into seven internally homogenous regions, each consisting of 35 to 42 sample sites containing 4000 to 5000 preschool age children (figure 1). The sample sites in each region were selected by a stratified multistage randomized technique, using the National Intercensal Population Survey's sampling frame. The sample size was chosen on the basis of the statistical requirements utilizing the WHO minimal criteria for a significant public health problem, and the competing priorities of practical constraints of time, money and

personnel. Each sample site was a cluster of 100 to 200 households, from which a total of 120 preschool age children were examined. To avoid the omission of presumed high risk groups in poor urban communities, 20 urban sites each containing 500 preschool children were selected from 16 large cities. (Table I). Every attempt was made to visit each sample site. Only three of all the selected sample sites were dropped because they were inaccessible.

The survey was conducted by three teams each composed of an ophthalmologist, a nutritionist, a nurse, and five enumerators. The teams were first given three weeks of intensive training including standardization, before any sample sites were visited. Sample self-coding forms designed and pretested in the field were used to record basic socio-economic data on every family, and the health and dietary history, height and weight, and result of the eye examination on each child.

Upon arrival at a sample site the clinical team established a central examination point while the enumerators accompanied by local aides visited every house to compile socio-economic data and collect preschool children for their examination. At the central examination point every child's height and weight was measured, both eyes examined, and dietary data collected from all xerophthalmic cases, their age-sex-locale matched controls, and a 20 per cent random subsample of all children. All abnormal eye lesions were photographed using a simple

close-up camera. All data were sent to study Headquarters in Bandung, transferred to IBM cards and will be analyzed by computer. Preliminary hand tabulated data are already available.

RESULTS AND DISCUSSION

Magnitude and Distribution of the Problem

The overall picture of the problem is shown in figure 2. Eleven of the 23 provinces included in the survey had prevalence rates of the disease higher than the WHO criteria for a significant public health problem. Table II shows the prevalence of conjunctival disease, X1B, corneal xerosis and ulceration, X2, X3, and corneal scars, XS, in the high risk areas. As can be seen from this table, the prevalence rates of active corneal disease X2 and X3 are extremely high, whereas those of conjunctival xerosis with Bitot's spot, X1B, which is not a direct determinant of nutritional blindness, are mostly below the WHO criteria. The prevalence rates of corneal scar are also low. In fact, a comparison of low corneal scar rate and high active corneal disease rate suggests that in Indonesia a large percentage of preschool children with corneal xerophthalmia probably die.

Preliminary results of a separate longitudinal field study undertaken in West Java indicate the annual incidence of active corneal xerophthalmia is 4 per 1,000 and noncorneal disease 104 per 1,000 every year. Since the prevalence

rate in the countrywide survey is similar to that in the longitudinal study area, we can assume the same incidence rates probably apply and estimate that 80,000 children in Indonesia suffer from potentially blinding corneal disease and 1.5 million from noncorneal xerophthalmia every year. That is, 2 per cent of all Indonesian children will develop corneal lesions and 50 per cent will have noncorneal abnormalities before reaching their fifth birthday.

The prevalence rates of xerophthalmia are not uniform throughout Indonesia. The countrywide survey demonstrates that the prevalence of active corneal xerophthalmia varies from an alarming 33 per 10,000 in Lombok to zero in Ambon. The prevalence of noncorneal lesions varies from 3.4 per 100 in Aceh to 0.54 per 100 in Sulawesi. The survey also uncovered isolated areas of particular concern, such as Aceh and Lombok, where the rate of corneal xerophthalmia was 30 times the WHO criterion.

MEANS OF INTERVENTION

Two major forms of intervention exist: 1) supplementing the population at risk with additional synthetic forms of vitamin A, either by distributing massive dose vitamin A capsules or by fortifying food products with the vitamin; 2) increasing the intake of natural beta carotene and vitamin A rich foods.

Supplementation

A. Capsule distribution

Capsules containing 200,000 IU vitamin A and 40 IU vitamin E have been distributed to over one million children in Indonesia over the last 5 years. Experience indicates that distribution through use of independent, single purpose workers costs 38 US cents per child per year, although integration of massive dose capsule distribution into other on-going health delivery programs might reduce the cost considerably. The continual requirement for seeking out the same children every 6 months results in loss of enthusiasm on the part of the workers and ever decreasing coverage in subsequent rounds of distribution. The best programs seldom reach more than 80 per cent of target children on the first, most succesful round, and those who were missed are most likely the ones at highest risk. However, capsule distribution might prove useful when done as a concerted effort in limited high risk areas.

B. Fortification

The addition of any synthetic nutrient to foodstuffs should meet the following requirements :

a. The intake of the nutrient in question should be below the desirable level in the diet of a significant percentage of the population at risk.

b. The food carrier should be eaten by a large proportion of the population at risk, with only limited variation in intake; and should be centrally processed.

c. The nutrient added should be stable under proper conditions of storage and use.

d. There should be reasonable assurance against excessive intake that might lead to toxicity.

Preliminary findings of the survey indicate that the vast majority of children consume little vitamin A and carotene rich foods. Prior to the initiation of the survey, we identified seven potentially fortifiable foodstuffs. Amounts eaten and brands used were included in the dietary questionnaire. These were wheat products, refined sugar, monosodium glutamate, cooking oils, soysauce, sweetened condensed milk, and dried milk powder. It was immediately discovered that four of these foods were not useful. Soysauce and cooking oils are produced by a great number of small manufacturers, and neither milk product is widely consumed by preschool age children. Wheat flour is processed in three mills and MSG in eight manufacturers in the country. White sugar is made in 40 cane sugar industries which are mostly on Java. On an average, 50-70 per cent of all xerophthalmic children consume each of these foods, in amounts varying from 15 grams to 210 grams per month,

as shown in Table III. We must now select one or several products to be fortified. The final choice will depend upon production and marketing patterns of the products, and whether they can be targeted. In the case of wheat, for example, if lower grade flour which tends to be consumed by the low income groups at high risk of vitamin A deficiency can be fortified, while high grade commonly used by urban high income groups remains untouched, much more vitamin A can be added without risking toxicity among upper class maximum consumers. A feasibility study will be made to ensure this and to determine the optimal level of fortification, stability of the fortified food, equipment needed and cost. Food fortification alone should prove inexpensive and rapidly effective, eliminating 50-70 per cent of the disease, and thus preventing 25,000 to 50,000 new blindnesses every year in Indonesia. Some 30-50 per cent of the children at risk and more in the isolated high risk areas such as Lombok and Aceh would remain unprotected. Other means of intervention, such as distribution of massive dose vitamin A capsules and fortification of local foodstuffs, e.g. salt, might be effective.

Increasing Intake of Natural Foods

Reaching the 30-50 per cent of children at risk who are not covered by the fortification scheme and who are located in isolated high risk areas, but are distributed instead throughout the population, is much more difficult. Their treatment probably will require increased intake of readily available food sources. From a practical and economical point of view, this means

encouraging consumption of green leafy vegetables where available. The socio-economic and dietary component of the survey findings will help us determine the appropriate educational messages to accomplish this. For example, in those communities where the family eats green leafy vegetables but believes they are not good for children, their importance for children as well as adults would be emphasized. Demonstrating to mothers how to prepare and serve these foods to their child would also be useful. In communities where green leafy vegetables are not eaten, the message would need to be quite different. In those areas where such vegetables are not readily available, programs must be established to promote both their production and consumption.

SUMMARY

In summary, the potential value of the countrywide survey in development of effective xerophthalmia control programs has been demonstrated. It can:

1. Determine the magnitude of the problem.

   Our data indicate that xerophthalmia is more prevalent in Indonesia than previously suspected. Each year, some 80,000 children develop potential blinding corneal disease and another 1.5 million develop noncorneal lesions.

2. Locate high risk areas.

   The distribution of the disease is not uniform. Isolated high risk areas, such as Lombok and Aceh, are recognized.

3. Establish epidemiologic determinants of the disease.

   The data will indicate factors related to the development of xerophthalmia in various geographic and socio-economic environments.

4. Identify potentially fortifiable foods actually consumed by children at risk.

   We have identified three centrally processed food products widely consumed by xerophthalmia children; any of these should prove an effective vehicle for fortification.

5. Determine appropriate messages for a nutrition education program.

   Appropriate nutrition education messages will be designed based upon data indicating the reasons children at risk currently do not eat adequate carotene and vitamin A rich foods.

6. Establish a baseline for evaluating the effectiveness of subsequent intervention programs.

   The data from the present survey provide a basis for evaluating the effectiveness of future nutrition and xerophthalmia intervention programs which will go into effect during our third five-year National

Development Program. We look forward to describing the beneficial effects of these programs at the next International Congress of Nutrition.

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TABLE I

SAMPLE SITES OF XEROPHTHALMIA SURVEY

	RURAL	URBAN
LOMBOK	20	0
BALI	11	1
EAST JAVA	35	3
CENTRAL JAVA + JOGYA	38	4
WEST JAVA + JAKARTA	35	3
SUMATRA, 8 PROVINCES	35	3
KALIMANTAN, 4 PROVINCES	17	4
SULAWESI, 4 PROVINCES	33	2
AMBON	9	0
TOTAL	233	20

TABLE II

NUMBER OF CHILDREN EXAMINED IN XEROPHTHALMIA SURVEY

	RURAL	URBAN
LOMBOK	2415	0
BALI	1319	494
EAST JAVA	3959	1319
CENTRAL JAVA + JOGYA	4590	1817
WEST JAVA + JAKARTA	4004	1183
SUMATRA, 8 PROVINCES	4269	1406
KALIMANTAN, 4 PROVINCES	2068	1883
SULAWESI, 4 PROVINCES	3434	890
AMBON	1037	0
TOTAL	27095	8992

TABLE III

PREVALENCE OF XEROPHTHALMIA IN HIGH RISK AREAS

	X1B per 100	X2,X3 per 10,000	XS per 1,000
LOMBOK	1.94	33	0
BALI	0.88	8	0.8
EAST JAVA	0.95	8	0
CENTRAL JAVA	1.22	9	0.4
WEST JAVA	1.77	15	0.5
SOUTH SUMATRA	1.03	17	0
BENGKULU	0.65	22	0
ACEH	3.40	32	0
CENTRAL KALIMANTAN	1.00	22	0
NORTH SULAWESI	0.54	23	0
AMBON	2.41	0	1
WHO Criteria	$\geqslant$2.00	$\geqslant$1	$\geqslant$1

TABLE IV

XEROPHTHALMIC CHILDREN CONSUMING
THREE FORTIFIABLE FOODS (%)

	WHEAT	MSG	SUGAR
LOMBOK	62	38	66
BALI	82	79	89
EAST JAVA	57	77	77
CENTRAL JAVA	75	87	78
WEST JAVA	62	82	66
SOUTH SUMATRA	100	92	75
BENGKULU	100	80	40
ACEH	87	26	74
CENTRAL KALIMANTAN	90	50	90
NORTH SULAWESI	86	86	100
AMBON	96	92	100

Consumption 15-210 grams per month

FIGURE I

NATIONWIDE XEROPHTHALMIA SURVEY

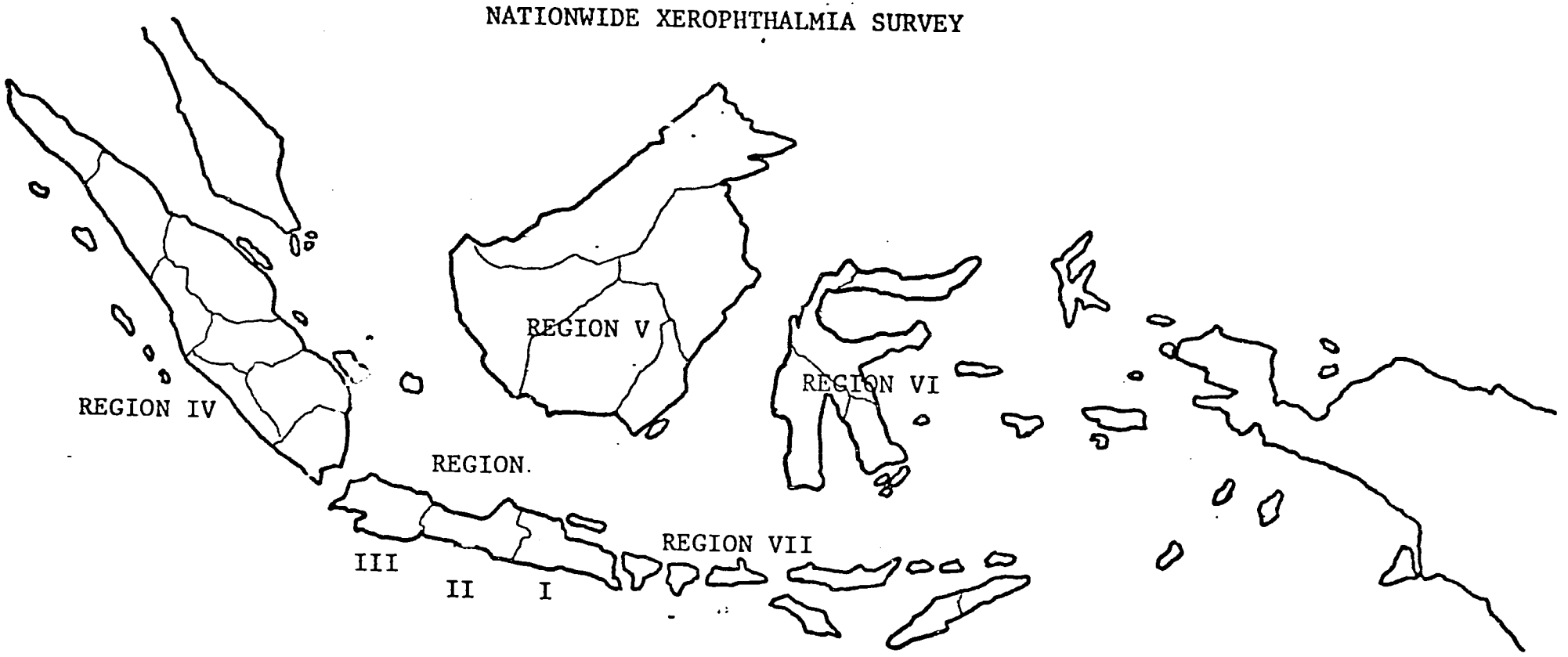
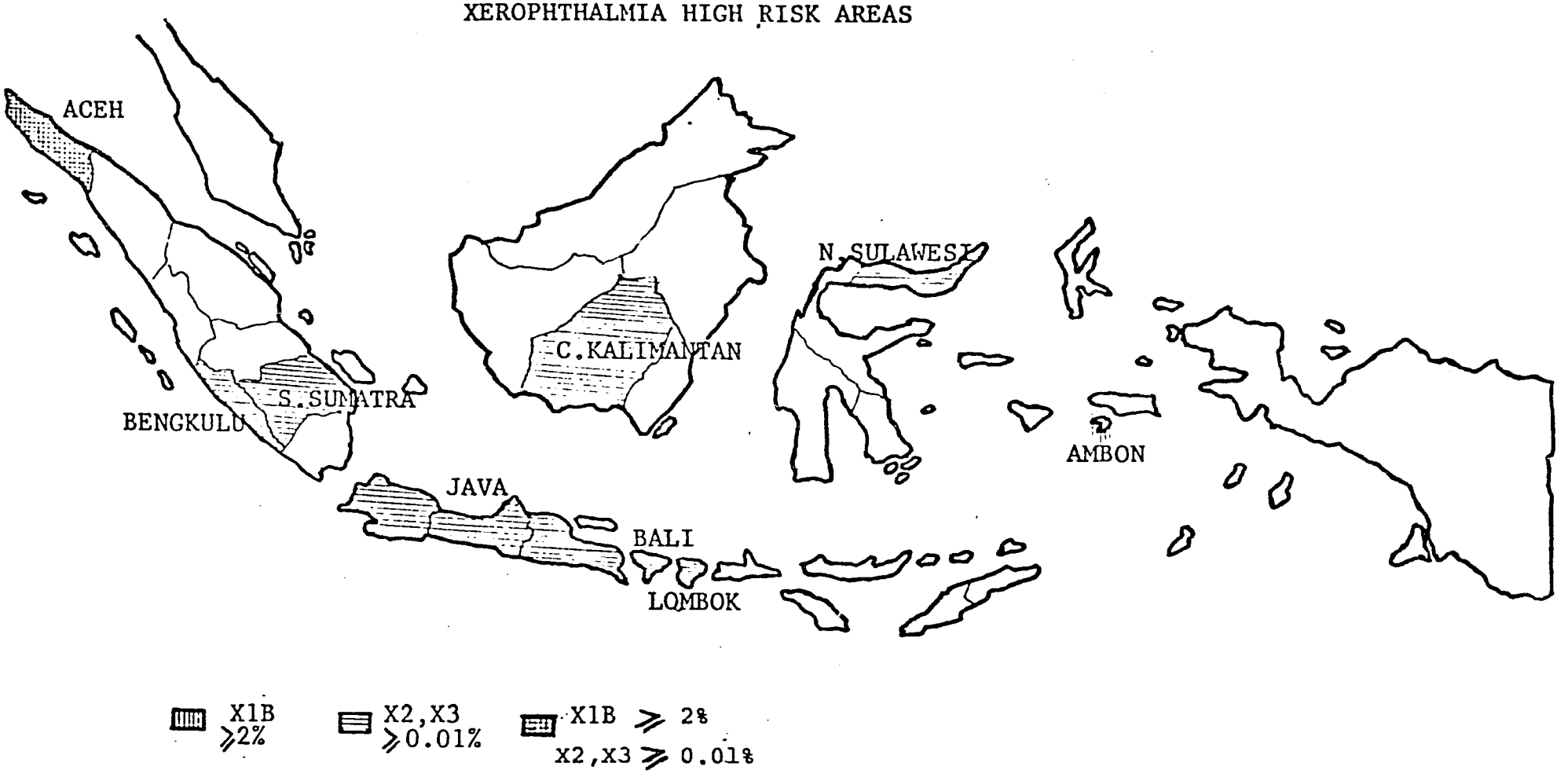


FIGURE II

XEROPHTHALMIA HIGH RISK AREAS



MASS DISTRIBUTION OF VITAMIN A FOR THE PREVENTION OF XEROPHTHALMIA

By

Vinodini Reddy, M.D., D.C.H.

