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AGGRAVATION OF VITAMIN A DEFICIENCY FOLLOWING DISTRIBUTION OF NON-FORTIFIED SKIM MILK. AN EXAMPLE OF NUTRIENT INTERACTION

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Malnutrition is one of the most serious problems facing the world today. The FAO in its Third World Food Survey estimated that at least 20% of the population of the developing countries are undernourished (receive too few calories) and that about 60% consume diets that are inadequate in nutritional quality (deficiency of protein, thiamine, vitamin A, etc.). One of the most ominous aspects of the problem is that despite the considerable efforts which have already been mounted, we are failing. There are today more hungry persons than ever before in the history of the world.

The President's Science Advisory Committee published a three volume report in May 1967 entitled "The World Food Problem." (1) The report of this panel of experts is one of the most comprehensive and sobering resumes yet assembled of the magnitude of the world food problem and the possible solutions. The panel began by pointing out the immense complexity of the current situation. World malnutrition and hunger are not capable of defeat at the hands of any one group of specialists alone. Prevention of widespread famine and malnutrition will require the joint efforts of experts in agriculture, family planning, economic development and many other fields in addition to the nutritionists. Massive funding on a worldwide basis will be necessary to insure the implementation of sound programs. The needs are critical and the time is short. In my opinion, the report of this committee should be required reading for everyone connected with development programs.

There is the very real danger, however, as the organizers of this conference realize, that the urgency of the needs may result in the launching of projects that have not been reviewed sufficiently as to their overall impact on the region or its population. Particularly this may happen where the potential

dangers are not readily visible to the reasonably well-educated layman. In such instances much harm may be done before corrective measures can be applied.

Most laymen are aware of the basic facts of good nutrition; the need for adequate daily supplies of the various macro and micro nutrients. Most are unaware, however, of the relationships which exist among nutrients or between nutrients and environmental factors. Moreover, conventional medical training and practice in this country may also ignore many of these interdependencies. Yet, they affect markedly the physiology of the consuming organism and such interactions are the rule rather than the exception.

In order to illustrate this point more fully let us consider the case of the interrelationship of protein and vitamin A, two nutrients which are in deficient supply in many populations and which have profound deficiency symptoms.

Vitamin A is one of the class of fat soluble vitamins. It participates in a number of biochemical processes and is necessary for a normal rate of growth, for night vision and for the maintenance of the state of health of epithelial structures of the eye, respiratory tract and gastrointestinal tract. A mild deficiency of vitamin A may result in loss of ability to see in dim light, growth retardation and a dermatosis characterized by dryness, roughening and itching of the skin. If the deficiency is more severe, the conjunctiva and para-ocular glands become abnormal and unable to produce their usual supply of lubricating fluids. This condition, called xerophthalmia, may be readily followed by secondary infection, ulceration, softening of the cornea (keratomalacia) and perforation. If therapy is begun at the stage of uncomplicated xerophthalmia, the prognosis is good. Otherwise, partial or total blindness is likely to result.

Protein, on the other hand, is one of the macronutrients. Proteins are large polymeric molecules formed from smaller compounds called amino acids. Protein serves a structural role as the primary material of muscle and other cells. It is also required for the production of enzymes, the regulators of biochemical processes.

Protein deficiency (kwaskiorkor) and protein-calorie malnutrition (marasmus) are the two most widespread nutritional deficiencies in the world today. Failure to consume adequate amounts of protein and calories leads first to growth failure followed by wasting and ultimate death, often complicated by secondary infections. There are, of course, many degrees of deficiency between the two extremes. Vitamin A deficiency is also common in underdeveloped regions. The geographic areas chiefly affected are almost all of the countries of South and East Asia and certain parts of the Near East, Africa and Latin America. It is particularly prevalent in urban slums where neither whole milk or green or yellow vegetables (two major sources of vitamin A) are available in good supply. The most susceptible age group is the pre-school child, in which dietary deficiency of vitamin A accounts for the major proportion of blindness and makes a considerable contribution to mortality.

