MEDICAL PROGRESS

MALNUTRITION IN UNDERDEVELOPED COUNTRIES*

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VARIATION with time, place and person is an inherent characteristic of disease. Nutritional disease illustrates this particularly well. With few exceptions the patterns of malnutrition in underdeveloped countries today were those of the developed countries thirty to fifty years ago. Pellagra, ariboflavinosis and beriberi were still commonly seen in the southern United States in the 1930's, scurvy, rickets and endemic goiter in the 1920's, and "Mehlnärshaden," or "starch dystrophy," a form of kwashiorkor, in Europe in the 1900's. Furthermore, as in the underdeveloped areas today, diarrheal disease and the common communicable diseases of childhood had a higher fatality because of the poorer nutritional status of the population and less adequate medical care. At any time nutritional deficiencies can be sharply delineated by geographic areas for a variety of political, social and economic reasons. The physical aspects of the environment may or may not be important to the variation. Even in the countries where they are common, nutritional deficiencies are sharply limited to the less privileged segments of the population.

Nutritional disease in underdeveloped countries, therefore, is not unique and unrelated to the previous experience of more privileged nations, nor is it static. In 1960 goiter was hyperendemic in Guatemalan schoolchildren. Two years later it was no longer a public-health problem because of the successful iodization of salt. Beriberi, still common in the Philippines and other Far Eastern countries, could be eliminated in a few months through the vitamin enrichment of rice and yet is increasing in Thailand, Malaysia and Vietnam as machine-

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milled white rice replaces that separated at home by pounding. In a number of countries the introduction of low-cost protein-rich foods for feeding infants and young children holds promise for the prevention of kwashiorkor.

An attempt to list the nutritional disorders of each underdeveloped country would be repetitive and dated. The nature of their nutritional difficulties is so similar that there is little to be lost in describing them collectively. It is necessary to remember, however, that the seriousness of a given problem is likely to be related directly to the degree of social and economic progress of a country. Similarly, the specific solutions to nutritional problems of the underdeveloped countries vary greatly with local dietary habits, cultural practices, agricultural patterns and availability of food. Such variations result in differences in the relative importance of one or another of the nutritional syndromes common to such populations.

This article will discuss the patterns of nutritional deficiency characterizing the underprivileged, who make up such a large part of the populations of underdeveloped countries. Since malnutrition and infectious diseases whose spread is favored by poor environmental sanitation are commonly associated in underdeveloped countries, their synergistic interaction must be given due emphasis. Because most of these countries are tropical or subtropical the nutritional effects of some predominantly tropical diseases of infectious origin must also be included.

Protein-Calorie Malnutrition

Protein-calorie malnutrition is widespread and of major public-health significance. It contributes importantly to a high mortality in areas where it is prevalent and is responsible for adverse effects upon the health and general well-being of a large sector of the population. The world distribution of protein-calorie malnutrition is shown in Figure 1. The areas most affected include the countries where large proportions of the population are living under conditions of limited social and economic development.

Protein-calorie malnutrition is more than a medical problem. In underdeveloped countries, it results from two main factors, a diet that is quantitatively and qualitatively inadequate and superimposed stress, usually of infectious origin. A deficient diet results in turn from varying combinations of low food production, inadequate preservation and distribution of foods, restricted purchasing power, poor food habits and deficient knowledge of the relation between diet and health. The excessive incidence of infectious disease is a consequence of poor environmental conditions, inadequate knowledge of epidemiologic factors, poor personal hygiene and insufficient health services. These factors are interrelated and act synergistically to the detriment of nutritional status.

The clinical result depends on many determinants — on the severity and duration of the nutritional deficiencies of protein and calories, on the relative importance of the deficiency of protein to that of calories, on the nature and severity of other associated nutritional deficiencies, on the age of the person affected and on the presence of other complications. The mild and moderate forms, in children, frequently unrecognized or misinterpreted, are primarily characterized by inadequate growth and development. In adults they reduce work performance and resistance to infection.

Mild and Moderate Forms

In underdeveloped countries the average weight and height of children at birth are close to the values for North American or European children. Infants also grow normally during the first four to six months of life, for they are usually breast-fed, and their nutritional needs are adequately met. During the second six months, however, rates of growth decrease, and height and weight begin to depart from established normal values. Growth and maturation may come close to a standstill in the second or third year. Only when children approach school age do they again grow at a rate nearer that of normal children. During school years rates of growth generally parallel those of well nourished children but at a much lower level. Consequently, when growth stops with the closing of epiphyses, their stature is smaller. Epiphyses seem to close at much the same chronologic age despite the lesser size of the child. Mainly for this reason, adults in underdeveloped countries are usually smaller than those in developed countries. Although genetic differences are also involved they are probably less important.