Deputy Director
National Institute of Nutrition
Hyderabad - 500 007, India.

Paper for presentation at the symposium on 'Vitamin A deficiency', XI International Congress of Nutrition, Rio de Janeiro, Brazil, August 27 - September 1, 1978.

Vitamin A deficiency is a major public health problem in many developing countries and is an important cause of blindness, especially in young children of poor communities. Since inadequate dietary intake of vitamin A is the most important cause for the widespread prevalence of the disease, the most rational approach to prevent this condition would be to improve their diets to ensure adequate intake of the vitamin. As a short term measure, however, distribution of massive doses of vitamin A has been suggested for the prevention of xerophthalmia. This approach has been found to be feasible in extensive field trials carried out in India by the National Institute of Nutrition, Hyderabad.

Studies in preschool children showed that following a single dose of 200,000 I.U. of vitamin A, approximately 50 per cent of the dose was retained in the body,[1] and satisfactory levels of serum vitamin A were maintained for nearly 6 months after the massive dose.[2] Field studies conducted in some of the villages near Hyderabad showed that the incidence of ocular signs of vitamin A deficiency was significantly reduced among the children who received the massive dose.[3] Such a program has now been implemented on a large scale in many countries including India, Bangladesh and Indonesia.

Vitamin A Prophylaxis Program in India

The national program for the prevention of vitamin A deficiency and blindness in children has been in operation in India for the last 7 years. Under the program, which is sponsored by the department of Family Welfare, Government of India, a dose of 200,000 I.U. of vitamin A in oil is given orally every 6 months to children between 1 and 5 years. The State Nutrition Officer and State Family Planning Officer are jointly responsible for the implementation of the program. The actual distribution of vitamin A is done by the peripheral health workers.

The program, which began in 1970 in 7 states covering 1.6 million children, has been extended to nearly every state in the country. Last year, 24 million children were covered, based on the doses of vitamin A supplied to the different states. [4]

In 1972, evaluation of the massive dose program was carried out in two states, Karnataka and Kerala, where baseline data were available regarding the prevalence of xerophthalmia. The results, confirming earlier observations,[5] indicated a significant reduction in the incidence of vitamin A deficiency signs following the massive dose.

A Simple Method of Program Evaluation

Although the vitamin A prophylaxis program has been in operation in several states in the country, no systematic evaluation has been taken up except in the two states mentioned above because baseline data are not available regarding the ocular signs of vitamin A deficiency. Recently, an evaluation method in which baseline data on the incidence of deficiency signs are not essential has been developed at the National Institute of Nutrition. This is based on the observation that prevalence of vitamin A deficiency signs exhibits a clearcut trend paralleling the increasing age of children.[6]

Since the diagnosis of conjunctival xerosis is not always easy and is subject to investigator bias, only Bitot spots were used as a sign of vitamin A deficiency. The main observation made in this study was that the prevalence of Bitot spots increased steadily with increasing age in the control areas, while in the experimental areas where the preschool children had received a massive dose of vitamin A every 6 months, the rate of increase up to 5 years of age was minimal and insignificant. The values of regression coefficients of control areas were not only found to be significantly higher from those of experimental areas but they were found to be lying outside the 99 per cent confidence zone of experimental areas. These data indicate that the efficacy of the vitamin A prophylaxis program can be assessed simply by studying the age

trends in prevalence of Bitot spots as a vitamin A deficiency sign, even in the absence of baseline data.

Evaluation of the Massive Dose Program

Using this method, a survey being taken to evaluate the effectiveness of the massive dose program in all the states in India where it has been in operation for more than two years[7] has been completed in nine states in the country. In each state, four Primary Health Centres (PHC) were selected at random. In each center, approximately 1,000 children between 1 and 10 years were examined during house to house visits. Efforts were also made to evaluate the operational aspects of the program by interviewing the staff of the PHC's.

Data obtained from 16 PHC in 4 states, Andhra, Karnataka, Orissa, and Rajasthan, have so far been analyzed. The results of clinical evaluation based on regression analysis indicated that the program was effective by reduced prevalence of Bitot spots in 11 out of 16 centers. In the remaining five centers, the regression coefficient was significantly different from population regression, indicating that the program had not been effective.

The coverage of beneficiaries ranged from 60 to 90% in areas where the program was effective, to less than 60% in areas where it was not effective. Lack of personnel, inadequate supplies, and poor coordination appeared to be the main reasons for incomplete coverage. The operational aspects must be

studied in more detail to suggest corrective measures. Lack of built-in evaluation is the major draw back of this program. It is, however, gratifying to note that in spite of various administrative problems which are bound to occur in any public health program, distribution of massive doses of vitamin A has significantly reduced the prevalence of vitamin A deficiency in most of the areas.

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THE TECHNOLOGY OF VITAMIN A

Dr. J.C. Bauernfeind

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Summary

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THE TECHNOLOGY OF VITAMIN A

J. C. Bauernfeind
Nutrition Research Coordinator
Roche Research Center
Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

INTRODUCTION

Last year, 1977 was the 30th anniversary of the chemical synthesis (1,2) of vitamin A, one of the outstanding accomplishments in improving world-wide public health. Large-scale commercial manufacture and process efficiency improvements in the immediate years following synthesis have enabled this vital biochemical to be produced in virtually unlimited quantities at a fraction of its initial cost (Figure 1). Yet, today significant segments of the world's population suffer because of vitamin A dietary insufficency. Problems of inertia, unsuccessful or inadequate education programs, resistance to the concept of vitamin nutrification of foods as a public health approach, and particularly, inadequate food distribution systems need to be overcome to eradicate vitamin A deficiency and the subsequent blindness which frequently follows.

Vitamin A, retinol ($C_{20}H_{29}OH$), is the isoprenoid polyene alcohol, 3,7-dimethyl-9-)2'6'6'-trimethyl-1'-cyclohexen-1'-yl) 2,4,6,8,-nonatetraene-1-ol, also known as axerophthol, the antixerophthalmic vitamin and the anti-infective vitamin. With a trimethylcyclohexenyl ring and a methylated side chain containing four conjugated double bonds (Figure 2), it can exist in different isomeric forms, each with different biological

activities. The all-trans isomer possessing the highest biological activity is primarily produced commercially by chemical synthesis. Vitamin A complexed with protein (retinol binding protein) is the principal form of transport of the vitamin in blood from the liver. Vitamin A esters are the liver storage form and vitamin A aldehyde (retinal) in the retina combines with protein to form the essential photosensitive pigment, rhodopsin, in the visual process of man and animals. Vitamin A palmitate, propionate, or acetate, also of the all-trans type manufactured by chemical synthesis, are employed most frequently in food and feed applications. The chemical properties of vitamin A compounds are fairly well known (Table 1) and a technology of application has been well developed (3) as has occurred with the other vitamins (4).

Synthesis

All industrial syntheses (2) of vitamin A are based on β-ionone (Figure 3). In 1947, Roche researchers and others announced the synthesis of vitamin A. In 1950, full scale commercial production of vitamin A was begun, the world's first commercial synthetic vitamin A production. The Roche total synthesis of vitamin A from acetone proceeds via methylheptenone, dehydrolinalool, and pseudoionone, and twice makes use of a condensation with isopropenyl ether. The vitamin A procedures of BASF and Roche lead directly to vitamin A acetate, which is fairly stable, crystallizes easily, and is therefore the basis of most commercially available forms. The synthesis by Philips first gives vitamin A aldehyde, which is reduced to the alcohol and only then esterified to the acetate or palmitate ester. In the BASF process, β-ionone is converted to β-C_{15}-vinyl carbinol by acetylene addition and partial hydrogenation; this gives in a Wittig

reaction with 2-acetoxytiglic aldehyde, vitamin A acetate. The present Roche process is, in principal, identical with the original vitamin A synthesis. It is regarded as an economical process and this view finds support in the fact that more than two-thirds of the world's production has been so produced (2). Vitamin A is produced in various countries of the world, USA, Switzerland, Scotland, India, France, Germany, Holland and the USSR.

Lability and Stability

The stability characteristics of the vitamin A (a labile structure) and its derivatives are influenced by a number of factors such as:

a. Oxygen or ozone. In the absence of antioxidants vitamin A is very unstable toward oxygen.

b. Other oxidizing agents. Chemical agents having oxidizing potential are a threat to unprotected vitamin A structures. This can be demonstrated with exposure of vitamin A to oxides, dioxides and peroxides of inorganic and organic structures. Peroxidases influence these reactions.

c. Acids. Vitamin A is sensitive toward acids, which can cause rearrangement of the double bonds and dehydrations, eventually followed by cis-trans isomerization.

d. Heat. Thermal application to solutions and dispersions of all-trans vitamin A will result in the formation and eventual equilibrium of several cis isomers with trans vitamin A.

e. Moisture and trace elements. Trace metals such as copper, iron, manganese and vanadium accelerate oxidative changes initiated by heat, oxygen, and moisture. Moisture and pH are somewhat more

critical for the acetate ester versus the palmitate ester of vitamin A in respect to maximum stability in a water-base product.

Vitamin A is fairly stable when heated to moderate temperatures in an inert atmosphere in the absence of light, but it is unstable in the presence of oxygen or air or when exposed to ultraviolet light. In the presence of alkali, vitamin A is quite stable so that alkaline saponifications of vitamin A containing materials may be carried out without serious loss of vitamin A. The presence of trace metals may also accelerate the oxidation of vitamin A. Therefore, in handling vitamin A, the same precautions are: (a) an inert atmosphere; (b) subdued light; (c) avoidance of trace metals and a strongly acid environment. Stability performance in food products (5) and other products is difficult to predict in advance because insufficient details are usually known on pH, moisture content, packaging, storage conditions and other significant variables.

Application Forms

Vitamin A is offered in a number of application forms: (6,7). The principal methods of stabilizing vitamin A involve (a) sealing under vacuum or inert gas, (b) storage at low temperatures, (c) addition of antioxidants, (d) absorbing and/or sealing with a protective matrix such as a gelatin or vegetable gums or wax composition, and (e) chemically complexing with other compounds. The first two methods are common methods of storing any unstable compound, but they are not always convenient and practical. The use of antioxidants to conserve vitamin A is quite common practice. One is confined in this respect, however, to those antioxidants that are completely acceptable in a given country for food or pharmaceutical use.

This list may include tocopherols, ascorbic acid and derivatives, butylated hydroxyanisole (BHA), butylatedhydroxytoluene (BHT), propylgallate, etc. When preparing vitamin A in an acceptable dry particle form, the selected matrix or absorbant must be nontoxic, edible, digestible, impervious to oxygen, relatively resistant to moisture, easy to handle, relatively economical and available. Much effort (8) has gone into the development of dry, stable, fat-soluble vitamin compositions as detailed by Klaüi et al. (Table 2).

Basically the application forms of vitamin A fall into two categories, liquid products and dry products. Where a maximum concentration of vitamin A in liquid form is desired, vitamin A palmitate at a label potency of 1,650,000 to 1,820,000 per gram as well as vitamin A esters diluted with a vegetable oil to a standardized potency of 1,000,000 IU per gram are available. Specialty liquid vitamin A formulated products in emulsion form are produced where water-dispersibility or spray-on characteristics are desired in food application use. Dry vitamin A products prepared from the various esters, at potencies of 250,000 IU or more per gram, have been developed in various particle sizes and shapes with digestible coatings. In some instances the product is consumed in dry form; in others, the dry form must become water-dispersible at a given temperature before it is consumed, thus special characteristics are required for the intended end use. In addition to physical characteristics the application forms of micronutrients must have certain chemical and physiological properties which contribute to, for example, adequate performance when used for the intended purpose. (8,9). When liquid or dry vitamin forms are used in the nutrification of foods and intended for human use, they should not influence significantly the color, appearance and flavor of the nutrified food, should be fully available

biologically, should be reasonably stable and should be relatively economical to use (10-13,49). To monitor the content in foods (14) and tissues (15), qualitative and quantitative methods of analyses for vitamin A have been published. Most foods to be successfully nutrified require centralized processing locations, followed by food distribution programs which will insure regular access to and consumption of the nutrified foods.

Application Form Use

Over the past thirty years a continuous effort (Figure 4) has been made to meet the demands (16) of the food, feed and pharmaceutical industries for suitable vitamin A formulations. In practice, vitamin A can be given as an oral supplement or it can be administered by various parenteral routes. It can also be added to a variety of foods and feeds by nutrification. Nutrification, defined, is the incorporation of micronutrients into foods for nutritional improvement. In addition to vitamin A products, variations include combination with vitamins D and/or E in stabilized form. Premixes of vitamin A may include the water-soluble vitamins (e.g., folic acid, ascorbic acid, etc.) and minerals (e.g., iron, iodine, etc.) as well. Thus, many application-market forms are possible with their respective specifications and uses (3,7,17,19).

Vitamin A can either (a) be consumed daily in foods in amounts to meet physiological needs, or (b) be consumed intermittently in amounts greatly beyond daily needs and the excess vitamin stored in the liver for future needs. Those delivery systems dealing with vitamin A of chemical synthetic origin can be divided into two principal categories:

I Prevention of Vitamin A Deficiency

A. Short-term measures:

1. Intermittent massive oral dosing

B. Longer-term measures

1. Nutrification of regularly consumed indigenous foods

2. Regular ingestion of a daily dietary supplement

II Treatment of Vitamin A Deficiency

A. Emergency measures

1. Initial intramuscular injection of a water-dispersible preparation

2. Subsequent oral ingestion of an oil-soluble preparation.

Intermittent Dosing (10,19-24)

For intermittent massive oral dosing of young children (or adults) a technology exists for the manufacture of sealed soft gelatin capsules of vitamin A ester, usually palmitate, (with vitamin E) which can be swallowed directly, or the contents squeezed out onto the tongue of the child not yet old enough to swallow the capsule. Soft gelatin capsules are made and filled continuously on the rotary die process machines by skilled operators from ribbons of gelatin forming the capsule which is simultaneously filled. Content variation among capsules is very small. The vitamin A palmitate (200,000 IU), α-tocopherol (40 IU) in oil formulation is filled into a six minim, one-piece, clear, soft gelatin capsule (photograph) with a nipple or nozzle tip. The tip may be cut off if the contents are to be squeezed out. After swallowing the capsule, dissolution occurs within 10 minutes. Capsules containing less or more vitamin A can be prepared; however, due to the lengthy preparatory steps in machine adjustments and its operations,

commercial runs of less than one half million capsules are difficult to arrange. Stability of vitamin A in the capsules is excellent as determined by assay data (Table 3). Field use studies (19,20,22,24) indicate that one capsule should be given every six months, as a minimum program, to young children as an xerophthalmia preventing measure. If cost and distribution systems permit, one given every three to four months would give additional assurance, particularly for the older children whose vitamin A requirements are higher and to catch young children missed in the previous dosing schedule. Objections to the capsule approach are (a) the skipped child, (b) the possibility of regurgitation of contents after swallowing, or not swallowing the capsule and (c) the association that one has to take "medicine" to prevent blindness, not really an educational approach, as faulty diet is the real cause. Capsules have been used intensively in India and Bangladesh and to some extent in other countries, such as Haiti, Indonesia, Philippines, El Salvador, etc.