The relationship of deficiencies of vitamin A and protein is complex. In studies with experimental animals, the amount of dietary protein provided influences the pathological picture. Animals fed a good protein diet apparently consume their body stores of vitamin A rapidly and develop eye lesions at an earlier time than their slower growing litter mates fed rations low in protein (2). Clinical evidence with human infants suggests that they behave in a similar fashion (3). Children with grossly retarded growth often have no ocular

lesions despite low vitamin A intakes and blood levels but they may develop xerophthalmia if vitamin A supplements are not included with the treatment for protein malnutrition. The picture is further complicated by the fact that serum proteins act as carriers for vitamin A in the blood. Thus, mobilization as well as utilization of stored vitamin A may be stimulated by protein supplements in children previously receiving low protein diets.

With this information as background, one may speculate that prolonged intake of a marginal level of both vitamin A and protein could result in a juvenile population in which growth retardation was present but not severe and where the body reserves of vitamin A were minimal. Sudden famine, brought on by drought, floods, revolutions, etc., would precipitate protein calorie malnutrition but the concurrent acute growth restriction or weight loss would prevent the outbreak of visible signs of vitamin A deficiency. The distribution of a high quality protein low in vitamin A to children in this condition would yield a spurt of growth and rapid mobilization and consumption of the remaining meager body stores of vitamin A. The acute stage of vitamin A deficiency with its potential for partial or total blindness could then follow.

One of the first persons to draw attention to the danger of feeding a high protein, low vitamin A food to human infants as a major food item was de Haas (4). His observations in Java between 1935-40 led him to regard the sale and consumption of sweetened skimmed condensed milk as a principal cause of vitamin A deficiency. (Skimmed milk products have been treated to remove lipids so as to improve their stability in storage. Vitamin A being a lipid soluble compound is also removed by this treatment). Although his major concern was probably with the low intake of vitamin A imposed by this regimen rather than

the potentiating effect of simultaneous consumption of a good quality protein, his observations were sound and were implemented by the major post World War II relief agencies into their distribution policies. Although these agencies (UNICEF, etc.) did utilize dry skim milk powder as a major item in famine relief, they were careful to insist upon the distribution of vitamin A capsules along with the milk powder with the instructions that the children might lose their sight if they were not consumed as directed. They also restricted distribution through responsible groups such as health centers rather than allowing sale of the product on the open market. What was not known was the number of children who actually received the recommended amounts of vitamin A as suggested. Lacking data on this point, one may presume it to be likely that these warnings were either ignored or forgotten by many uneducated and destitute parents despite the conscientious efforts of the distributors.

Fortunately, it appears that few instances of widespread and serious complications have occurred. Perhaps most recipient populations were not in the required state of balance to be susceptible in large numbers. Perhaps the instructions concerning the consumption of the vitamin A capsules were carried out more faithfully than one might anticipate. It is also possible, however, that the difficulties of obtaining reliable medical statistics in underdeveloped countries has obscured the true incidence of the problem. Documentation of the incidence of xerophthalmia and keratomalacia in a given region requires the efforts of physicians specifically alerted to the problem and actively seeking cases away from the hospital population (3). Without this special emphasis, a significant increase in vitamin A induced eye lesions might easily go unnoticed.

There is reason to believe that protein supplements low in vitamin A were related to the aggravation of a chronic vitamin A deficit in a specific locale familiar to the author, namely the city of Recife in Northeast Brazil. Recife, the capital of the state of Pernambuco, is a city with a population of approximately one million located on the coastline of the eastern bulge of South America. It is the major population center for an eleven state area covering a total land area of some 476,000 sq. mi. About 70% of this total land area of Northeast Brazil is within the so-called "drought polygon." The population of the drought region was approximately 13,000,000 in 1960 or about 20% of the total population of Brazil. Most of these persons reside in small villages where they are engaged in subsistence agriculture. Rainfall within this area is extremely irregular. During the past 400 years, there have been some 55 droughts so severe as to cause widespread crop failure, an average of a major drought every seven years (5). In times of crop failure, large numbers of persons migrate to Recife in the attempt to find work and famine relief. Thus the misery of the region comes into focus in the squatter's slums of Recife. Under such circumstances, malnutrition is inevitable and the deficits of protein and vitamin A are serious, well-established, and of long-standing (5).

A series of particularly severe droughts occurred in Northeast Brazil during the 1950's resulting in an unusually large influx of indigents into Recife and other major urban centers. The resources of UNICEF and other relief agencies were mobilized to meet this crisis. Following the usual practice, skim milk powder was dispensed accompanied by vitamin A capsules with the warnings as to the consequences of failure to follow instructions. On this occasion, however, reports soon began to circulate from the major hospitals

noting a sharp increase in keratomalacia and xerophthalmia following the distribution of the skimmed milk.