The period of retarded growth, from about the sixth month up to school age, is that when dietary inadequacy and frequency of infections are most pronounced. During the second six months of life breast feeding continues, but with insufficient or improper supplementation. After weaning, the usual diet is cereal grains, starchy roots, overdiluted milk or even cornstarch. In most cases this regimen not only fails to provide the needed calories but also is deficient in many essential nutrients, particularly proteins of high biologic value.[1]

Although the diet received may include some legumes, vegetables and occasional meat, cheese or other animal products, it is usually poor in proteins of high biologic value. Not until the third to the fifth year of life is the usual child in underdeveloped countries permitted an adult type of diet.

The period of greatest dietary inadequacy coincides in general with increased exposure to an unsanitary environment and a greater frequency of

FIGURE 1. *World Distribution of Protein-Calorie Malnutrition.*

diarrheal and parasitic diseases, measles, whooping cough and other diseases of early childhood. By the time children enter school this critical period of high morbidity from infection is largely past because of an acquired immunity and a better nutrition.

The assumption that reduced growth of children in underdeveloped countries is due more to environmental than to genetic factors is supported by observations of children of different races living under similar adverse conditions. Conversely, well nourished children of the same genetic origins usually follow the growth pattern of well fed North American or European children in a healthy environment.

Since growth retardation is most marked in the parts of the body with the highest rates of growth during the period of the malnutrition, disproportions develop in anthropometric measures. The shorter limb-to-trunk ratio often observed in poorly nourished population groups is largely from this cause. Retarded growth is paralleled by retardation in bone maturation as evidenced by the number and rates of appearance of ossification centers of wrist and hand in x-ray studies.

There is also some evidence that children with early retardation in growth experience a similar retardation of psychomotor development that persists at least through the school years.[2] Further studies are necessary to verify this correlation, to determine the permanency of the effect and to establish the extent to which malnutrition is responsible.

Adult protein-calorie malnutrition. The consequences of an observed mild to moderate chronic malnutrition in some adult populations of underdeveloped countries has been little studied. It is probable that it seriously reduces work capacity and thereby contributes to the low social and economic development in these areas. The effects of such malnutrition on resistance to stress, particularly that resulting from infectious disease, also needs further attention. Pregnant women and lactating mothers are a particularly vulnerable segment of adult populations of underdeveloped countries. Many women do not gain a normal amount of weight during pregnancy, but average weights of children at birth are not much affected. The main effect is on the mothers. Breast-feeding often continues for as long as two years, and a further loss of weight with long lactation is usual. The consequences of repeated pregnancy and lactation on poorly nourished mothers have received too little attention. It is noteworthy that such women look older than their chronologic age.

Marasmus. In our concept, marasmus in children is the result of insufficient food, a form of starvation.[3] The extremely low-calorie diets responsible for the syndrome are obviously also deficient in proteins and many other essential nutrients. Since the number of calories is the main factor, the child utilizes amino acids from the skeletal muscles and other less essential tissues, as well as deriving energy from fat deposits. Growth stops, but the amino acids and other nutrients liberated from the child's own tissues make possible a continuing synthesis of serum albumin, enzymes and other essential metabolites. For this reason, no serious metabolic disturbances are observed.

The child with marasmus (Fig. 2) looks and is emaciated owing to a loss of subcutaneous fat, extreme muscle wasting and atrophy of most organs.[4] Although the liver and other essential organs are much reduced in size, histologic changes are minimal. Despite the apt description of being reduced to "skin and bones," the child remains clinically alert and maintains an appetite.

Marasmus is generally a disease of infants; kwashiorkor is more likely to develop in the second or third year of life. Children under one year of