Parenteral Dosing (19,22-25)

When a patient (child or adult) is recognized as having signs of corneal ulceration with xerosis and there is danger of keratomalacia and irreversible loss of sight, effective application of vitamin A is indicated Intramuscularly (IM) injected oil solutions of vitamins have been found to be relatively ineffective compared to water-dispersible vitamin A palmitate parenterals which are quick-acting. A water-base formulation of vitamin A palmitate (100,000 IU) containing appropriate emulsifiers, antioxidants and preservatives, heat sterilized in one or two ml glass ampules for hospital use, may be administered IM in a sterile syringe. IM administered vitamin A from this type of formulation moves quickly into the blood stream and the

excess is stored in the liver (24,25) as can be shown by animal experiments (Figure 5). Liver stores will maintain blood levels as long as such stores remain and protein foods are consumed as part of the diet. Properly formulated vitamin A parenterals are quite stable in respect to vitamin A potency as monitored by storage assay data (Table 4).

Current recommended schedule of treatment by WHO (22) and IVACG (23) of severe xerophthalmia is as follows:

Treatment Schedule	Preparation
Immediately upon diagnosis	Inject IM, 100,000 IU water-dispersible vitamin A
Second Day	Give orally, 100,000 IU oil solution, vitamin A
Prior to discharge	Give orally, 100,000-200,000 IU oil solution vitamin A

All hospitals in countries with recognized cases of vitamin A deficiency coming to the hospital should keep in stock at all times ampules of water-dispersible vitamin A and oral capsules of oil solutions of vitamin A.

Nutrified Foods (3,7,9,13,17,18,26-30)

Vitamin A has been successfully added (7) to salad oils, margarine, peanut butter, liquid skim milk, canned evaporated or condensed milk, nonfat dry milk, ice cream, mellorine, parevine, butter, cheese, white flour, bread, cakes, cookies, corn grits, corn meal, white rice, breakfast cereals, snacks, potato chips, potato flakes, potato granules, fruit juice beverages and powders, infant and geriatric liquid and dry formulas, confectionaries, tea dust, tea leaves, refined crystalline sugar, and seasonings such as refined white fine crystalline salt and monosodium glutamate.

Oils and Fats (31-36)

Oils or fats (shortening, butter, margarine, ghee, vanaspati, etc.) are dietary ingredients of most populations. Liquid vegetable oils (cottonseed, maize, olive, peanut, soybean, etc.) used in light cooking or consumed with leafy vegetables or other foods can be nutrified with added vitamin A. After the liquid vegetable oil in a bulk container during processing has been clarified, a liquid vitamin A ester concentrate in a proper amount is added and agitated for uniformity before placing the nutrified oil product in sealed containers. While nutrification of oils is not practiced to a large extent in commerce, it is feasible if the oils are packaged in sealed opaque or dark colored glass containers to eliminate the effect of light, a stimulant to oxidative processes. Edible antioxidants may also be added to protect both the vegetable oil and the added vitamin A ester from oxidation. Inert gas replacement for the air in the headspace of the container is advisable at the time of initial packaging, if practical to do so. Currently there is some interest in the Philippines for vitamin A nutified edible oils.

Margarine, commonly used as a bread spread interchangeable with butter, is generally nutrified with vitamin A ester (20,000 to 50,000 IU per kg) to equal or exceed the average levels of this nutrient in butter. Nutrification of margarine with vitamin A is now carried on in Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Costa Rica, Denmark, Finland, Germany, Greece, Israel, Italy, Japan, Mexico, The Netherlands, Newfoundland, Norway, Philippines, Peru, Portugal, South Africa, Sweden, Switzerland, Turkey, Venezuala, UK, USA and USSR. Nutrification of margarine with vitamin A or vitamins A, D and E is relatively simple. Vitamin A, premeasured in amounts of the vitamin for the batch size of the

margarine oil tanks used in a particular margarine factory, is added to one tank of oil, a simple act and an easy factory control operation. If synthetic β-carotene is also to be used, both color and vitamin A can be added simultaneously. A safe color, β-carotene provides color and much of the required vitamin A activity. Available data (Table 5) indicate that added vitamin A is quite stable (33-35) during the margarine manufacturing operations and during use of the nutrified product in the home. Furthermore test results demonstrate, in biscuits, cakes, and breads prepared with vitamin A nutrified fats, that 80 to 100 percent of the added vitamin survives the baking process. Lard, shortening, ghee, vanaspati and other fats, likewise can be easily nutrified with added vitamin A.

Beverages

When carriers of supplementary micronutrients such as vitamin A are considered, foods which can be served as beverages might be considered to have special merit since in illness when solid foods may be refused, there is a greater tendency to drink, if only to meet one's need for the water in the beverage.

Milk (37-42)

When fat is removed from whole fluid milk all fat-soluble vitamins including vitamin A are likewise removed. That the resulting skim milk can serve as a vehicle for added fat-soluble vitamins has been well documented. All skim milk or low-fat liquid or dry milk products should have vitamin A added and, if given to infants, should probably have vitamins D and E and possibly C added as well.

Two techniques have been developed for the nutrification of nonfat dry milk (skim milk powder).

a. Wet Technique

A liquid form pure vitamin A palmitate (preferably with added antioxidants) with or without vitamin D is diluted in hydrogenated coconut oil. This warm oil dilution is homogenized into liquid condensed skim milk to make a high-fat premix. The required amount of the premix is blended into a known quantity of condensed skim milk and mixed thoroughly. The mixture is spray dried and then, if desired, instantized in the usual manner. The use of coconut oil has been found desirable for good stability of the added vitamins. The amount used increases the total fat content of nonfat dry milk (about 0.1 to 0.2%). Blending of the premix into the condensed skim milk may be done on a batch basis or on a continuous basis, the latter requiring controlled metering of the introduced vitamin A premix with the flow rate of the condensed milk.

b. Dry Technique

A dry, stable, water-dispersible form of vitamin A ester (Type 250-S or 250-CWS) is used. This product is blended with a weighed quantity of nonfat dry milk to form a premix. An aliquot or proper portion of the premix is added to a given quantity of nonfat dry milk and mixed in to produce the final nutrified product. Blending may be done batch style in a suitable dry blender, such as a ribbon mixer, or continuous blending may be employed, metering in the dry vitamin A or the prepared premix in proportion to the flow of the dry milk product.

Both the wet and dry methods are practical and proven. The dry technique provides slightly better stability but is slightly more costly than the wet technique because the dry forms of vitamin A are somewhat more costly than the liquid vitamin concentrates and also because of the extra labor involved in the dry mixing operation. Problems to be aware of in the nutrification of dry skim milk are (a) uniformity of introduction of vitamin A in the continuous process, (b) good blending in both the continuous and batch systems, and (c) avoidance over processing which leads to off-flavors. Stability of synthetic vitamin A added to nonfat dry milk is good to excellent (Table 6). Data also show that synthetic vitamin A added to dry milk is fully available biologically (40). Proper packaging does influence the vitamin A stability of the dry product; packages with high moisture resistance are preferred. When reconstituted (39,41), nutrified nonfat dry milk retain its added vitamin A content (Table 7).

Nonfat dry milk exported from the USA under the Food for Peace Program has been nutrified with vitamin A and vitamin D over the past decade. After adequate experiments had demonstrated vitamin A to be stable in nonfat dry milk, the product was nutrified with 5,000 IU of vitamin A and 500 IU of vitamin D/100 g for the P.L. 480 overseas distribution in May 1965. Some years thereafter, these levels were reduced to 2200 IU of vitamin A/100 g and 440 IU of vitamin D/100 g. to coincide with the same levels in nutrified nonfat dry milk initiated for the USA in 1968. World Health Organization (WHO) still recommends nutrification for developing countries at 5000 IU of vitamin A and 500 IU vitamin D/100 g, which has been adopted by the EC in Brussels. The vitamin A nutrification of nonfat dry milk has been long favored by WHO. UNICEF, over a decade ago (40)

encouraged studies resulting in the developed technology for incorporating vitamin A in the product. Once again in 1977 WHO (43,44) stresses the desirability of nutrifying nonfat dry milk with vitamin A as one means of improving vitamin A intake and hence preventing xerophthalmia blindness in children. To assure consumers of vitamin A nutrified nonfat dry milk that vitamin A is actually present, a simple qualitative test has been devised which can be used in the field (45).

Tea (46)

Tea is widely consumed in some parts of the world. A food habits survey conducted in the Western India states by the Protein Food Association (1969) revealed that 87% of the villagers give tea to their children, including 84% of those in the lowest income families. The idea of using tea as a vehicle for conveying meaningful quantities of vitamin A to an entire population was conceived at the New Delhi Mission of the Agency for International Development as early as 1967.

It was determined that tea dust could be nutrified by dry mixing the dust with a fine powdered vitamin A palmitate product (Type 250-SD). Tea dust, so nutrified, retained 85% of the vitamin A activity after storage for one year at room temperature (23°C). Tea leaves required another approach. Trials were made with emulsions of vitamin A palmitate or acetate sprayed onto the leaves. The emulsions were made by homogenizing the vitamin A ester into thick acacia or dextrin solutions at a concentration of 500,000 IU of vitamin A per gram. When diluted with 50% sucrose solution and sprayed on tea leaves, satisfactory stability resulted as judged by storage trials for as long as one year.

Since added vitamin A must survive brewing, the retention of vitamin A was measured after brewing the nutrified tea products. The initial target was a five minute boiling time period, since this does produce a drinkable tea. However, a review of tea making practices revealed that tea is often left on the fire for as long as an hour. Trials indicated that boiling can be detrimental to some of the vitamin A ester emulsion products. However, vitamin A palmitate applied in both the powdered form to the dust and an emulsion form sprayed onto leaves showed 100% retention after one hour of boiling (Table 8).

Tea dust or tea leaves can be readily nutrified with properly selected forms of vitamin A.The initial studies were aimed at nutrifying dry tea to a level of 125 IU of vitamin A per gram. The usual adult cup holding 150 ml of tea brewed from 3 g of dry nutrified tea would supply 375 IU of vitamin A, however, other vitamin A levels are possible. Trials on a commercial scale in a tea factory in South India have demonstrated the feasibility of nutrifying large quantities of tea during its processing, either in individual factories or in tea blending plants. Presumably tea leaves would be sprayed after the fermentation stage near the final drying stage. Some interest in nutrifying tea has been shown in the past in India and Pakistan. By a similar technology it is probably possible to nutrify coffee, if merit exists for such a product.

Cereal-Grain Products (18,47-55)

Cereal-grain products usually constitute an important calorie source of many populations. In some countries, Mexico, India, Africa, they make up 55-65% of the daily caloric intake (55). In the USA it is estimated that about 26% of the daily caloric intake (51) comes from products based

on cereal-grains (wheat, corn, rice, etc.) and their by-products. In 1974 a proposed nutrification policy (51) for USA cereal-grain products was set forth by the Panel of the Committee on Food Standards and Fortification Policy of the Food and Nutrition Board, National Research Council, National Academy of Science. Since cereal-grain products are suitable carriers for the addition of nutrients and since the Panel had evidence of potential risk of deficiency of vitamin A, thiamin, riboflavin, niacin, pyridoxine, folacin, iron, calcium, magnesium and zinc among significant segments of the population, the Panel suggested the nutrification of cereal-grain products with these ten nutrients. The recent studies of Anderson et al. (52) Cort et al. (53), Rubin et al. (54) and others attest to the technical feasibility of cereal-grain product nutrification. In the past, nutrification of cereal-grain products with added thiamin, riboflavin, niacin and iron has been fairly widely adopted in the USA and has spread to other countries (56) since that time.

Weaning food, principally with a cereal-grain base, usually mixed with a vegetable protein or milk and nutrified with micronutrients, have been tried or considered in Egypt, Algeria, India, Iran, Morocco, Tunisia, Turkey, Guyana, Jamaica, etc., as a nutrient delivery system for infants. Varying degrees of success have been observed. Extruded cereal-grain, vegetable protein product mixtures, are of current interest in Sri Lanka, Bolivia, Costa Rica, Honduras, etc.

Flour, Maize Meal

The development in the last decade of stable dry forms of vitamin A ester of smaller ranges of particle size (50) has greatly broadened the type of food products amenable to vitamin A nutrification. Foremost among

these food products are cereal-grain products as white flour, corn or maize meal, white rice, etc. The need for the nutrification of cereal-grain products with vitamin A for the developing countries was first suggested by UNICEF personnel. The small particle, dry vitamin A ester product (Type 250-SD), introduced into cereal-grain products in premix form in laboratory trial runs, has shown good stability in corn meal (15% moisture), namely, 86% retention of initial values after six months at room temperature (23°C), and in wheat flour (11% moisture), 90% after the same time interval. Furthermore, when incorporated into nutrified cereal-grain products and baked into chappaties, breads, and tortillas, vitamin A retention values between 87 and 95% were observed. Vitamin A premix for white wheat flour is designed to be metered into the continuous flow of flour with the aid of a mechanical feeder (Figure 6) at the rate of 1/4 oz (7.09 g) per 100 lb (45.5 kg) of flour without problems of bridging, compression, lumping or segregation. The fine particle size of the dry vitamin A form permits rebolting (screening), if necessary, of the flour with a coarse screen without excessive loss or physical separation of the vitamin A particles from the flour.

In recent years it has become necessary to retest the stability of vitamin A when incorporated into white flour, corn meal and white rice as a multi-micronutrient premix as part of the feasiblity studies of the 1974 proposed NAS-NRC-FNB nutrification program for cereal-grain product. Two premixes were prepared, Premix A containing vitamin A plus five other vitamins (thiamin, riboflavin, pyridoxine, niacin and folacin) and four minerals (iron, calcium, magnesium and zinc) and Premix B, like A but without two minerals (calcium and magnesium). Nutrified flour was prepared in commercial bakery facilities with Premix A and B, and breads were baked

from each nutrified flour. Nutrified flour samples were stored and assayed for nutrient content, likewise the baked breads (53,54). Tabular data (Tables 9 and 10) show excellent retention of the added vitamin A in the multi-nutrient nutrified flour and good to excellent retention in bread baked with such flours. Bread characteristics such as color, grain score, and flavor, although slightly modified when closely compared with unnutrified controls, were suitable and with slight modification of the magnesium and/or calcium levels were judged to be very acceptable products with all ten added nutrients present. In some of these studies, vitamin E (as α-tocopheryl acetate) was added in the micronutrient premix and subsequent flour and bread studies demonstrated excellent stability of added vitamin E (53). Yellow corn (maize) meal and corn grits were likewise nutrified with a multi-nutrient premix and the nutrified products observed for nutrient retention after storage and when cooked to make ready for consumption (Tables 11 and 12). While the added vitamin A showed some losses, 80% or more was retained in the storage tests and 70% or more in the cooking tests of the nutrified corn products (53,54).

Vitamin A nutrification of corn meal became a part of P.L. 480 purchase specifications for export food from the USA on December 1, 1968 and flour on May 1, 1969. The range specified was 4,000 to 6,000 IU/pound. Currently, additional nutrified foods sent abroad from the USA under the USA-AID or Food for Peace Program have the following specifications: soy-fortified corn meal, 2-3 mg thiamin, 1.2-1.8 mg riboflavin, 16-24 mg niacin, 4000-6000 IU vitamin A, 13-26 mg iron and 500-750 mg calcium per lb; soy-wheat flour blend, 2-2.5 mg thiamin, 1.2-1.5 mg riboflavin, 16-20 mg niacin, 4000-6000 IU vitamin A and 500-1107 mg (for 6% soy) or 750-1364 mg (for 12% soy) calcium per lb; other foods have other specifications.