Unfortunately, so far as the author is aware, the only written records describing this outbreak are in the archives of the Recife newspapers published at that time and possibly in hospital records. I know of no scientific publication in which the incidence of keratomalacia and xerophthalmia was recorded during the "epidemic" months and evaluated in terms of the dietary history of the patients. Two sources may be cited, however, as providing supporting evidence that such an event actually occurred. One source (3) is a report entitled "A Global Survey on Xerophthalmia" authored by Drs. H. A. P. C. Oomen, D. S. McLaren, and H. Escapini and published in Tropical and Geographical Medicine 16: 1964. This publication is a summary of the findings of these men during an extensive survey of the worldwide problem of hypovitaminosis A. Based upon their interviews with local physicians, they concluded that an epidemic of xerophthalmia had occurred at the time of the skimmed milk distribution and that it appeared likely to be a result of a failure of the recipients to use the vitamin A capsules in the correct manner. The second source of information is the interviews conducted in 1963 with Recife physicians by members of the ICNND Nutrition Survey Team of which the author was a member. The team members are listed in the agency report (5). The reliability of such evidence is always subject to question. In view of the known relationship of vitamin A and protein and the uniform agreement among experienced local physicians, however, it would seem reasonable to conclude that in this instance the problem probably did exist as described.

UNICEF was not unaware of the potential hazards imposed by the necessity of separate distribution of the skim milk powder and vitamin A supplements. For example, the Joint FAO/WHO Expert Committee on Nutrition at its fourth meeting (FAO Nutr. Meetings Report Svc. No. 9, 1955) urged the continuation of investigations already sponsored by FAO on the development of additives which could be mixed with the milk powder before distribution to the consumers. This became technically feasible in the early 1960's with the development of a stable, water-dispersible vitamin A derivative by chemists at Hoffman-LaRoche (6). Tests with rats showed the additive to be effective even with low fat intakes. The possibility still remained, however, that humans in the affected area might respond differently because of unsuspected variations in conditions (parasite loads, chronic deficiencies, etc.). It seemed advisable, therefore, to carry out studies in recipient subjects themselves to assure the safety and effectiveness under field conditions. Such a project was commenced in 1965 and completed in 1967 in Recife by Dr. Fernando Figueira and his co-workers of the Instituto de Medicina Infantil de Pernambuco and by Dr. Nelson Chaves and his associates at the Instituto de Nutricion of the Federal University of Pernambuco under the joint sponsorship of the AID mission to Brazil and the Nutrition Section of the Office for International Research[1]. The data obtained from these studies supported the animal tests and encouraged the widespread employment of the additives in human feeding programs.

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[1] The author participated in these studies as a consultant in biochemistry to the two laboratories. John W. Reynolds, M.D., of the Department of Pediatrics of the University of Minnesota Medical School served as the clinical advisor.

The purpose of this presentation is not to find fault with any of the agencies involved in the food relief programs for Northeast Brazil. I believe that they were cognizant of the possibilities and made a reasonable effort to minimize the danger. I do believe, however, that this example points out the necessity for careful planning and consultation with nutrition experts before the implementation of relief or development projects dealing with food commodities. Suppose for example, that an administrative decision had been made to economize by omission of the vitamin A supplements altogether on the grounds that they were unnecessary since few cases of xerophthalmia were being reported. Such a decision would probably have seemed quite sound and safe to a person unfamiliar with the nutritional history of Northeast Brazil and the interrelationship of these two nutrients. Yet it would have caused immense medical havoc and suffering.

As mentioned earlier nutrient and environment interdependencies are not rare in the study of nutrition. Several more examples might be instructive. One such example is the relationship between the amino acid tryptophan and the vitamin niacin. The studies of Goldberger, Elvehjem and many others during the period of 1915-1935 on pellagra in humans and blacktongue in dogs established that these conditions were responsive to dietary supplements of the vitamin niacin. These investigations as well as those of other major contributors on this problem have been clearly and completely chronicled by McCollum (7). Having shown the importance of niacin in the treatment of pellagra, nutritionists found it difficult to harmonize the high incidence of the disease among maize-eating people with the discovery that several other staple cereal grains never associated with pellagra were actually lower in niacin content then corn.