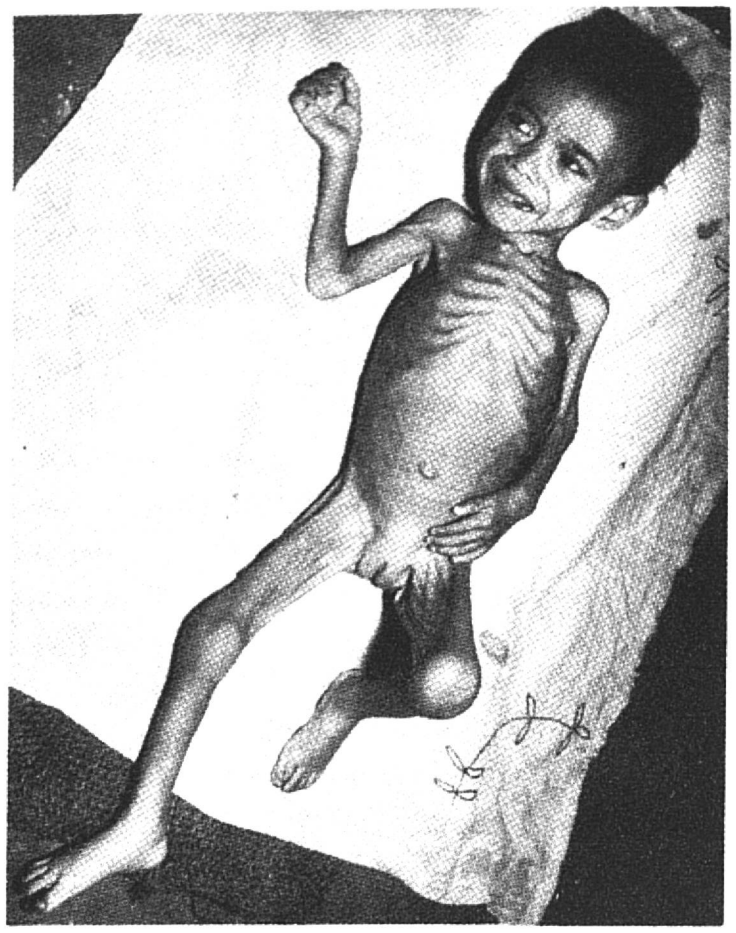

FIGURE 2. *Appearance of a Child with Marasmus.*

age grow more rapidly and require more calories and protein per kilogram of body weight. They are also more likely to be fed watery gruels extremely deficient in both calories and protein. Consequently, marasmus develops. Later, when more calories are given without added protein, kwashiorkor is superimposed on the original condition, especially when infection increases protein needs.

On the basis of observed normal function of the adrenal cortex in marasmus, and decreased glucocorticoid production in kwashiorkor,[5] we have proposed the following hypothesis: the severe restriction of calories in children in whom marasmus develops results in increased production of ACTH by the anterior pituitary gland that in turn stimulates the adrenal cortex to produce more corticosteroids. These hormones assure catabolism of muscle and other labile proteins sufficient to furnish amino acids to the liver for gluconeogenesis and likewise provide the liver with amino acids for synthesis of metabolically essential proteins. This mechanism does not come into play when the child receives a diet with enough calories to meet minimal energy needs even though it is extremely deficient in proteins. Under these circumstances children do not mobilize amino acids from their muscles and instead present the serious metabolic disturbances of protein deficiency without further muscle wasting. The result is kwashiorkor. This hypothesis is now being tested experimentally.

Kwashiorkor. In contrast to marasmus there is a lack of essential amino acids available to the liver in kwashiorkor. The low concentration of dietary protein in relation to calories results in serious metabolic, physiologic and pathologic alterations.[3,6-8] Clinically, the syndrome of kwashiorkor presents a pitting edema of varying degree, from a mild form