In December 1967 fortification of white bread with vitamin A, the B vitamins, and iron was instituted in a new government-owned bakery in Bombay (48). Vitamin A was an ingredient of the fortification mixture at a level to provide 8,000 IU of vitamin A per kg of bread made from both dark and light wheat flour. This program was started in the largest flour mills in major population centers and was to be extended to nearly 200 flour mills. Programs have been considered in other countries such as Chile, Tunisia, Pakistan, Jordan and Iran. In the past Guatemala and South Africa have shown an interest in nutrified maize meal. The technology exists for the incorporation of vitamin A into wheat and maize products in amounts capable of making substantial improvement in the diets of consumers without impairing significantly the acceptance of the nutrified products. Other cereal grain products made from barley, sorghum, rye, etc., can be nutrified.

Rice(53,54,57)

Rice is consumed as a whole kernel product which makes nutrification more difficult than for a meal or flour product. Nutrification difficulties are compounded further by the custom of housewives washing rice before cooking. The added nutrients must be placed on rice in a rinse-resistant coating, yet in one which dissolves during the cooking process releasing the nutrients. White rice nutrification requires, therefore, an entirely different approach from that of flour or meal. Rice nutrification is accomplished by mixing one nutrified grain or kernel with 199 kernels of regular white rice. The nutrified kernel can be made by either coating white rice kernels with the nutrients or by producing simulated kernels made from a cereal dough composition containing the nutrients. Commercially, only the

former is being carried out at the present time. There are two procedures for manufacturing the nutrified rice grains. One of these, referred to as the HLR-Mickus procedure, was developed at Hoffmann-La Roche many years ago and described by Mickus (57). This procedure entails essentially soaking the rice in an acidified mixture of water-soluble vitamins, then adding various coatings, followed by a powdered iron source, vitamin A and calcium in a Trumbol mixer, finally whitening and polishing the nutrified grains. A second variation is the Wright process in which all the vitamins and minerals are introduced in powder form with suitable coating agents. Both procedures yield a stable coated product, good vitamin A retention (Table 13), rinse resistance and the nutrients biologically available in the cooked rice. With any nutrified rice product, excess water should not be used in cooking as water poured off after cooking will mean some loss of nutrients.

Sugar (Sucrose) (10,11,58-64)

A vehicle food carrier to be nutrified must be one or several which are consumed on a regular basis over the seasons of the year by the population of the involved country. For the Central American countries crystalline white sucrose was found to be such a food ingredient. The average consumption of sugar by the population of Central American countries was determined from data collected during the regional nutrition surveys of eating habits carried out in 1965-67 by the INCAP-OIR-National Governments cooperative effort. The chosen amount of vitamin A to be added to sugar would provide the FAO-WHO Recommended Daily Allowance for an adult man, namely, 750 μg or 2500 IU of vitamin A.

A project was initiated at INCAP with the cooperation of Roche in 1969 to test and implement the nutrification of sugar with a suitable form of vitamin A. Of the vitamin A types on the market, vitamin A palmitate, Type 250-SD or Type 250-CWS, were found to be adaptable to the project. Product Type 250-CWS was finally chosen. It is a pale yellow beadlet product with particles approximately 100 to 450 microns in size. Separation of the vitamin A particles from the sugar crystals is prevented by providing an edible bonding agent when blending the dry vitamin A with the crystalline sugar. In the nutrification of sugar, a vitamin A-sugar premix is first prepared. This premix is added in a set ratio, by means of a mechanical feeder, to the flow of nutrified sugar, followed by adequate mixing to insure uniformity of the final vitamin A nutrified product. At the concentration of vitamin A in nutrified sugar (50 IU per g), no significant color or flavor problems were encountered when consumed in hot coffee, tea, or orange, pineapple and lemon beverages and other food products. Biological effectiveness of the added vitamin A in sugar was demonstrated by animal assay and by increased vitamin A levels of blood serum of mothers, babies and children, and in the milk of nursing mothers after the consumption of vitamin A nutrified sugar. Stability data (Table 14) demonstrate adequate retention of added vitamin A in the product for time periods involved in manufacturing, marketing and consumer use. Long storage of vitamin A nutrified sugar is not necessary since sugar and vitamin A are regularly available for the nutrifying operations. Nutrification of sugar is commercially practiced in Costa Rica, Guatemala, Panama and Honduras and is expected to occur in El Salvador and Nicaragua. Interest has been shown in Brazil and Chile.

Seasonings

Seasonings in the past have been considered carriers of nutrients. Objections to seasoning as nutrient carriers are that (a) there is no uniform volume or weight of daily consumption, and (b) use is by individual preference. Salt is universally consumed and in some population units it may be one of the few processed items secured outside their agricultural economy. To consider it a vehicle or carrier for missing or inadequate nutrients consumed by these populations is a natural expectation.

Salt (NaCl)

Technical problems exist in the nutrification of salt. If the salt is of a pure grade, of low moisture content, of a uniform small particle size and will be packaged in moisture resistant containers, this type of salt can be successfully nutrified with a dry form of vitamin A ester as is evidenced by data (Table 15) secured on white fine crystalline (Diamond) salt. This salt was nutrified with a premix containing vitamin A palmitate (Type 250-SD), thiamin, riboflavin, pyridoxine, niacin and ascorbic acid. Over 90% of the vitamin A was retained after one year of storage. In the USA vitamin nutrified uniform crystal salt (Morton) is employed by some bakers for the nutrification of bread, buns and rolls with thiamin, riboflavin, niacin and iron. Another nutrified salt has been developed for snack toppings such as potato chips to provide supplementary vitamin A, thiamin, riboflavin, niacin and ascorbic acid. The general experience with nutrified high grade, uniform crystal salt therefore is similar to that with nutrified sucrose. Both must be centrally produced, have some degree of standardized quality, and be subjected to proper controls in the nutrification process and in subsequent packaging and distribution programs.

Salt from several countries (India, Java, etc.) received for the purpose of nutrification trials has been damp, of high moisture content (as high as 4%), of highly variable crystal size (up to 12 mm or more), and containing dissolved trace mineral impurities. As mentioned earlier vitamin A is a labile compound subject to these stress factors found in impure salt. These stress conditions overcome the stabilizing characteristics built into the dry vitamin A products. There is no known technology today that can bring about the successful uniform nutrification of these cruder salt products. Salt, it must be remembered, is a hygroscopic compound and unless it contains a dessicant and/or is packaged in relatively moisture resistant packages it will absorb moisture eventually.

MSG (12,65)

There are situations, with some seasoning items wherein small volume packaging is practiced and daily or uniform use of such packages is employed. Such is the case in the Philippines where surveys sponsored by the Cebu Institute of Medicine indicated that 94% of the children consumed monosodium glutamate (MSG) in seasoned food prepared in the home, that little variation existed in the per capita consumption, and that MSG was centrally produced and marketed by two local firms. MSG is produced as a pure crystalline substance of uniform physical characteristics and of low moisture content. The survey also revealed that one or two 2.4 g packets of MSG were added to the daily series of meals depending on the size of the family. With the cooperation of Philippine personnel and Cornell consultants, a study was initiated at Roche to nutrify MSG as all indications showed MSG to be a promising vehicle for conveying vitamin A to the

Philippine population. A technology was developed to bring about uniformity of particle distribution of a vitamin A nutrified MSG. Packets (15,000 IU) were prepared and stored to determine vitamin A stability (Table 16) which was found to be good to excellent over a six month period. Since MSG is locally available in the Philippines there is no need for long storage requirements. Biochemical and clinical studies have shown vitamin A nutrified MSG to be an effective delivery system.

SUMMARY

The availability of vitamin A and its esters manufactured by chemical synthesis in unlimited quantities has enabled populations around the world consuming inadequate amounts of this vital micronutrient and subject to potential loss of sight or other manifestations of vitamin A deficiency, to have hope for a better future life. A technology exists for the utilization of synthetic vitamin A toward this purpose by the creation of varied market application forms either (a) for the prophylaxis of vitamin A deficiency by oral intermittent massive dosing, (b) for therapy by means of intramuscular injection, and (c) for the addition of vitamin A to food (nutrification). Since vitamin A is a nutrient associated with the food supply, by the process of nutrification many commonly consumed foods may be made carriers or vehicles of vitamin A to assure deficient populations of a sufficient intake of the antixerophthalmic and anti-infective vitamin.

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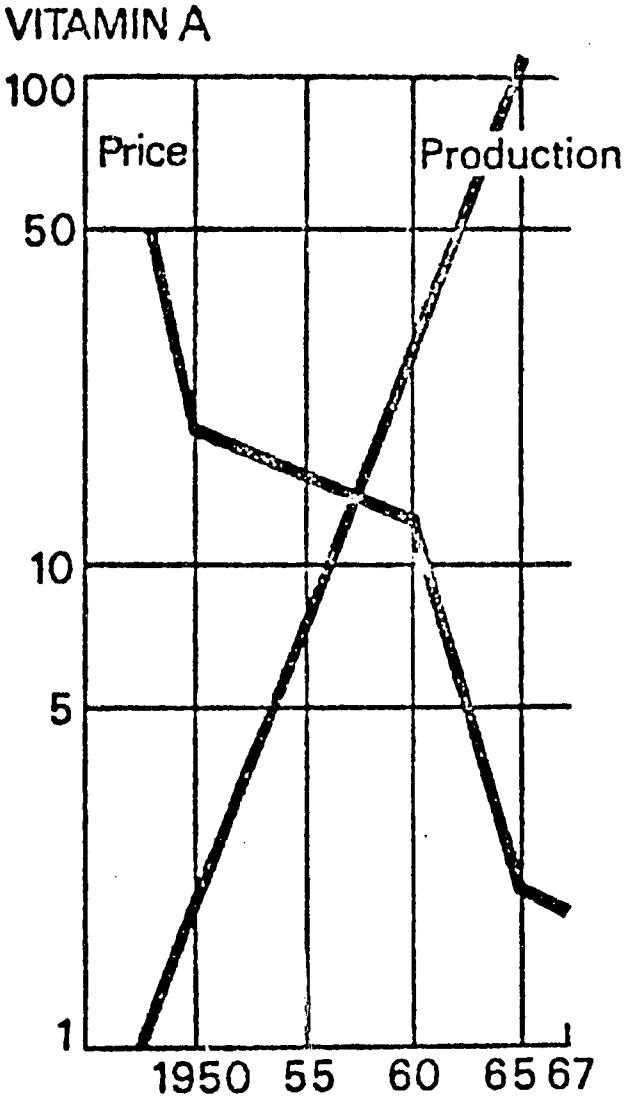
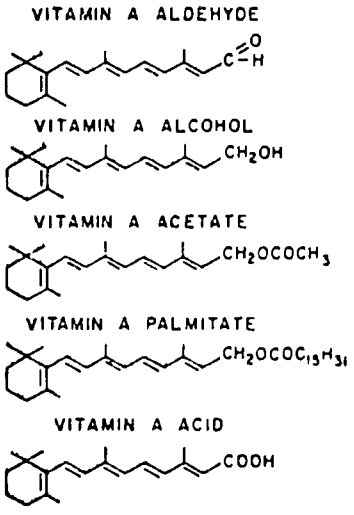
FIGURE 1



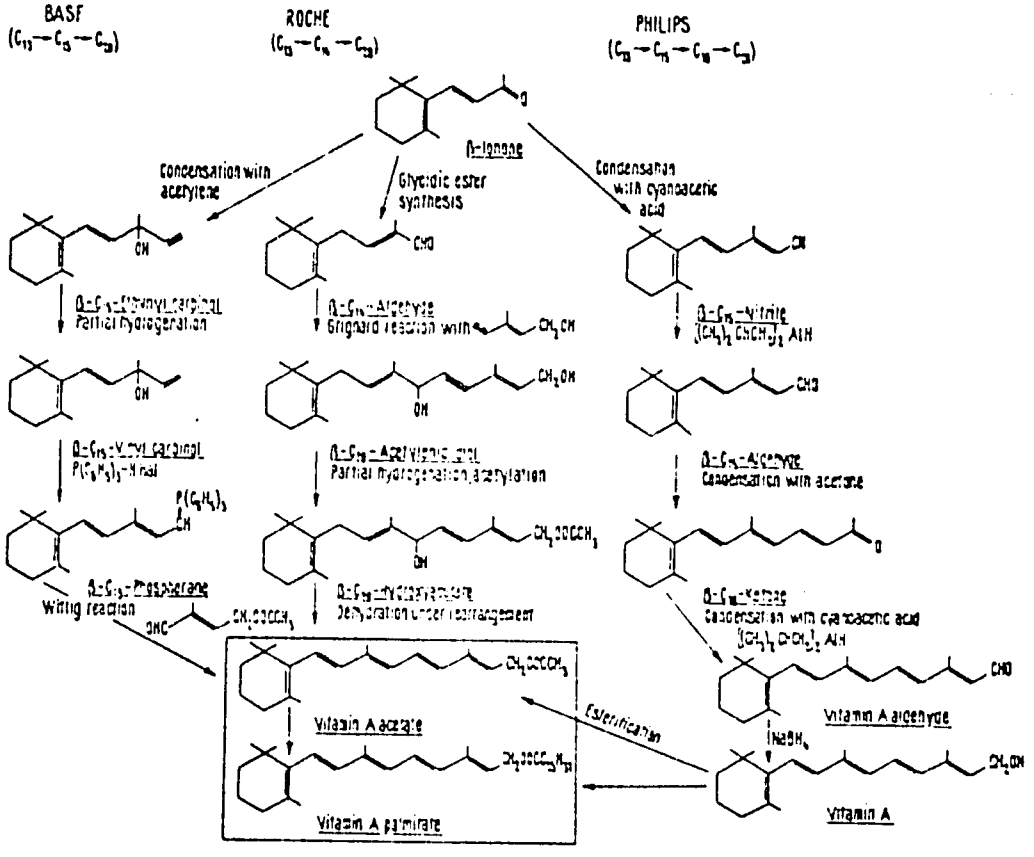
Logarithmic production - price pattern of vitamin A with time

FIGURE 2



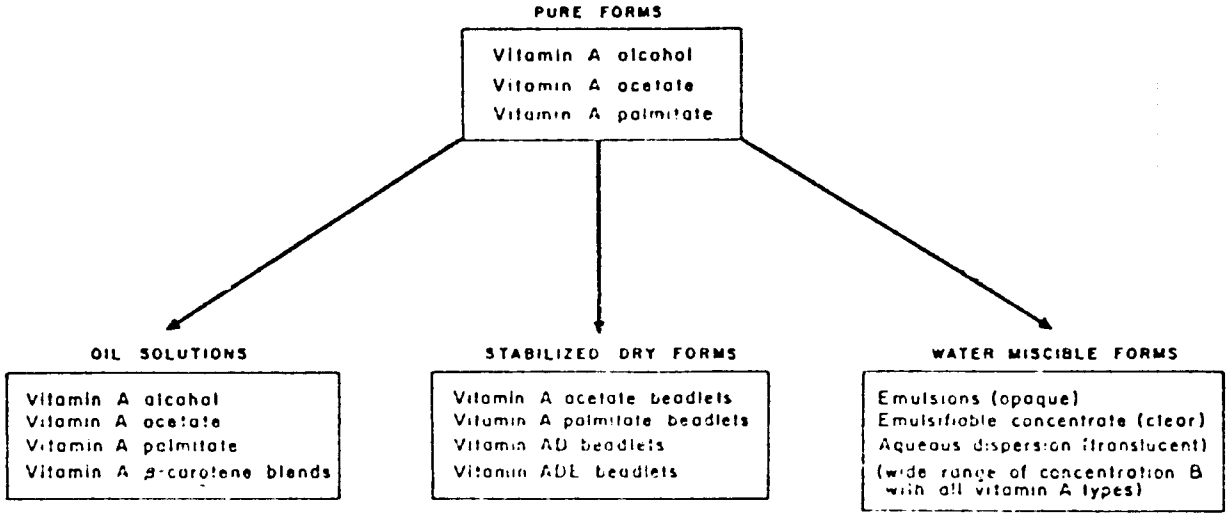
Structural formulas of vitamin A compounds