This situation was clarified, however, by the subsequent finding that a small proportion of the amino acid tryptophan could be converted to niacin by the metabolic pathway illustrated in Figure 1. Thus the condition of pellagra was a result not of a single deficiency but of a dual deficit in both niacin and tryptophan.

A second example of some interest is the recent series of reports by Caddell and Goddard (8, 9) of the benefit of magnesium supplements in children suffering from protein-calorie malnutrition. These workers as well as a number of others have determined that magnesium deficiency may occur in such patients as a conditioned deficiency; that is, the body magnesium deficit is a result of excessive losses associated with the muscle wasting, diarrhea and vomiting. Thus during the treatment and recovery phase, these children require magnesium supplements in excess of the normal requirements in order to compensate for the previous high losses. This conditioned deficit was not recognized earlier because the patients failed to develop classical signs of magnesium deficiency. Quite frequently, however, dual deficiencies will present a syndrome in which the classical symptoms are obscured. Inclusion of magnesium as part of the therapy of protein-calorie malnutrition was found to improve clinical recovery by a substantial degree.

The third example I have chosen is a case of interaction between nutrition and parasitology. Infestation with a heavy parasite load is quite common among economic lower classes in underdeveloped nations. Considering the lack of sanitation and education, it could hardly be otherwise. Some of the parasites are not regarded as particularly dangerous organisms by physicians if they cause only minimal residual damage to the host. One organism of

substantial concern, however, is Entamoeba histolytica. This organism ordinarily invades the intestinal wall of the host causing scarring and loss of function of the affected areas. A patient suffering from the effects of this invasion is said to have clinical amebiasis, a very serious condition.

In view of the usual behavior of this organism, a joint team from Tulane University and the Universidad del Valle, in Cali, Colombia engaged in a parasitological survey in Colombia were surprised to find only occasional cases of amoebiasis among a population of about 1000 persons with approximately 40% infestation of E. histolytica according to fecal examinations (10). The sample population was found to have a daily nutrient intake which was deficient by U. S. standards in practically all of the macro and micronutrients tested. As is frequently the case, locally available foods low in protein but high in starch (plantain, yucca, potato) were consumed as the major dietary staples.

In the course of the fecal examinations, the investigators also noted the appreciable amount of undigested starch grains in the stool specimens. They concluded that a major factor contributing to the indigestibility of the starch was the poor protein intake of the subjects and the subsequent low production of starch digesting enzymes. This point has been explored by Platt (11) in a paper on malnutrition and the pathogenesis of disease.

Considering all these factors, Faust and Read (10) hypothesized that the protozoan organisms in the large intestine were being provided with a much greater supply of starch in subjects with poor dietary protein intakes as compared to well fed persons. The organism was therefore utilizing the starch as an energy source in preference to the invasion of the intestinal wall. The authors also described their evidence that E. histolytica readily digested

in vitro the starchy foods typical of the local dietary pattern. By such a mechanism, a normally highly pathogenic organism was carried as an essentially asymptomatic infection. Obviously, this hypothesis would need to be taken into consideration as part of a protein feeding program in any underdeveloped nation.

In conclusion, an attempt has been made in this paper to show that nutrient interrelationships are common and may have profound effects if ignored. The case of the interaction between vitamin A and protein and the experience in Northeast Brazil of aggravation of a vitamin A deficit by the feeding of high protein supplements has been cited as a specific example of this condition. Emphasis has also been placed on the fact that such interactions are not readily obvious to the reasonably well educated lay public.

It should be evident that there are many factors to be considered before changes in dietary patterns are recommended or put into effect. In order to minimize the potential for tragic unsuspected results, it would seem justified to make the following recommendation. Any agency considering a dietary supplementation or alteration, however minor it may appear on the surface, should seek the services of appropriately trained and experienced nutrition experts before any action is begun. The American Institute of Nutrition[2] can provide a list of qualified individuals to serve in this capacity. It would also seem reasonable to encourage the continued support of research in basic biochemistry and nutrition as the means of providing fundamental knowledge of nutrient interrelationships and the pathological consequences of faulty nutrition.

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[2] American Institute of Nutrition, 9650 Rockville Pike, Bethesda, Maryland 20014.

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