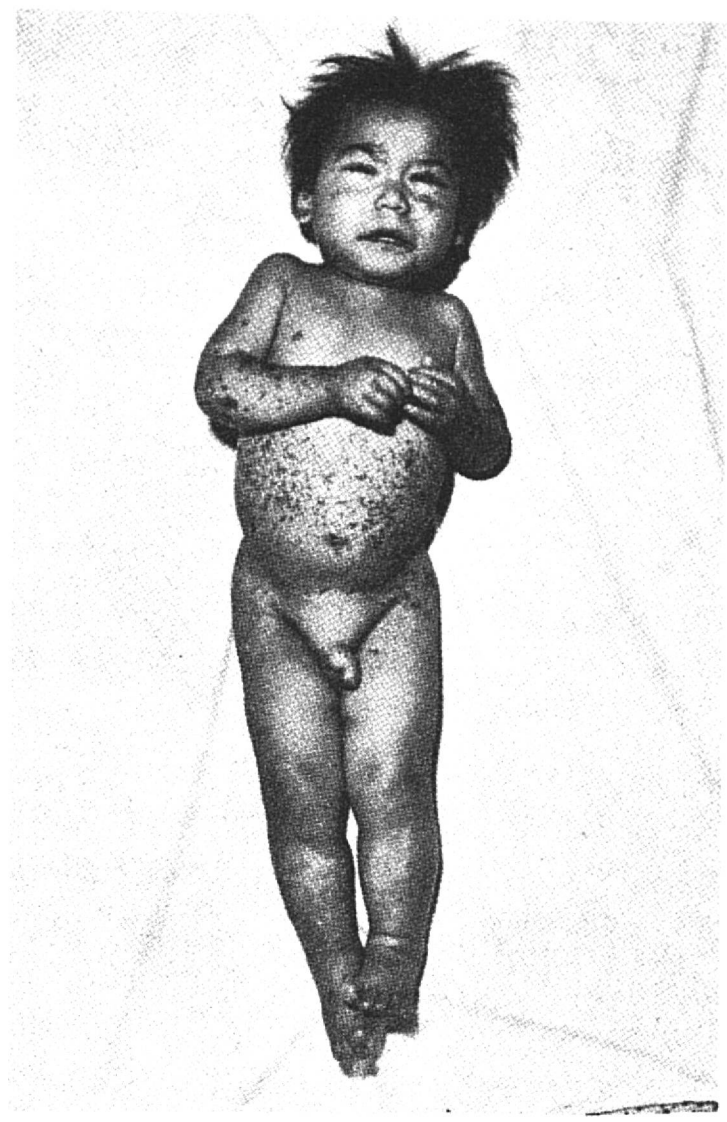

FIGURE 3. *Appearance of a Child with Kwashiorkor.*

localized in feet and ankles to severe and generalized edema, with eyelids swollen shut (Fig. 3). Movement of the extremities may be limited, and fluid accumulates in the peritoneal cavity. Patients are usually extremely apathetic, with a weak and monotonous cry if disturbed. Anorexia is present in most of them and is frequently severe, and diarrhea is an almost constant finding.

The characteristic alterations of the skin resemble the dermatosis of pellagra, with which they have been mistakenly identified. The lesions are pigmented, dry, hyperkeratotic and sometimes desquamating and of a size varying from punctiform to large, confluent areas. They are most numerous where subject to irritation, especially the perineal region. They frequently occur on extremities and face and may extend to the trunk.

The hair becomes dry, fine, brittle and straight, when normally curly. It is easily pulled out or may even fall out. It may become reddish, yellowish or even white. These pigmentation changes are often observed in stripes, indicating successive periods of normal and abnormal growth of the hair (Fig. 4). The extremities are frequently cold and cyanotic. The abdomen may be distended owing to flaccid abdominal muscles. Hepatomegaly is seen in some localities.

The principal biochemical characteristics[3] include alterations in protein metabolism manifested by low serum concentration of albumin, beta globulin, transferrin, ceruloplasma and beta-lipoproteins. Other protein compounds of metabolic im-