FIGURE 3



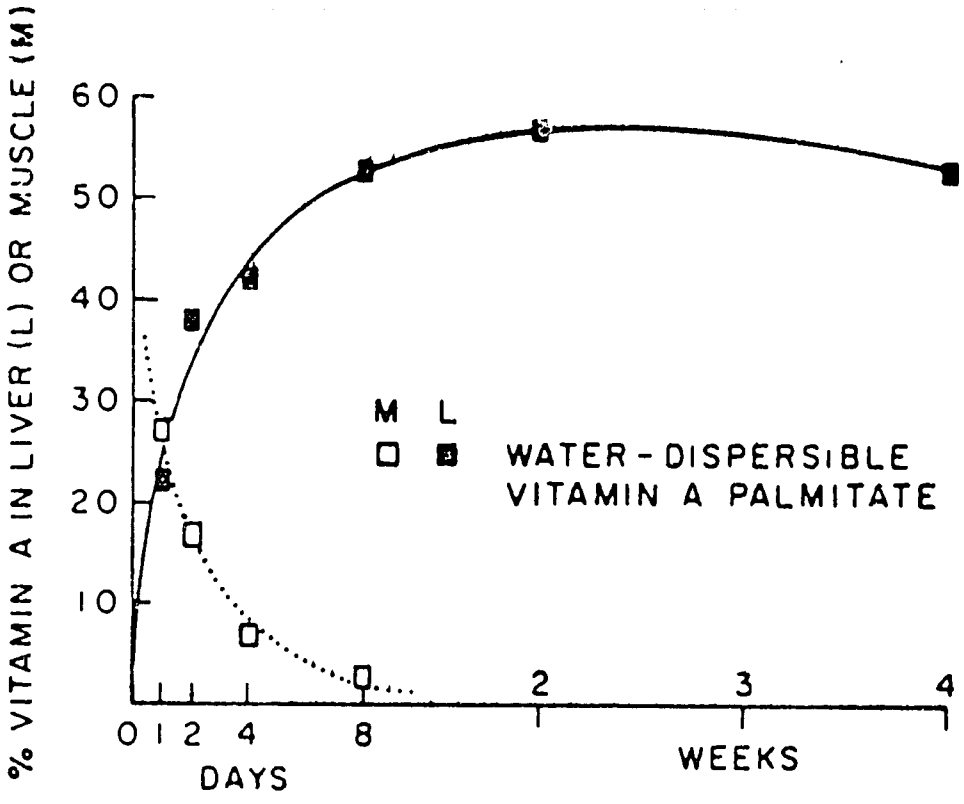
Technical synthesis of vitamin A esters

FIGURE 4



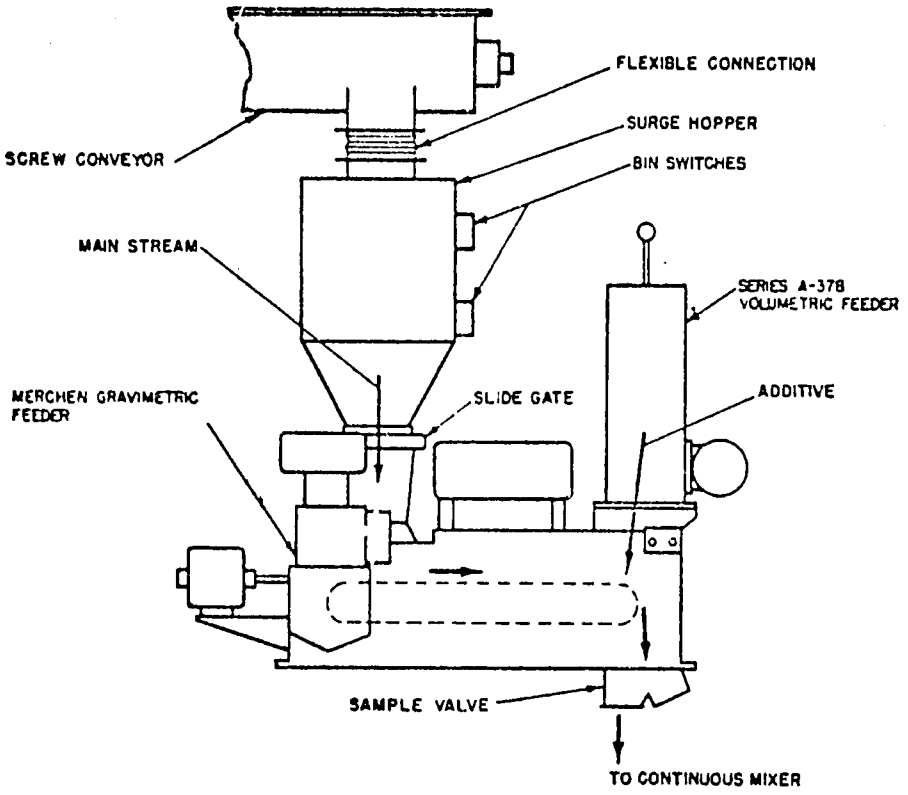
Chemical and physical forms of vitamin A in commercial production

FIGURE 5

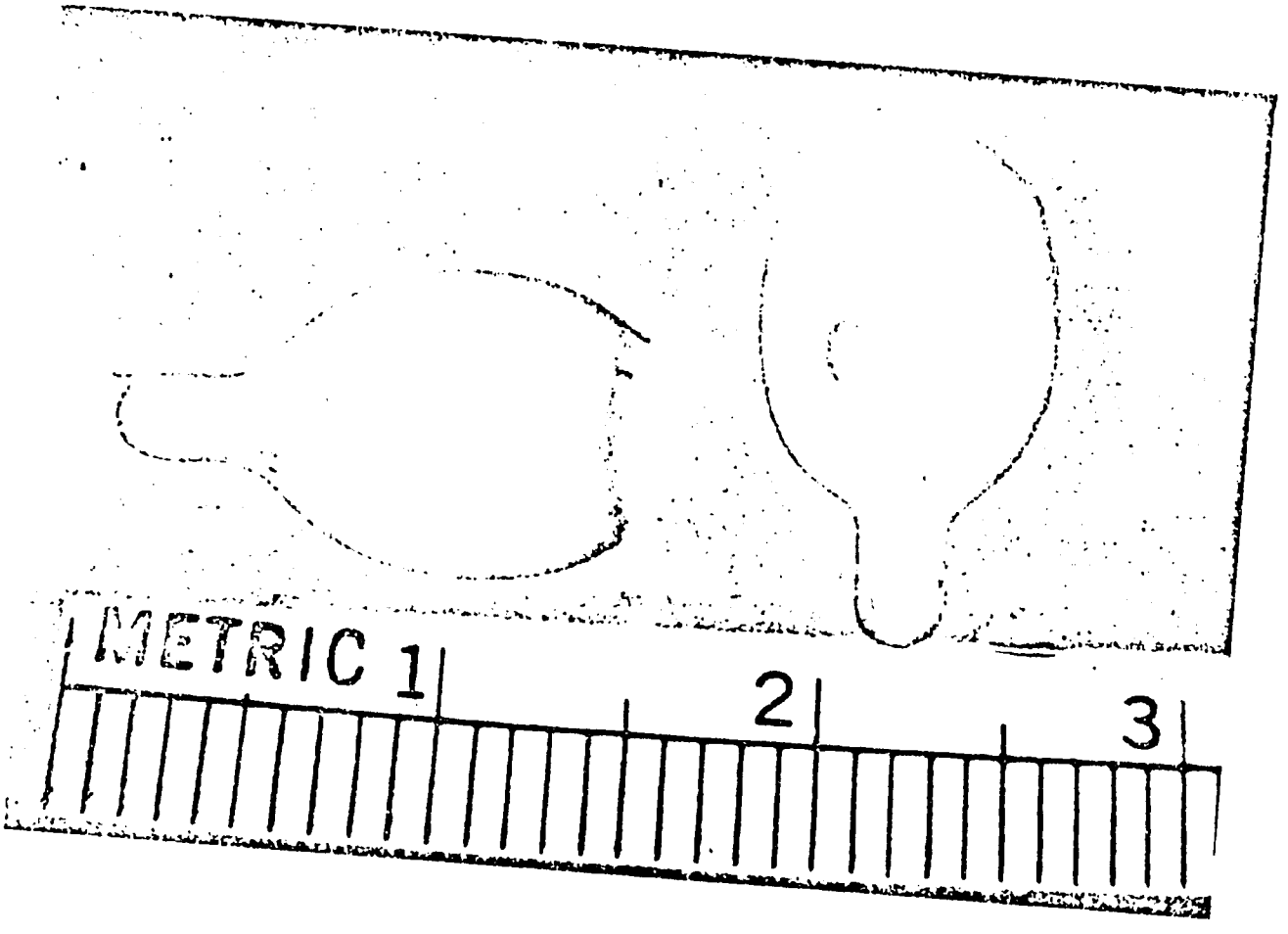


Translocation pattern of an effective water-dispersible vitamin A formulation injected IM in the muscle to the liver

FIGURE 6



Combination of gravimetric feeder for food product and volumetric feeder for micronutrient premix before the mixing unit in continuous food processing line (Courtesy Wallace & Tiernan)



Photograph of vitamin A-E capsule used in intermittent oral dosing

TABLE 1

PHYSICO-CHEMICAL DATA ON VITAMIN A

Item	Vitamin A palmitate	Vitamin A acetate	Vitamin A alcohol
Color of crystals (pure)	semi-solid, yellow	light yellow	light yellow
Melting point (°C)	28–29	57–58	62–64
Molecular weight	524.9	328.5	286.4
Solubility (%), 20°C			
Fats, oils, ether, chloroform	> 50	> 50	> 50
95% ethanol, isopropanol	< 10	< 10	< 10
Spectrophotometric data max. at 325 nm $E^{1\%}_{1cm}$ (ethanol)	975	1550	1835
Biological Activity Vitamin A value (IU/g)	1.82×10^6	2.9×10^6	3.33×10^6

TABLE 2

Stabilized Dry Forms of Fat-Soluble Vitamins and Processes

Products	Form or Type	Processes
1. Adsorbates and mixtures	Powders Granulates	Mixing, air-mixing, spray-mixing Granulating Crushing
2. Fat-based powders	Microspheres ("Fat-beadlets") Flakes Powders	Spray-congealing Drum-c ing Spraying or dropping into liquids Comminuting, (crushing of chilled mass), deep freezing and grinding Dispersion in aqueous liquids Mixing, air-mixing, spray-mixing
3. Dried emulsions and suspensions	Spherical or spheroidal beadlets Flakes Powders	Spray-drying (spraying into "hot gas") Spraying into liquids ("liquid catch") Spraying into powders ("powder catch") Spraying onto moving or stationary surface Double dispersion process (dual emulsion) Drum drying Air suspension coating Comminuting sheets of dried emulsion
4. Microcapsules	Spherical or spheroidal beadlets Agglomerates	Coacervation Air suspension coating (Wurster/WARF, USA) Multiorifice encapsulation (Southwest Research Institute, USA) Vacuum encapsulation (National Research Corporation, USA)
5. Inclusion compounds and various products (including chemical derivatives, precipitates and coagulates)	Crystals Powders Granules	Crystallization Precipitation and coagulation Chemical reaction

TABLE 3

Retention of Vitamin in Stored Soft Gelatin Capsules

Capsulation Run	Vitamin A Value (IU/Capsule) Initial	After Storage	
A	214,000[a]	---	211,000 (20 mo)
B	205,000	---	219,000 (25 mo)
C	209,000	---	206,000 (29 mo)
D	214,000		207,000 (31 mo)
E	303,000	294,000 (17 mo)[b]	296,000 (42 mo)
F	295,000	313,000 (17 mo)	300,000 (42 mo)
G	300,000	293,000 (17 mo)	292,000 (42 mo)
H	290,000	280,000 (17 mo)	297,000 (42 mo)

[a]All values by duplicate chemical assay

[b]Months of storage, 23°C.

TABLE 4

RETENTION OF VITAMIN A IN STORED WATER-DISPERSIBLE VITAMIN A PARENTERALS (INITAL ASSAY 120,000 IU/ml)

Storage Conditions	Per cent Retention
6 wks., 45°C	91
3 mo., 37°C	94
6 mo., 23°C	98
12 mo., 23°C	94
18 mo., 23°C	90
12 mo., 5°C	100
24 mo., 5°C	97

TABLE 5

Retention of Vitamin A and β-Carotene in Commercial Margarine

Manufacturer	Form of vitamin A	Initial assay	After 2 Months Storage			After 6 Months Storage		
			40°F.	40°F. & 75°F.	75°F	40°F.	40°F. & 75°F.	75°F
			(U.S.P. Units of Vitamin A Activity per Gram)					
J	Vitamin A	13,900	12,000 (86)	12,000 (86)	11,300 (81)	14,700 (106)	13,500 (97)	13,600 (98)
	Carotene	6,400	6,700 (105)	6,300 (98)	6,000 (94)	6,100 (95)	5,900 (92)	5,500 (86)
	Vitamin A	13,300	13,100 (99)	13,300 (100)	13,100 (99)	.....	.....	.....
	Carotene	6,100	5,900 (97)	5,900 (97)	5,900 (97)	.....	.....	.....
K	Vitamin A	13,800	14,400 (104)	13,500 (98)	13,800 (100)	.....	.....	.....
	Carotene	5,300	5,200 (98)	5,100 (96)	4,900 (93)	.....	.....	.....
	Vitamin A	12,300	13,100 (107)	12,700 (103)	12,300 (100)	.....	.....	.....
	Carotene	5,300	5,100 (96)	5,100 (96)	4,900 (93)	.....	.....	.....
L	Carotene	6,100	.....	.....	.....	6,100 (100)	5,700 (93)	5,200 (85)
M	Vitamin A	11,000	.....	.....	.....	10,600 (96)	.....	10,100 (92)
	Carotene	5,200	.....	.....	.....	4,800 (92)	.....	4,800 (92)
	Vitamin A	10,300	.....	.....	.....	10,600 (103)	.....	10,400 (101)
	Carotene	5,200	.....	.....	.....	5,000 (96)	.....	5,300 (102)
	Vitamin A	13,400	13,400 (100)	13,400 (100)	13,800 (103)	13,100 (98)	12,800 (94)	.....
	Carotene	5,200	5,050 (96)	5,200 (100)	4,850 (92)	5,300 (102)	4,700 (91)	.....
N	Vitamin A	13,350	.....	.....	.....	11,900 (89)	12,000 (90)	11,100 (83)
	Carotene	5,950	.....	.....	.....	5,400 (91)	5,400 (91)	5,300 (89)
	Vitamin A	12,700	13,000 (102)	12,500 (98)	11,800 (93)	15,600 (107)	12,800 (101)	11,800 (93)
	Carotene	6,400	6,300 (98)	5,800 (91)	5,800 (91)	6,700 (105)	6,300 (98)	5,300 (83)
O	Vitamin A	14,200	13,900 (98)	12,800 (90)	13,200 (93)	13,400 (94)	13,700 (97)	12,700 (89)
	Carotene	5,850	5,900 (101)	6,100 (104)	5,800 (99)	5,900 (101)	5,800 (99)	5,500 (94)
	Vitamin A	13,500	13,100 (97)	12,300 (91)	12,600 (93)	14,200 (103)	13,500 (100)	12,800 (95)
	Carotene	6,050	6,200 (103)	6,200 (103)	5,900 (98)	5,700 (94)	5,100 (84)	5,200 (86)
	Vitamin A	11,800	11,600 (98)	11,000 (93)	10,500 (89)	12,000 (102)	12,800 (108)	10,900 (92)
P	Carotene	5,750	5,700 (99)	5,600 (97)	5,400 (94)	5,600 (97)	5,500 (96)	4,900 (85)
	Vitamin A	13,500	13,000 (96)	13,800 (102)	13,800 (102)	12,400 (92)	12,800 (95)	11,500 (85)
	Carotene	6,000	5,700 (95)	5,700 (95)	5,400 (90)	6,100 (102)	5,900 (98)	.....
	Vitamin A	11,800	11,400 (97)	12,000 (102)	11,600 (98)	12,000 (102)	11,800 (100)	.....
	Carotene	5,550	5,300 (96)	5,200 (94)	5,100 (92)	5,700 (103)	5,500 (99)	5,200 (94)
	Vitamin A	12,300	12,000 (98)	13,100 (107)	12,300 (100)	12,100 (98)	12,100 (98)	12,300 (100)
	Carotene	5,050	4,900 (97)	4,900 (97)	4,800 (95)	5,400 (107)	5,050 (100)	4,500 (89)
Q	Vitamin A	12,400	12,500 (101)	12,600 (102)	13,100 (106)	12,100 (98)	11,700 (95)	10,900 (88)
	Carotene	5,500	5,600 (102)	5,600 (102)	5,400 (98)	5,300 (96)	5,200 (95)	4,700 (86)
	Vitamin A	13,000	12,900 (99)	14,200 (109)	11,400 (87)	11,500 (88)	12,600 (97)	11,300 (87)
	Carotene	6,500	6,400 (99)	6,300 (97)	5,900 (91)	6,300 (97)	6,200 (95)	5,400 (83)
	Average							
	Vitamin A		(99)	(99)	(96)	(98)	(98)	(92)
	Carotene		(99)	(98)	(94)	(99)	(95)	(89)

NOTE: Figures in parentheses are % retention based on initial assay value.

TABLE 6

Retention of added vitamin A in stored nonfat dry milk

Sample no.	IU/lb Vitamin A added	IU/lb Initial assay	% retention: Polyethylene bags Wk/98°F. 3	6	12	Polyethylene bags Wk/113°F. 3	6	12	Kraft-foil bags Wk/98°F. 3	6	12	Kraft-foil bags Wk/113°F. 3	6	12	Tin cans Wk/98°F. 3	6	12	Tin cans Wk/113°F. 3	6	12
1	10,000	10,100	93	97	100	101	88	89	104	99	100	111	100	86	99	100	95	92	88	85
2	10,000	10,400	100	91	95	97	88	86	99	100	98	109	100	87	90	88	94	82	91	82
			Mo/75°F. 3	6	12	Mo/40°F. 3	6	12	Mo/75°F. 3	6	12	Mo/40°F. 3	6	12	Mo/75°F 3	6	12	Mo/40°F 3	6	12
1	10,000	10,100	108	87	69	100	76	85	104	79	78	109	74	84	111	82	85	115	85	96
2	10,000	10,400	93	82	85	106	80	84	103	78	77	121	79	107	108	85	89	115	78	94

TABLE 7

STABILITY OF VITAMIN A FOLLOWING RECONSTITUTION OF VITAMIN A FORTIFIED NONFAT DRY MILK

Sample[a]	Reconstitution storage (hr at 40°F)	% vitamin retention Wet[b]	Dry[b]
A	24	102	99
	72	101	96
B	24	96	95
	72	86	89
C	24	99	97
	72	98	95
D	24	92	98
	72	92	96
E	24	96	99
	72	92	97

[a]Samples chosen for reconstitution studies already had a variable history of storage in the dry state, for example, sample A, 1 month at 75°F; sample C, 3 months at 98°F; and sample E, 12 months at 75°F. Values represent duplicate vitamin A assays.

[b]Technique of nutrification

Table 8

Retention of Vitamin A in Brewed Tea

Tea type	Form of Vitamin A	How applied to tea	Percent recovery in brewed tea	
			5-min cooking	1-min cooking
Dust	Palmitate 250-SD powder	Dry mixing	100	100
Leaves	Palmitate special water-soluble oil[a]	Sprayed	45	30
Leaves	Palmitate emulsion[a]	Sprayed	100	100
Leaves	Acetate emulsion[a]	Sprayed	50	4

[a] Diluted in 50% sucrose solution

TABLE 9

STABILITY OF THE VITAMIN-MINERAL PREMIX IN FLOUR (12% H_2O)

Supplement	IU or mg per 100g			% Retention	
	Initial Assay			6 mo. at 23°C	
	Label Claim	Premix A[a]	Premix B[b]	Premix A[a]	Premix B[b]
Vitamin A[c], IU	1600	1730	1800	101	100
Vitamin B_1, mg	0.64	0.76	0.71	99	101
Vitamin B_2, mg	0.40	0.39	0.40	100	100
Vitamin B_6, mg	0.44	0.48	0.56	100	100
Niacin, mg	5.29	5.60	5.60	100	100
Folic acid, mg	0.07	0.063	0.07	100	96
Iron, mg	8.81	9.34	9.46	97	100
Calcium, mg	198.2	209.0	NR[d]	NR	---
Magnesium, mg	44.1	47.0	NR	NR	---
Zinc, mg	2.2	2.3	NR	NR	NR
Moisture, %		11.6	12.1	11.8	12.5

[a]Fortified with the complete vitamin-mineral supplement

[b]Vitamin-mineral supplement without calcium and magnesium

[c]Type 250-SD

[d]NR = Not run

TABLE 10

RETENTION OF ADDED VITAMINS-MINERALS IN BAKED BREAD (38% H_2O)

Nutrient	Level Added IU or mg/lb	% Retention			
		After baking		5 Days at RT	
		Premix A[a]	Premix B[b]	Premix A[a]	Premix B[b]
Vitamin A, IU	992	83	95	83	95
Vitamin B_1, mg	1.8	101	101	101	100
Vitamin B_2, mg	1.1	105	101	108	101
Vitamin B_6, mg	1.2	100	105	100	105
Niacin, mg	15.0	100	102	100	106
Folic acid, mg	0.19	94	105	80	102
Iron, mg	24.8	104	105	NR[c]	NR
Calcium, mg	558.0	NR	---	NR	---
Magnesium, mg	124.0	107	---	NR	---
Zinc, mg	6.2	NR	NR	NR	NR

[a]Fortified with the complete vitamin-mineral supplement

[b]Vitamin-mineral supplement without calcium and magnesium

[c]NR = Not run

TABLE 11

STABILITY OF VITAMIN-MINERAL PREMIX IN YELLOW CORN MEAL (6.5% H_2O) AND IN CORN GRITS (11.4% H_2O) AT ROOM TEMPERATURE (23°C)

Nutrient (IU or mg/lb)	Corn Meal			Corn Grits		
	Initial	3 mo.	6 mo.	Initial	3 mo.	6 mo.
Vitamin A[c], IU	6000 IU	5820 IU	5880 IU	6000 IU	5700 IU	4850 IU
Thiamin, mg	3.17	3.25	3.07	3.83	3.81	3.86
Niacin, mg	26.0	25.7	NR[b]	36.0	36.0	NR
Pyridoxine HCI, mg	4.5	4.0	4.5	4.4	4.3	4.5
Folic acid, mg	0.6	0.5	0.5	0.49	0.45	0.5
Riboflavin, mg	2.02	1.81	1.96	2.82	2.64	2.58
Iron, mg	41.0	39.0	40.0	55.0	52.1	56.0

[a]Type 250-SD

[b]NR = Not run

TABLE 12

RETENTION OF VITAMIN A IN COOKED GRITS AND COOKED YELLOW CORN MEAL

	Per cent Retention after Cooking Time (minutes)				
	4	5	6	10	30
Quick grits	80	---	75	70	---
Regular grits	---	---	---	---	66-75
Yellow corn meal	---	87	---	---	---

TABLE 13

STABILITY OF HLR-MICKUS NUTRIFIED RICE PREMIX AND RETENTION AFTER COOKING OF NUTRIFIED RICE

Nutrient	Per lb of premix			Per lb of rice	
	Initial	6 mo. room temp. (23°C)	4 wk (45°C)	uncooked rice with premix diluted 1:200	rice cooked nutrified (1380g)[a]
Vitamin A[b], IU	1,200,000	1,050,000	1,050,000	6,000	5,800
Pyridoxine, mg	400	400	390	2.1	2.5
Folic acid, mg	46	44	41	0.23	0.27
Vitamin E, IU	3,240	3,210	3,200	16	15.9
Thiamin, mg	550	530	NR	2.6	NR

[a] 1 lb of uncooked rice = 1,380 g of cooked rice

[b] Type 250-SD

NR = Not run

TABLE 14

STABILITY OF VITAMIN A IN NUTRIFIED SUGAR

			Percent Retention of Vitamin A						
			45°			23-25°			
Product	Trial	Type Vitamin A	1 mo.	2 mo.	3 mo.	1 mo.	2 mo.	3 mo.	6 mo.
(Premix)[a]									
A	1	250 - CWS	92	83	--	99	98	--	99
B	1	250 - SD	87	79	--	97	95	--	96
C	2	250 - CWS	--	--	86	--	--	92	94
D	2	250 - SD	--	--	77	--	--	93	89
E	3	250 - CWS	93	--	81	97	--	90	90
F	3	250 - SD	92	--	74	100	--	95	93
(Nutrified Sugar)[b]									
G	4	250 - CWS	91	--	76	96	--	96	92
H	4	250 - SD	90	--	73	100	--	88	85

[a]Vitamin A - sugar premix (50,000 IU/g)

[b]Vitamin nutrified sugar (50-70 IU/g)

TABLE 15

RETENTION OF ADDED VITAMIN A[a] IN NUTRIFIED SALT[b]

	IU/15g	% Retention
Initial value	4300	---
3 mo., 26°C	4200	98
6 mo., 26°C	4110	96
9 mo., 26°C	4100	95
12 mo., 26°C	4030	94

[a]Fine crystalline Diamond salt.

[b]Data of Cort, Roche Product Development Dept.

TABLE 16

Retention of Added Vitamin A in Nutrified MSG

with Fe and A (Storage Data)

Time Temperature (°C)	Per cent Retention		
	Vitamin A[1] Only	Vitamin A plus F[2] Low[3]	High[4]
1 mo., 45°C	82	92	89
2 mo., 45°C	61	---	---
3 mo., 37°C	78	95	89
6 mo., 37°C	75	81	73
12 mo., 37°C	---	62	60
3 mo., 23°C	---	100	100
6 mo., 23°C	89	89	83
12 mo., 23°C	79	87	84

[1]Vitamin A palmitate type 250SD (60 mg or 15,000 IU/packet)

[2]Storage trial started 8-1/2 months after A nutrification

[3]Ferric orthophosphate (13.5 mg Fe/packet)

[4]Ferric orthophosphate (27 mg Fe/packet)

XI INTERNATIONAL CONGRESS OF NUTRITION.

DIETARY DEFICIT OF VITAMIN A IN POPULATIONS. APPROACHES TO CORRECT IT.

Guillermo Arroyave[1], Juan Rodolfo Aguilar, [2]

Marina Flores[3]

Institute of Nutrition of Central America and Panama
(INCAP)

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1 Chief of the Program of Control of Hypovitaminosis A in Central America and Panama, Division of Biology and Human Nutrition, INCAP
2 Field Director, Program for the Control of Hypovitaminosis A in Central America and Panama, Division of Biology and Human Nutrition, INCAP
3 Chief, Section of Dietary Investigations, Division of Applied Nutrition, INCAP

The multiple causes of food and nutrition problems have been increasingly recognized in recent years, and any solutions to such problems must confront their social and economic causes. Since the broad socio-political changes that would permit such an approach are seldom forseeable, however, scientists and technologists must design short term nutrition interventions which attack individual dietary deficits and/or nutrition problems of a population in order of priority.

Table 1 illustrates the results of an analysis of dietary/nutrition problems for Central America. The extent of hypovitaminosis A, one of the five most serious problems identified in the analysis, was amply documented in 1965-67 through dietary and biochemical studies shown in Tables 2 and 3.[1]

More recent studies confirmed that the hypovitaminosis A problem had continued and had increased in severity during the last ten years.[2] The basic dietary characteristics of the rural populations of the area directly related to this problem are: a) the absence or insignificance of animal foods containing retinol in the diet; and b) the consequent dependence on sources of carotenes (leafy green and yellow vegetables).

For a number of reasons, some not well understood, the consumption of these sources of provitamin A is very low, however. Evidence from the literature also indicates that under the best circumstances the biological utilization of carotenes is quite inferior to that of retinol and may be more drastically affected by such interfering factors as intestinal alterations and parasitism.[3]

In 1969, research was initiated to develop a process through which retinol could be added to a "universal" food vehicle to deliver this needed nutrient to essentially all the population.[4] White sugar was selected and a water dispersable retinyl palmitate was chosen as the enriching material based upon satisfactory results concerning chemical stability, taste acceptability and biological availability. A segregation problem of the vitamin A preparation from the sugar was solved by the development of a premix where the two ingredients become attached. Although the premix can be added manually at the level of the centrifuge of the sugar factory, simple, inexpensive feeders have been developed and locally manufactured in Guatemala and Panama. With this process available, INCAP proposed the implementation of National Programs of Sugar Fortification with vitamin A to all its member countries. Four countries (Costa Rica, Guatemala, Panama and Honduras) have approved compulsory fortification and are conducting intervention programs.

Although vitamin A fortification of sugar had demonstrated effectiveness in the laboratory and in pilot studies with small population groups, its effectiveness and cost had to be assessed at the national level. An evaluation program was, therefore, designed and implemented in Guatemala to determine the biological effectiveness; assess the feasibility and efficiency of the delivery system; and estimate the cost of intervention. Baseline information was secured about the vitamin status of the population prior to the initiation of the program and vitamin A status was evaluated at six-month intervals during the two-year period. The major variables studied were:

1) intake of food sources of vitamin A; 2) intake of sugar; 3) blood serum retinol levels of children below six years of age; 4) retinol concentration of human milk; 5) clinical examination with particular emphasis on signs associated wtih vitamin A deficiency; 6) hospital and clinical registration of cases of eye lesions attributed to hypovitaminosis A; and 7) retinol content of liver samples from coroners' autopsies from a General Hospital.

The data indicated marked improvement in the biochemical parameters of the population, suggesting a significan effect of this major public health nutritional intervention. Findings concerning children's blood serum and human milk are summarized in Tables 4 and 5, respectively. Analysis of the dietary data shows complete stability of the population regarding intake of vitamin A from natural sources, indicating that the changes observed are due to the fortification.

The studies referred to above were conducted in population samples of each of the major ecological regions of Guatemala. The study is based on the premise that the application of a public health intervention without adequate built-in evaluation is wasteful because the potential of the intervention for application to similar situations elsewhere would be undetermined. Since most population groups in the underdeveloped world are suffering from vitamin A deficiency, the implications of a successful sugar fortification program in Central America would be of interest to many countries.

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TABLE 1

ANALYSIS OF THE NUTRITIONAL PROBLEMS AND IMMEDIATE PLAN OF ATTACK IN CENTRAL AMERICA AND PANAMA

What are the nutrient deficits of the population?	Source	Action
Calories Proteins	Basic foods, Ex.: corn-beans, rice-beans, wheat, sugar, fats and oils etc.	The production availability and effective demand of basic foods as defined by the National Food and Nutrition Policy is a Government responsibility as part of the National Development Plan (by direct means: government-producer or by indirect means: subsidies, other incentives)
<u>Other nutrients</u>		
Iodine Vitamin A Iron etc.	Addition of the needed nutrients to appropriate food vehicles	Implementation of simple inexpensive technology for food enrichment or fortification applicable to underdeveloped countries (in some cases already available: iodine, vitamin A).

Table 2

NUTRITIONAL SURVEY IN CENTRAL AMERICA AND PANAMA (1965-1967)

Country	Number of families surveyed	Level of adequacy of vitamin A in diet (percent of adequacy)				
		< 25	25-49	50-74	75-99	100 or more
		- Percent of families at each level -				
Guatemala	200	45	22	10	6	17
El Salvador	278	69	19	7	3	2
Honduras	323	57	26	9	2	6
Nicaragua	331	45	23	13	8	11
Costa Rica	414	44	26	11	7	12
Panama	352	42	32	13	5	8

TABLE 3

NUTRITIONAL SURVEY IN CENTRAL AMERICA AND PANAMA (1965-1967)

Prevalence of Hypovitaminosis A in Children Younger than 15 Years
(Determined According to Serum Levels)

Country	0-4 years		5-9 years		10-14 years		0-14 years	
	Percent prevalence	Number of cases	Percent prevalence	Number of cases	Percent prevalence	Number of cases	Percent prevalence	Number of cases
Guatemala	26.2	219,100	16.2	108,300	11.1	62,700	18.8	390,100
El Salvador	43.5	241,200	43.5	190,700	22.4	82,300	37.8	514,200
Honduras	39.5	137,000	29.0	81,200	21.9	51,609	31.3	269,800
Nicaragua	19.8	56,900	18.5	50,500	6.4	14,400	15.5	121,800
Costa Rica	32.5	96,600	25.6	60,300	11.7	22,400	24.6	179,300
Panama	18.4	38,300	12.1	20,600	9.7	13,600	14.0	72,500
Total	31.2	789,100	24.7	511,600	14.3	247,000	24.4	1,547,700

Note: Based on population estimates of July 1965.