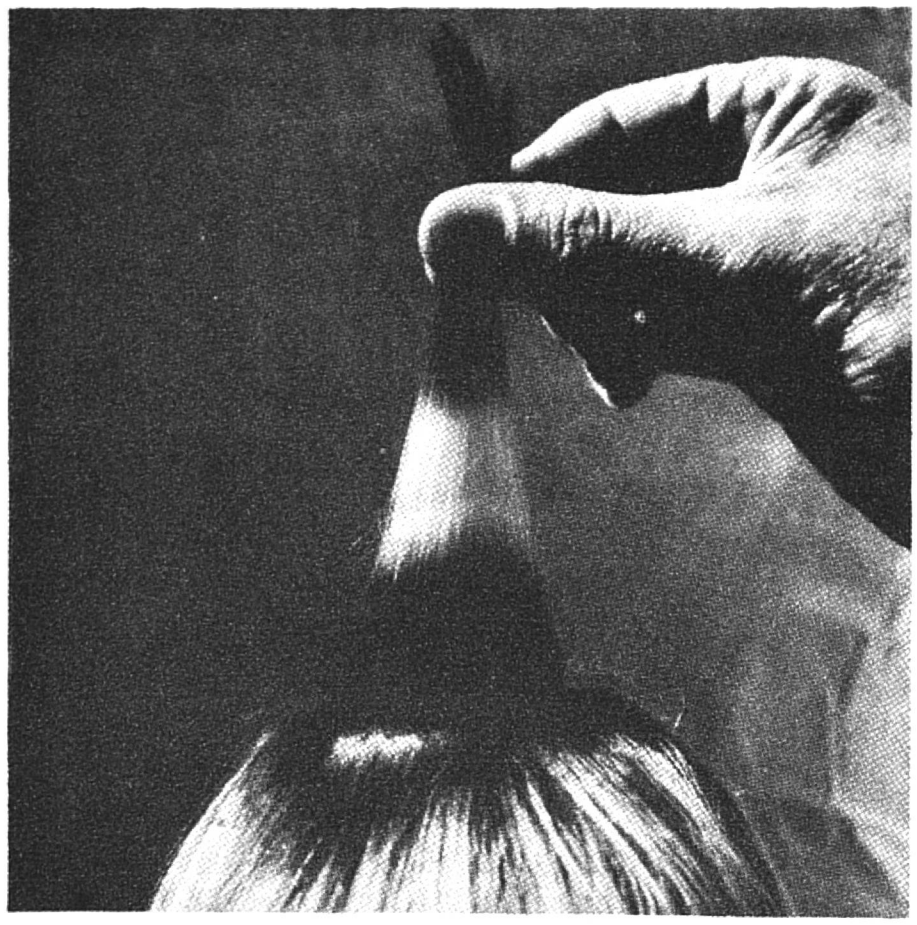

FIGURE 4. *Appearance of the Hair in Kwashiorkor.*

portance, particularly enzymes, are reduced. The activities of pancreatic enzymes are drastically reduced as are those of serum amylase, pseudocholinesterase and alkaline phosphatase. Except for xanthine oxidase and amino acid oxidase, liver enzymes are more resistant.

The essential amino acids in plasma are consistently and markedly decreased, especially valine, leucine, isoleucine and tyrosine.[9] The total free amino acid level, however, is not significantly altered because nonessential amino acids increase proportionally. Alpha-amino nitrogen in the urine is increased, and abnormal nitrogen metabolites suggestive of alterations in amino acid metabolism may be found. Low plasma urea values correlate with a low urinary excretion of this metabolite.

Many other metabolic and physiologic alterations are related to the reduced protein consumption when there is no corresponding decrease in calorie intake. Reduced lipid transport as well as defective lipid absorption occurs. An increase in total body water, with potassium depletion and sodium retention, is a constant occurrence, and magnesium deficit has been reported. Reduced basal metabolism, plasma flow and glomerular filtration rate are all observed.

The main pathological alterations[3] include fatty changes in the liver, of the large droplet type, beginning in periportal areas of the lobule and extending progressively to the central vein. The pancreas and other endocrine glands become atrophic, along with marked atrophy of the intestinal mucosa, to give changes like those in primary malabsorption. The skin shows atrophy of the epidermis, with varying degrees of hyperkeratosis and parakeratosis.

The correction of dehydration and the treatment of infections are the immediate demands in management of protein-calorie malnutrition. The basic requirement, however, is a diet providing all essential nutrients.[10,11] Three to 4 gm. of protein of high biologic value and 100 to 140 calories per kilogram of body weight are useful in children with kwashiorkor, and up to 200 calories in those with marasmus. All the forms of severe protein-calorie malnutrition just described are also observed in adults, although less commonly, and the principles of treatment are the same.

Infectious processes are common complications of severe protein-calorie malnutrition and responsible for many deaths.[12] Bronchopneumonia is the frequent final episode, often without the characteristic fever and leukocytosis. Respiratory insufficiency may suddenly occur, with death in a few hours, and only autopsy reveals the severe bronchopneumonia.

Severe syndromes of the kwashiorkor type, with anorexia and frequently diarrhea and vomiting, require much care in returning to a satisfactory diet. If food is administered with patience and regularity the anorexia disappears, and vomiting and diarrhea are corrected within a few days. Complete recovery, however, usually requires at least three months.

Coexisting Deficiencies

The clinical manifestations of protein-calorie malnutrition are further complicated by the presence of other nutritional deficiencies. Vitamin A deficiency with severe ocular lesions is frequent in both marasmus and kwashiorkor. Concurrent deficiencies of components of the vitamin B complex, particularly riboflavin, are also common. The mild normocytic, normochromic anemia attributable to protein deficiencies is often complicated and becomes much more severe because of simultaneous deficiencies of iron, vitamin E, folic acid and other hematopoietic factors of the vitamin B complex. A recent report suggests that vitamin E deficiency is sometimes responsible.[13]

Dehydration and serious electrolyte imbalance are usual because of the coexisting diarrhea. Both present special features because of the overhydration, sodium retention, potassium depletion and renal disturbances present as a direct consequence of the deficiency in protein.