TABLE 4

EVALUATION OF FORTIFICATION OF SUGAR WITH VITAMIN A
BLOOD SERUM RETINOL CONCENTRATIONS* IN PRE-SCHOOL
CHILDREN

Guatemala, 1975-1977

Survey period		No. cases	Percent of serum level by category			
			<10	10-19.9	20-29.9	30 > *
Basal	Oct-Nov 75	549	3.3	18.2	34.4	44.1
1	Apr-May 76	586	1.0	13.1	35.5	50.4
2	Oct-Nov 76	645	0.3	4.8	25.6	69.3
3	Apr-May 77	674	0.9	10.2	28.0	60.9
4	Oct-Nov 77	721	0.3	8.9	36.1	54.6

* μg/100 ml

TABLE 5

EVALUATION OF FORTIFICATION OF SUGAR WITH VITAMIN A

CHANGES IN RETINOL CONCENTRATION OF HUMAN MILK*
ASSOCIATED WITH FORTIFICATION OF SUGAR

Guatemala, 1975-1977

Survey period		No. of cases	Percent of cases	
			<30*	30>*
Basal	Oct-Nov 75	283	61.2	38.8
1	Apr-May 76	312	54.1	45.9
2	Oct-Nov 76	237	41.3	58.7
3	Apr-May 77	289	29.4	70.6
4	Oct-Nov 77	254	39.4	60.6

* μg/100 ml

NUTRITION STRATEGIES: FORTIFICATION OF MONOSODIUM GLUTAMATE

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Florentino S. Solon, M.D., M.P.H.
Tomas L. Fernandez, M.D., M.P.H.
Michael C. Latham, M.D., M.P.H.
Barry M. Popkin, M.S., Ph.D.

ABSTRACT

Fortification of monosodium glutamate (MSG) was undertaken in Cebu, Philippines as one of the intervention strategies for vitamin A deficiency by the Cebu Institute of Medicine and Cornell University, under the auspices of the Nutrition Center of the Philippines.

The fortified product was developed and tested with the cooperation of Union Chemicals, Inc. (Manila) and Hoffman-La Roche, Inc. of USA and Switzerland. Each 2.4 gram MSG packet was fortified with 15,000 IU of vitamin A and loss rates studies showed an average retention of 12,085 IU after a storage period of twelve months at room temperature.

Distribution of fortified MSG to sample families was done weekly on a two pack per family per day basis. Subsequent weekly supplies were given to the number of empty packs presented.

Feedback from mothers showed that the fortified product was very acceptable to them and the children.

The MSG fortification program reduced the active clinical signs of xerophthalmia by 76% compared to reductions of only 73% and 44% by the high dosage capsule and the public health-horticulture intervention strategies respectively. The mean serum A levels in the MSG group increased by some 7.5 mcg per cent as against a decrease by about 3.6 mcg per cent in the non-MSG group. Further, the MSG fortification program raised the mean serum A values in the deficient groups by 19 mcg per cent and those in the low groups by 14.4 mcg per cent on.

It appears that MSG fortification is most effective in that it reduced significantly the active clinical signs of xerophthalmia and raised the serum A levels of both deficient and low level groups.

A three-province expanded pilot MSG fortification program is now being conducted in the Philippines.

I. INTRODUCTION

An investigation of vitamin A deficiency was undertaken in four ecologic zones in Cebu Philippines, representing the urban slum, the urban fringe barrios, the rural coastal or fishing villages, and the rural hinterland or semi-mountainous barrios. This study was undertaken jointly by the Cebu Institute of Medicine in Cebu Philippines and Cornell University in New York, USA under the auspices of the Nutrition Center of the Philippines, and with support from the National Science Development Board, the World Health Organization, the US Agency for International Development and the Ministry of Health.

The 3 year pilot phase included three stages:

1. the determination of the magnitude of vitamin A deficiency
2. The identification of the various determinants of the problem and the determination of alternate means of prevention, control, and/or elimination.
3. the implementation and evaluation of intervention strategies:
   - 3.1. Public Health Intervention (PHI)
     a program of comprehensive health services aimed at disease control and prevention, increased home vegetable production, improved vegetable consumption by children and included community organization, establishment of a barrio pharmacy and the training of leaders and youths.
   - 3.2. Distribution of massive dosage capsules containing 200,000 IU of vitamin A and 40 IU of vitamin E every 6 months to children age 1 to 16 years.
   - 3.3. Fortification of monosodium glutamate (MSG) with vitamin A.

The total study sample included some 1715 children age 1 to 16 years in 626 families.

Prevalence of Xerophthalmia

Ocular examination of some 1715 children showed comparatively high prevalence of conjunctival xerosis, nightblindness, and Bitot's spots with conjunctival xerosis (Table 1).

Table 1. PREVALENCE OF XEROPHTHALMIA - NEW CLASSIFICATION

CLASSIFICATION	SIGNS-PRIMARY	PREVALENCE per cent
X1A	Conjunctival xerosis	2.0
X1B	Bitot's spots with conjunctival xerosis	1.4
X2	Corneal xerosis	0.9
X3A	Corneal ulceration with xerosis	0.0
X3B	Keratomalacia	0.0
	SIGNS-SECONDARY	
XN	Night blindness	1.6
XF	Xerophthalmia fundus	0.0
XS	Corneal scars	0.3

N = 1715

The above results were gathered by out trained research physicians and all positive findings were verified by a consultant ophthalmologist.

Serum A values in the low and deficient categories were found in 57% of the children using the ICNND Standard (Table 2).

Table 2. DISTRIBUTION OF SERUM A VALUES ICNND STANDARDS BASELINE STUDY

Serum A value mcg%	ICNND CATEGORY	Per Cent
below 10%	DEFICIENT	17
10 - 19	LOW	40
20 - 49	ACCEPTABLE	40
50 plus	NORMAL	3

N = 1715

Our definition of a case of vitamin A deficiency, however, was based on a comgination of the presence of the clinical criteria as set forth in the WHO classification and either low or deficient serum A levels according to the ICNND Standard.

The preponderance of the nutritional problem, vitamin A deficiency, was found in males, especially in the 7 to 16 years age group and in the urban slum or squatter areas.

The lowest prevalence was seen in the rural hinterland and among females in the 7 to 16 years age group in the rural coastal zone (Table 3).

Table 3. PREVALENCE OF XEROPHTHALMIA: CLINICAL SIGNS PLUS LOW OR DEFICIENT SERUM A LEVELS

BY SEX, AGE, AND ECOLOGIC ZONE

Per Cent

ZONE	AGE & SEX GROUPS					
	1-6 YEARS		7-16 YEARS		TOTAL	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
URBAN						
Squatter	4.3	5.1	12.7	4.3	7.2	4.8
Fringe barrio	3.7	3.9	1.9	4.4	3.1	4.0
RURAL						
Coastal	4.1	2.9	3.1	0.0	3.8	2.0
Hinterland	3.4	2.1	5.5	1.4	4.1	1.8
TOTAL AVERAGE	4.0	3.5	5.9	2.6	4.5	3.2

N = 1715

Community Diagnosis

To determine the presence of a significant nutritional problem, we compared the results of the baseline study with the IVACG criteria for community diagnosis (Table 4).

Table 4. BASELINE SURVEY RESULTS VS. CRITERIA FOR COMMUNITY DIAGNOSIS OF XEROPHTHALMIA AND VITAMIN A DEFICIENCY

CRITERIA	BASELINE RESULTS
CLINICAL	
1 X1B > 2.0%	1.7%
2 X2 + X3A + X3B > 0.01%	0.5%
3 XS > 0.1%	0.3%
BIOCHEMICAL	
Serum A < 10 mcg % > 5%	17%

This clearly shows that the results of the baseline study exceed almost all the criteria signifying the presence of a significant nutritional problem.

This paper will deal mainly with fortification implemented with two other intervention strategies, the program effects and a short discussion summarizing the Cebu experiment. It will also briefly present the results of the MSG Consumption Survey conducted in two other provinces and the on-going pilot MSG fortification project.

II. MATERIALS AND METHODS

Fortification of foods with appropriate amounts of vitamin A has the advantage of reaching all those who consume the fortified food and requires neither the active participation of the population nor an elaborate and costly delivery system The problem, however, is to select a food vehicle for fortification that:

1. is widely consumed, especially by children at risk
2. passes through a manufacturing process where fortification is feasible
3. shows little variation in per capita consumption
4. is organoleptically suitable after it is fortified
5. is stable once fortified.

Consumption Survey

To determine which food or combination of foods could provide the role of universal carrier, information on the frequency of intake, method of cooking, and method of obtaining a variety of foods was collected through a survey of 626 households in the study area.

The identified potential carriers are presented in Table 5.

Table 5. CHILDREN REACHED WITH FORTIFIABLE FOOD ITEM AT LEAST ONCE A WEEK, 12 CEBU BARRIOS 1974

FOOD ITEM	PERCENTAGE WHO CONSUME THIS ITEM
Biscuit/Bread	97
Table Salt	95
Monosodium glutamate (MSG)	94
Corn Grits	93
Refined White Sugar	63
Margarine	39
Rice	38

N = 1779

Biscuits, bread, and other flour-based products lead the list of fortifiable items. Since the number of bakeries is too great, it was not considered practical to fortify this item for the purposes of the study.

Small producers ordinarily produce table salt by drying sea water under the sun. They, like bakeries, are so many that fortification of this item would not be practical.

The same is true for corn grits. In some rural hinterland areas, for example, milling of the corn grains may be done through home-made stone mills and therefore is not controllable. The pople in the study are predominantly corn-eating, which explains the low position of rice in the consumption scale. In areas where rice is the chief staple, the converse will be obtained.

Selection of Monosodium Glutamate (MSG)

Monosodium Glutamate (MSG) is marketed under some three or four brand names, but approximately 90% of the market is controlled by the brand AHI-NO-MOTO which is produced and distributed in the country by one company. The high position of MSG in the consumption list, its manufacture and distribution by only one firm, its control of 90% of the market, and the physical feasibility of fortification were the considerations made in choosing this item.

Also, MSG was found to be available in small stores even in remote areas and the average daily consumption rate per family was approximately two 2.4 g packets. These results are based on a detailed study of the MSG consumption patterns of 227 households.

Mechanics of MSG Fortification

The mechanics of adding vitamin A to the MSG were worked out by Hoffman-La Roche of USA and Switzerland. Since MSG comes in granules, its physical state was changed to fine powder and each 2.4 g packet was fortified with 15,000 IU of vitamin A. Subsequent analyses for content and loss rates showed that after a storage period of 12 months at room temperature (23°C), the average content per packet was 12,085 IU. While it is true that temperatures higher than 23°C might be obtained in the country for most months of the year, possible increased losses may be offset by fortification on a short term interval basis to avoid prolonged storage.

Possible Harmful Effects of MSG and Vitamin A Toxicity

Our review of the literature and consultation with a number of authorities satisfies us that the dangers of toxicity either from the MSG or from the vitamin A are negligible. One of the advantages of MSG, like salt (and unlike sugar, tea, and other suggested vehicles for fortification) is that persons currently using MSG are unlikely to increase their consumption of the product to any great degree. MSG, if used daily by a family is used to the same extent whether the family is in the upper or lower income groups.

Toxicity from excess consumption of vitamin A would not occur from fortification of MSG at the suggested levels, for the same reason that toxicity has not been reported as a result of vitamin A fortification of margarine and other foods in Europe or North America.

MSG Distribution Strategy

Fortified MSG was distributed to sample families at the rate of two packs per day on a weekly supply basis. The mothers were asked to keep the empty wrappers and to exchange them for an equal number of new packets the following week. The information provided to the mothers included the fact that the MSG given was fortified with vitamin A, that they continue to use it in the manner they were used to, that they observe any changes in the food to which the MSG had been added, that they make the young children the priority for food, and that they try to watch for any effects.

Some feedback obtained randomly from mothers included comments that:

1. the fortified MSG improved the taste of cooked food much better than the commercial non-fortified MSG;

2. the children consumed more of the food to which the fortified MSG had been added;

3. the food to which fortified MSG had been added had a "vitamin" smell;

4. they had "more regular" bowel habits after consuming food with fortified MSG for some time;

5. they and the children slept better.

These observations may be coincidental and perhaps even unrelated to the consumption of fortified MSG, but at the very least, they show the high acceptability of the item.

The period of distribution of fortified MSG to families lasted for twelve months.

III. RESULTS AND DISCUSSION

Effect on Active Clinical Xerophthalmia

The MSG fortification program eliminated most of the cases of night blindness, the majority of corneal xerosis, and Bitot's spots with conjunctival xerosis, representing an overall reduction of active clinical xerophthalmia by about 76% (Table 6). This means that for every 100 children who had active clinical signs before MSG fortification, only about 24 would have signs after 12 to 18 months of program implementation.

Table 6. EFFECT OF MSG FORTIFICATION ON ACTIVE CLINICAL XEROPHTHALMIA

	CLINICAL CATEGORY	Per Cent BEFORE	AFTER	CHANGE	REDUCTION
XN	Night blindness	1.9	0.2	-1.7	88%
X1B	Bitot's spots w/xerosis	1.5	0.6	-0.9	64%
X2	Corneal xerosis	0.8	0.6	-0.6	75%
X3	Keratomalacia	0	0	0	-
	TOTAL ACTIVE SIGNS	4.2[1]	1.0	-3.2	76%

N = 452

NOTE: X1A not included, WHO report states "conjunctival xerosis - X1A not recommended for community diagnosis."

The high dosage capsule strategy reduced active clinical xerophthalmia by only about 73% while public health intervention reduced it by only 44%.

[1] Chi Square significant at .001 level

Effect on Serum Vitamin A Levels

The mean value for serum A increased by about 7.5 mcg between baseline and evaluation and the percentage of children with low and deficient levels decreased by some 14% (Table 7).

Table 7. EFFECT OF MSG FORTIFICATION ON SERUM A LEVELS

	BEFORE	AFTER	CHANGE
Mean Serum A mcg/100ml	21.0	28.5	+7.5
Per cent children with low and deficient serum A levels	51	37	-14%

N = 387

The increase in serum A values was noted only in the MSG group. In the non-MSG groups, a slight decrease of mean serum A values was observed (Table 8).

Table 8. EFFECTS OF MSG FORTIFICATION ON SERUM A LEVELS COMPARED WITH OTHER INTERVENTIONS

	Non-MSG Group Mean Serum A mcg/100 ml	MSG Group Mean Serum A mcg/100 m.
BEFORE	19.3	21.0
AFTER	15.7	28.5
CHANGE	-3.6	+7.5[1]

Perhaps the more important consideration regarding the impact of MSG fortification on serum A values is the effect on low and deficient level groups. The program caused an increase in Serum A values from 6.4 mcg per cent to 25.4 mcg per cent in the deficient group and from 14.4 mcg per cent to 28.8 mcg per cent in the low level group, representing mean increments of 19.0 mcg per cent and 14.4 mcg per cent respectively (Table 9).

[1] The before and after levels using a paired t-test are significantly different at the 0.01 level.

Table 9. EFFECTS OF MSG FORTIFICATION ON SERUM A VALUES USING ICNND CLASSIFICATION

ICNND CATEGORY	Mean Serum A mcg %	N
DEFICIENT (Below 10 mcg%)		
BEFORE	6.4	
AFTER	25.4	63
CHANGE	+19.0	
LOW (10-19 mcg%)		
BEFORE	14.4	
AFTER	28.8	139
CHANGE	+14.4	
ACCEPTABLE (20-49 mcg%)		
BEFORE	29.3	
AFTER	27.8	173
CHANGE	-1.5	
NORMAL (50+ mcg%)		
BEFORE	57.9	
AFTER	27.5	12
CHANGE	-30.4	

IV. COST/EFFECTIVENESS

Based solely on the criteria of effectiveness in (a) raising serum vitamin A levels and (b) reducing active clinical signs of xerophthalmia, it is clear that MSG fortification is the most effective intervention (6.7).

The cost of such a fortification program is relatively small. In fact, it is feasible for such a national program to be introduced without any cost either to the government or to the general public. The major initial expense would be for a mixer (estimated cost, $22,000) and the only recurrent cost would be the staff to supervise the operation. It is recommended that vitamin mixture be added to replace a small quantity of MSG in every pack and not be in addition to the 2.4 grams of MSG currently in each packet. The final cost to the purchasers of fortified MSG would be the same as the currently unfortified MSG. The total revenue accruing to the manufacturers and retailers would also remain unchanged by the program.

The program would be expected to diminish to a great extent both blindness and mortality resulting from xerophthalmia in the Philippines. The main beneficiaries of the program would be children at risk of vitamin A deficiency, especially young children in the low socio-economic group of the population. However, adults and older children would also benefit by increased intake of vitamin A.