VITAMIN-DEFICIENCY SYNDROMES

Vitamin A

Vitamin A deficiency is responsible for thousands of cases of blindness in young children in south and east Asia and for many hundreds more in Latin America, Africa and the Middle East.[14] Furthermore, children with such a deficiency suffer an

exceedingly high mortality owing to the increased susceptibility to infections. In some areas as many as 1 per cent of all children have residual corneal damage sufficient to interfere with vision, and about a fourth of the children in whom xerophthalmia develops do not reach adulthood.[15] Apparent loss of dark adaptation is widespread among adults in the same areas although the condition has not been systematically studied.

Oomen[16] describes the "too, too frequent case in which a mother, after long hesitation, ventures to the doctor, because her small child did not open his eyes for ten days. The doctor then finds two corneas irretrievably gone. But xerophthalmia is also seen in the school child . . . with a contusion of his forehead . . . [who] ran into a pole the preceding evening at dusk, because he is night-blind and he has Bitot spots on his eyes."

Much the same conditions responsible for the worldwide occurrence of kwashiorkor and marasmus account for the geographic distribution of xerophthalmia and their frequent presence in the same child. Supplementary foods for young infants are prepared from rice or other cereals deficient in carotene as well as protein. Families of unskilled laborers without land, whether urban or rural, tend to subsist on satiety-producing cereals to the neglect of vitamin-containing vegetables and fruits. Much vitamin A deficiency occurs in the greenest places on earth, where carotene-containing leaves should be readily available, but the end result is the same as in arid rural areas with a sheer lack of carotene sources for most of the year. Parts of North Africa and northeast Brazil are examples of the latter.

Clinically, xerophthalmia is an affection of the only transparent epithelial structures of the body that are exposed to air and light, the conjunctiva and the cornea. A fatty dryness of the conjunctiva is typical, with thickened wrinkles at the corners and hyperpigmentation. Thick, whitish flecks may be seen on the surface, where they accumulate as the frothy-appearing Bitot spots. With adequate vitamin therapy the conjunctiva at this stage can again become transparent and moist within a few days, but the Bitot spot, lacking living cells, may remain for weeks and the hyperpigmentation may become even more pronounced.[16]

Involvement of the conjunctiva is often accompanied by xerosis of the cornea, which becomes hazy, rough, dry and sensitive. Punctate, superficial infiltrations or small surface erosions may lead, within a day or so, to protrusion of the iris and even prolapse or expulsion of the lens. The late stages are accompanied by inflammatory symptoms.

Keratomalacia is a colliquative necrosis of the whole cornea that follows xerosis. According to Oomen,[16] a rather sudden spongy swelling and melting down of the cornea progresses to eventual shrinkage of the eyeball. Since corneal changes are minimal in the germ-free rat with vitamin A deficiency,[17] secondary infection probably plays a part in the later stages of the disease in man.

In view of the close association of vitamin A deficiency with kwashiorkor and marasmus already emphasized, the training of personnel and institution of programs against xerophthalmia are important parts of any attack on malnutrition in underdeveloped areas. There is evidence that the administration of dried, powdered skimmed milk to malnourished children can enhance a pre-existing vitamin A deficiency.[18] At one time surplus skimmed milk from the United States was banned temporarily from Indonesia because it seemed to result in an increase in xerophthalmia. Simultaneous administration of capsules containing vitamins A and D is now standard policy of the United Nations Children's Fund (UNICEF) for milk distribution to children in areas with vitamin A deficiency. Alternatively, powdered milk for use in such circumstances can be enriched with water-miscible synthetic vitamin A.

In many tropical areas, red African palm oil is readily available as a rich source of provitamin A. Nutrition-education programs in such countries are placing particular stress on green and yellow vegetables as important foods in a balanced diet and on certain fruits, such as mangoes, papaya, squash and melons, which are useful sources of active carotene. The control and ultimate elimination of xerophthalmia is an important goal of nutrition programs in the underdeveloped areas. Furthermore, an increased attention to vitamin A as well as protein nutriture will result in improved resistance to the many infections that cause so much morbidity and mortality in underprivileged populations.

Scurvy

Clinical signs of ascorbic acid deficiency are fortunately uncommon in underdeveloped countries. Since most of them are tropical or subtropical, a variety of fruits rich in vitamin C are grown and widely consumed. Furthermore, common vegetables such as cabbage, brussels sprouts, cauliflower, peppers, chipilin, bledo, beno, nabo and yucca flowers are useful sources of this vitamin. For example, serum levels of ascorbic acid in schoolchildren of Central America[12] averaged 1.55 mg. per 100 ml. — more than twice the usual levels for children of most developed countries.[19] The occasional case of scurvy in children or in families not consuming fruit and fresh vegetables is readily treated on an individual basis.

Beriberi

Where highly milled rice is the principal food staple beriberi is an important public-health problem. In Japan rice enrichment and a more diversified diet have virtually eliminated the disease. In the Philippines and Indonesia the incidence has

also decreased, probably owing to some increase in variety of diet. In Thailand, Malaysia and Vietnam, however, beriberi has increased in recent years as more efficient small mechanical mills replace hand pounding, which left some of the germ and hull.[20] Moreover, most of the increase has been in infantile beriberi, with its recognized high fatality. Beriberi is almost entirely limited to underdeveloped areas of the Far East and for this reason receives relatively less attention among nutritional deficiencies than those more universally distributed.

Beriberi in both adults and older children is of three main types.[21] The chronic, dry, atrophic form and the acute, fulminating type are more serious and dramatic, but most cases are mild and subacute. The chronic, dry, atrophic type, with wrist and foot drop, is generally found only in the older adult, often associated with prolonged consumption of alcohol.

The third type, the mild and subacute form, has characteristic nervous manifestations, including alterations in tendon reflexes. Paresthesia is common. The extent of muscular involvement relates to length of the nerve, amount of work done by the muscle group involved and possibly the blood supply. Sensations of fullness or tightening of the muscles and muscle cramps are common at night. Cardiovascular signs and symptoms range from breathlessness on exertion and palpitation to tachycardia, cardiac dilatation and some degree of congestive heart failure. Coexisting deficiencies of ascorbic acid, riboflavin, niacin and vitamin A are common.

The development of infantile beriberi is due to low thiamine levels in breast milk. Among all deficiency diseases it is one of the most dramatic, for a child may be apparently well and yet die from this condition a few hours later.[22] Recovery with parental administration of thiamine is equally dramatic. Burgess[23] describes an initial stage of vomiting, restlessness, pallor, anorexia and insomnia. In acute infantile beriberi cyanosis, dyspnea and death ensue rapidly. In the subacute form further vomiting, puffiness of the face and extremities, oliguria, abdominal pain, dysphagia, aphonia and convulsions may appear. This type may go on to a fatal acute episode or may become chronic.

Chronic infantile beriberi sometimes evolves from the initial state without an intervening subacute stage. Vomiting, inanition, anorexia, aphonia, neck retraction, opisthotonos, edema, oliguria, constipation and meteorism are variously seen. There need be no signs of beriberi in the mothers of infants affected. Reports coming to the World Health Organization suggest that infantile beriberi is more of a problem today than clinical beriberi in older children and adults.

To contract beriberi or to transmit it to a nursing infant, a person must generally derive a high proportion of calories from polished rice. Increasing the thiamine content of milled rice by parboiling is feasible but not widely practiced. Similarly, enrichment of rice with components of the vitamin B complex has not thus far been politically or economically accepted in countries having the greatest need. Like many deficiency diseases associated with monotonous diets of a single staple, beriberi can be eliminated by greater variety in the diet.

Pellagra

Pellagra is still found seasonally in Egypt, Yugoslavia and some parts of Africa, where corn supplies more than 60 per cent of the daily calories. Because of the niacin supplied by beans[24] and coffee[25] it is not seen in Mexico and Central America, even among populations deriving up to 80 per cent of their calories from corn. On exposure to the sun, persons whose diets are deficient in niacin and contain no excess of tryptophan acquire a scaly, pigmented dermatitis over the exposed areas of skin. Depending on the type of clothing and occupational activities, the areas most affected are the face, neck, back of the hands, elbows, knees and front of the ankles. Patients with severe cases have atrophy and thinning of mucosal surfaces, leading to sore mouth and diarrhea.

Dementia, one of the classic "three D's" of pellagra, along with dermatitis and diarrhea, is rarely seen today. Anemias are frequent, presumably owing to associated deficiencies of other components of the vitamin B complex and of iron. The so-called "infantile pellagra" once reported from Yucatan and Africa is now recognized as kwashiorkor, the similarity of the skin lesions having led to the confusion.