V. MSG CONSUMPTION SURVEY IN TWO OTHER PROVINCES

A critical factor that will determine the effectiveness of the intervention with vitamin A fortified MSG is the natural consumption pattern or utilization rate of MSG by the people of the Philippines. A small survey was conducted in June, July, and August 1977 by Cornell University and the Nutrition Center of the Philippines to obtain information on the utilization patterns of MSG in two provinces, Marinduque and Nueva Vizcaya. Marinduque is an island located in the mid-portion of the Philippines while Nueva Vizcaya is an inland province located in the Northern island of Luzon. The two provinces represented ecological variations and differences in cooking and dietary habits of the people.

In Marinduque, 90% of 135 households interviewed had used MSG in the previous 24 hours, as ascertained by 24-hour recall. The mean household consumption of MSG was 1.9 g per day, and the mean daily consumption of MSG by preschool children was estimated to be 0.18 g per day. In Nueva Vizcaya, on the other hand, 77% of the 200 households sampled had consumed MSG in the previous 24 hours, and 74% of preschool children had consumed MSG. Although the rate of consumption of MSG in Nueva Vizcaya was lower than in Marinduque, the amounts of MSG were higher in Nueva Vizcaya, the average consumption of MSG estimated 2.9 g

per day, and consumption by preschool children averaged 0.27 g per day. These consumption rates and average daily intakes should be treated with some caution since the sample sizes are relatively small and the standard error of the estimates will be high. Complete analysis of the information from this survey of MSG utilization is not yet available, and the standard errors of the estimates are unknown. However, the study in these two provinces attested the wide-spread usage of MSG.

VI. CURRENT STATUS OF THE PROJECT

One of the recommendations arising from the Cebu study was to conduct a wider pilot program involving two or three provinces that can represent the characteristics of the entire Philippines to test further the effectiveness of this intervention in controlling vitamin A deficiency. For this reason, a study is being conducted in the provinces of Nueva Vizcaya, Marinduque, and Ceby. These three provinces possess different ecological conditions, dietary patterns, and other characteristics.

In this study, fortified MSG (15,000 IU per 2.4 g packet) is made available for sale through normal commercial channels, ultimately reaching the numerous small "variety stores" that are located in almost all parts of the country. Thus the sampled households will have the opportunity to buy MSG or not as desired, in the same manner as they were able to do so when there was no fortification. Thus the findings about the effectiveness of the intervention with fortified MSG could well be different from that of the intervention study carried out earlier in Cebu.

A control province (with unfortified MSG) has been included in the present study. The same parameters as in the experimental provinces will be monitored to assess the natural changes in serum vitamin A levels in an undisturbed population, and would thus answer questions about the real effectiveness of the intervention with fortified MSG.

Among the pertinent data being collected are:

1. serum vitamin A and carotene levels; 2. clinical evidence of the deficiency; 3. dietary consumption patterns of vitamin A, protein, fats, and calories; 4. consumption pattern of MSG; and 5. marketing data.

Follow-up surveys will be conducted at 12 month intervals (2nd and 3rd years) using an independent sample of children matched with the baseline samples and measuring the same parameters in order to quantitate changes. In all surveys, baseline and follow-ups, immediate treatment will be given to these children identified as having deficient or low serum vitamin A levels as well as those presenting active clinical signs of xerophthalmia. It is because of this ethical constraint imposed upon the investigators that the decision has been taken to adopt a cross-sectional rather than a longitudinal design. It is recognized that a

longitudinal design would be statistically more powerful in detecting changes in the parameters of interest, but the necessity of providing on the spot treatment as needed imposes the adoption of the cross-sectional design rather than longitudinal.

Fortification of MSG with vitamin A cannot be expected to produce other benefits besides its effect on vitamin A nutritional status. However, its wide use in the Philippines has opened the possibility of fortifying this product with other nutrients which are deficient in the Filipino diet. The obvious nutrients for consideration would be iron, because of the prevalence of iron deficiency anemia, and iodine. Goiter, though less prevalent than anemia, remains an important public health problem.

MSG fortification, however, is not the only action that the government must undertake. Other means include: 1. the use of vitamin A capsules for children; 2. Public Health intervention strategies including horticulture and education. These strategies must be encouraged and implemented as long-term measures. However, because of the necessity to reach as many targets at the minimum cost immediately in view of the prevalence of the deficiency. food fortification is deemed as the most practical approach.

The present study is expected to generate recommendations on a national fortification program and propriety of the level of fortification currently being used, and proposals for control of xerophthalmia in groups that are not likely to benefit from MSG fortification.

Fortification of foods commonly consumed will continue to occupy an important position among the tools for eradicating vitamin A deficiency.

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XI INTERNATIONAL CONGRESS OF NUTRITION

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Vitamin A Deficiency Symposium

"Ongoing Programs: Private Agencies"

by

Susan T. Pettiss, Ph.D.
Director of Blindness Prevention
Helen Keller International

The term "private agencies," as used in this paper, will refer to "non-profit organizations established to fill a public 'charitable' purpose."[1] In fact, many of the private or voluntary agencies are recipients of public funds, but they maintain independent governing bodies and operational integrity. Private agencies may be local agencies working within their national boundaries; they may be international voluntary organizations; or they may be national agencies operating at the international level. Most of the agencies to be discussed here fall within this latter category.

Just a word about the "pros" and "cons" of private agencies' activities. On the "pro" side, because of their independence, they are often in a position to stimulate and help governments to define goals and clarify operational plans, and they steer

1. Sommer, John G., Beyond Charity. Washington, D.C.: Overseas Development Council, 1977.

them to intergovernmental resources. Generally, they have greater operational flexibility than the more bureaucratic governmental or intergovernmental bodies. As a result, they can modify their plans and programs with facility and deal better with the uncertainties inevitable in developed or developing countries. Since limitations of resources usually necessitate a micro-approach, programs tend to be directed to the grass roots level and of manageable size. These agencies can be less fearful of negative results of program evaluation, and therefore more objective in their analysis.

Other positive common characteristics include the potential for creativity, which is often conducive to undertaking pioneer projects for demonstration or testing. These are usually minimally or moderately expensive programs that are encompassable for incorporation by governments. It is often easier and quicker for private international agencies to respond to local governments' expressed concerns than for the more cumbersome bilateral or multilateral governmental agencies, and they tend to be less political.

On the other hand, there are some "cons." Sometimes private agencies do not have access to the highly technical or expensive expertise they need. They may be laborious in moving from a demonstration phase of a program to the broad planning and policy phase to effect significant change. In some instances, sophisticated management and evaluation skills may be lacking. Since interests of a private agency may be narrowly focused, their programs may fit with difficulty into essential political and

administrative frameworks, and into broad economic priorities.

In this paper, the discussion will be concentrated on the private agencies that are engaged in activities to assist governments to assess the extent of xerophthalmia (the vitamin A deficiency ocular disease), to develop and evaluate intervention programs, and to carry out research to delineate more precisely the etiology and characteristics of the disease. Recognition is given to the fact that there are numerous national private organizations working in this field, such as associations for the blind and societies or organizations for blindness prevention. Since time is limited, however, only the programs of organizations operating at the international level will be mentioned.

Long-range solutions to the problem of vitamin A deficiency and xerophthalmia, of course, lie in the elevation of the standard of living to the point where populations can afford, have access to, and understand the importance of a diet with sufficient amounts of the nutrient. Many private agencies have joined with governments and local groups to help in the overall development process. Relevant activities include assistance to upgrade agricultural output, increase and diversify horticultural produce, improve health and sanitation conditions, broaden understanding of nutrition needs, raise income levels, and so on. Others have directed their resources and energies to health and nutrition services which are closely linked to causative factors in xerophthalmia.

For instance, the Christoffel Blindenmission (CB), a West German agency which operates in 58 countries around the world

to serve the blind and prevent blindness, integrates its concern for xerophthalmia into its programs in areas where the problem exists. Any high incidence of xerophthalmia is noted immediately by the staff at eye clinics, eye hospitals, and dispensaries in routine reports, and alerts them to initiate special programs for vitamin A education and treatment. In India, there is a special nutrition education demonstration program not only to show what kinds of nutritious foods to eat, but also to give tips on how to cook them, how to grow locally unfamiliar nutritious foodstuffs, and increase production of the familiar ones.

Operation Eyesight Universal (OEU), a Canadian agency which has primarily been providing assistance to eye camps and for eye care in India and Bangladesh, has alerted its staff to look for families which have children with ocular signs of xerophthalmia to provide massive dose capsules of vitamin A, refer them to the nearest treatment center, and discuss the relationship of the eye problem to faulty diet.

The International Eye Foundation (IEF), an American voluntary agency, undertook responsibility in 1977 for a six-week Vitamin A Training Project (financed by AID) to develop a group of physicians and ophthalmologists capable of providing the technical resources, training skills and multi-cultural experience necessary to plan, design, implement and evaluate low-cost, high-yield programs to identify and eradicate xerophthalmia. In its programs in developing countries to train manpower and develop facilities for delivering eye care in rural areas,

particular stress is laid on the recognition, treatment and prevention of nutritional blindness. For instance, in a comprehensive five-year project with the Government of Kenya, an assessment of the extent of xerophthalmia will be obtained as part of a general survey of blindness; manpower training at all levels will include diagnosis and treatment of xerophthalmia; and provision of ophthalmic services will be extended to vulnerable children.

The Royal Commonwealth Society f/t Blind (RCSB) of Great Britain works in partnership with governments and local organizations, chiefly in Asia, Africa, and the Middle East, in extensive programs through eye camps and mobile units to restore sight lost by cataracts and provide general ophthalmic care. Long a proponent of measures to prevent blindness caused by vitamin A deficiency, the Society has operationalized the concept of the intervention by nutrition education together with proper diet to children threatened with xerophthalmia and keratomalacia. A pilot Nutrition Rehabilitation Center was established in 1969 in Madurai, India, run by the Department of Ophthalmology and Pediatrics of the Government Erskine Hospital, with technical guidance and financial assistance from the RCSB. The Center has as its purpose "the provision of a proper, low-cost nutritious diet to cure early malnutrition and malnutritional eye diseases; to obtain knowledge which will be invaluable in starting similar nutrition centers in villages; and to build the Center into a teaching and training institution for workers in the medical,

para-medical and education departments." [2]

The Centre consists of twenty single-room houses similar to those in which the families live in their villages, with traditional stoves and pots. Mothers help prepare their children's food from foodstuffs (chiefly green leafy vegetables) purchased in the local market at a cost not too excessive for the village families. The mothers can watch the improvement and weight gain of the children while receiving nutrition education which will benefit not only the ill child but other children and members of the family when they return to the village. The Centre has a capacity for about thirty children, and there are arrangements for follow-up visits to the child's family after the return to the village home.

Similar Nutrition Centres are being established in Uttar Pradesh in India and planned for Bangladesh.

The Blindness Prevention Department of Helen Keller International (HKI) has, since its inception in 1972, concentrated its program on the prevention and control of xerophthalmia. HKI is a 63-year old American agency serving the blind at the international level; but only recently has it added the prevention component. It is working with governments in Afghanistan, Bangladesh, Haiti, and Indonesia to help them understand the extent of their nutritional blindness problem and to take steps to control it. Briefly, the status of current activities is:

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2. Nutrition Rehabilitation Centre, Government Erskine Hospital, Madurai. "Report on Nutrition Rehabilitation Centre" (Unpublished)

Afghanistan

Working with WHO and the Noor Eye Hospital, HKI will assist the Afghan Ministry of Health's Department of Preventive Medicine in a prevalence survey of ocular signs of vitamin A deficiency in children under six years of age. This is a joint HKI-WHO project, to be carried out as part of an Expanded Immunization Program. A system for emergency treatment of children with symptoms of xerophthalmia with massive dose vitamin A capsules is being introduced into hospital/clinic centers and any existing rural health services, along with nutrition education. If the survey findings indicate the need, a program for distribution of the vitamin A capsules will be incorporated into the immunization program.

Bangladesh

HKI has recently become involved in the five-year-old program of vitamin A capsule distribution being carried out by the Ministry of Public Health and Population. HKI is assisting in the expansion of that program to cover urban areas, all hospital/health centers, and special groups such as refugees; in training of professional medical and nutrition personnel in the recognition, treatment and prevention of xerophthalmia; in stepping up nutrition education aimed at changing dietary habits; and in the evaluation of the program. This project is a joint venture with UNICEF, the Institute of Nutrition and Food Science, the Bangladesh National Society for the Blind, and the Royal Commonwealth Society for the Blind.

Haiti

After a prevalence survey (under HKI auspices) indicated that xerophthalmia was a public health problem, the Government of Haiti, in consultation with HKI, initiated a program of vitamin A distribution and nutrition education. The program includes training seminars, preparation of educational materials, and the actual dispersing of 200,000 IU vitamin A capsules through the countrywide health delivery system to accessible ill and/or malnourished children and lactating mothers. Initiated in 1975, the project is scheduled to undergo an extensive evaluation in the coming year. The program is being integrated into the ongoing health services.

Indonesia

The Indonesian Government has been taking action since the early 1970s to document its xerophthalmia problem and to combat and prevent the disease. HKI has been providing consultation and technical assistance in these efforts since 1972. Currently, HKI is collaborating with the Government in a three-year Nutritional Blindness Prevention Project, "Characterization of Vitamin A Deficiency and Design of Effective Interventions" (substantially funded by AID). The research activities began in 1976 and at the present time data collection is near completion and analysis underway. Preliminary results indicate that the prevalence of xerophthalmia is higher than previously estimated. One million Indonesian preschool age children develop xerophthalmia every year, of whom 30,000-50,000 have gross corneal involvement, resulting in bilateral blindness in half. From the Indonesian

data HKI now estimates that as many as a quarter of a million children in Asia will suffer nutritional blindness each year.

HKI will continue the partnership with the Indonesian Government to plan and implement appropriate interventions based on the research findings and to arrange for ways to utilize and disseminate the knowledge gained for the widest possible benefit.

Universities may not fall easily into the category of "private agencies," but the activities of Cornell University's Division of Nutritional Sciences in regard to xerophthalmia in the Philippines should be mentioned. After first assisting the Philippine Government in a detailed investigation of the prevalence of xerophthalmia and factors related to its cause on the island of Cebu, three different forms of interventions were planned and are now being carried out and tested:

(a) massive dose vitamin A capsule distribution;

(b) fortification of mono-sodium glutamate; and

(c) public health--horticulture measures.[3]

And, finally, another agency with unclear "private agency" status is the important International Agency for the Prevention of Blindness (IAPB) which, along with WHO, has designated xerophthalmia as one of the four most important causes of preventable blindness. That agency, with affiliate national committees in

3. Xerophthalmia Club Bulletin. "Vitamin A Deficiency-Prevalence, Causes and Intervention in Cebu, Philippines." VII. February 1975.

more than fifty countries, is directing impressive efforts to raise the public consciousness to the devastating effects of nutritional blindness and how it can be controlled with political will, expeditious use of technology and adequate financing.

In conclusion, it might be pointed out that the extent of the effects of lack of vitamin A as a public health hazard is undetermined. It is conjectured that its resulting nutritional blindness is only the tip of the iceburg. Even so, to control that form of avitaminosis A will take massive efforts and diverse approaches by intergovernmental, governmental, and private agencies. The encouraging aspect is that it can be controlled as other nutritional deficiencies have been.

Annex I

Private Agencies

Christoffel-Blindenmission e.V.
Nibelungenstr. 124
D-6140 Bensheim 4
West Germany
Wolfgang Stein
Director, Overseas Services

Cornell University
Division of Nutritional Sciences
Savage Hall
Ithaca, New York, 14853
U.S.A.
Michael C. Latham, M.D.,
Professor of International Nutrition

Helen Keller International
22 West 17th Street
New York, New York 10011
U.S.A.
Susan T. Pettiss, Ph.D.,
Director of Blindness Prevention

International Agency for the
Prevention of Blindness
Commonwealth House
Haywards Heath
Sussex RH 16 3AZ
England
Sir John Wilson, President

International Eye Foundation
7801 Norfolk Avenue
Bethesda, Maryland 20014
U.S.A.
John Harry King, Jr., M.D.

Operation Eyesight Universal
P.O. Box 123
Calgary, Alberta
Canada T2P 2H6
A.T. Jenkins, President

Royal Commonwealth Society
for the Blind
Commonwealth House
Haywards Heath
Sussex RH 16 3AZ
England
Sir John Wilson, Director

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