Nutritional Anemias

Nutritional anemias due to insufficient intake of hematopoietic factors, their poor absorption or increased demands because of abnormal blood loss are frequent in tropical and subtropical areas. Although these anemias are known to be highly prevalent, little information is available on the magnitude or the nature of the problem. Most of the information is from patients in hospitals or clinics where anemia is a common diagnosis. Such data give little indication of prevalence in the general population. In Mauritius, one of the few population groups systematically sampled, anemia was present in over 50 per cent of the inhabitants.[26] The definition of anemia is a major problem since normal values for red-cell and hemoglobin concentrations of persons living under different environmental conditions, particularly altitude, have not been firmly established.

Pregnant women, infants and small children are most seriously affected in the areas where the problem exists. Mild to moderate cases in the general population are often highly prevalent and yet unrecognized. A deleterious effect of anemia on work performance and general well-being is suspected but not quantitatively determined.

Iron-deficiency anemia is the most common type

in tropical and subtropical areas. Roche[27] has obtained quantitative data in Venezuela on the iron losses incident to the presence of hookworms in the intestine.[12]

With heavy infections a good correlation between degree of the infection and level of hemoglobin was found. In a significant number of cases, however, the same type of anemia was observed without hookworm disease and similarly, although less frequently, in areas where hookworm does not exist. These Venezuelan studies suggest that less than a third of the iron-deficiency anemias observed in hookworm-infested areas are due solely to the parasites.

Increased loss of iron by sweat and dermal desquamation is a factor of unknown significance in areas where environmental conditions favor profuse sweating. Other possible factors interfering with iron absorption and requiring further study are the frequently associated infections and protein deficiency.

Total iron intake, as estimated by dietary surveys, is usually within recommended amounts, or even higher, in areas where iron-deficiency anemia is prevalent, either with or without hookworm disease. Absorption of the iron contained in the diets is less well known. Diets ordinarily include a large proportion of cereal grains and legumes as the principal sources of dietary iron. Recent studies suggest that the iron of cereals is not well absorbed, at least by anemic persons.

Megaloblastic anemias are less common than the microcytic hypochromic type associated with iron deficiencies. They are reported particularly in pregnant women and in severely malnourished children. Folate deficiency, either of dietary origin or from other factors interfering with its metabolism, seems to be a frequent cause. Vitamin B_{12} deficiency has also been reported, particularly in populations with a predominantly vegetarian diet and in pregnant women.

Nutritional anemias of even less clearly defined etiology are also common. Some, of a dimorphic type, seem to be associated with a combined deficiency of both iron and maturation factors. The role of protein deficiency as a direct or indirect factor has not been clearly defined despite the potential importance incident to its high prevalence. When frank protein malnutrition is present, neither the iron deficiency nor the megaloblastic type of anemia will respond completely to iron or folate combined with vitamin B_{12} treatment unless the diet is supplemented with protein.[3] The frequent anemia in severe cases of protein-calorie deficiency responds initially to a milk diet high in protein, without specific supplementation with iron or folate and vitamin B_{12}, even though milk is poor in these nutrients. The possible role of other specific nutrients in the etiology of the nutritional anemias in underdeveloped countries needs further study.

The World Health Organization (WHO) is presently interested in the magnitude and nature of the nutritional anemias as a public-health problem and is co-ordinating and helping epidemiologic, clinical and experimental studies now in progress in different laboratories around the world. These contributions and those of other investigators may provide more complete and accurate data. Meanwhile, the simple supplementation of basic staple foods with iron in areas where iron-deficiency anemia is highly prevalent can be extremely beneficial.

Endemic Goiter

Until recent years endemic goiter was primarily a place disease, peculiar to areas where geologic factors resulted in a lack of sufficient iodine in the local water and food supply. Historically, endemic goiter has occurred on every continent and in most countries.[28] In the developed countries, however, it has largely disappeared, in part because of the widespread availability and use of iodized salt, compulsory in many countries, and also because of the increasingly heterogeneous origin of the food supply from iodine-rich as well as iodine-poor areas. In most goitrous areas of the underdeveloped countries neither of these factors has yet become active.

High prevalence rates for goiter characterize most of the countries of Latin America except Guatemala, Colombia and Paraguay, where salt for human consumption is iodized. The incidence of goiter has declined promptly wherever iodization has been achieved. Much endemic goiter also occurs in West Africa, the high plateau of Ethiopia, southern Africa, the northern and southern slopes of the Himalayan Mountains, India and most of Southeast Asia, including Indonesia and the Philippines. The World Health Organization has devoted an entire monograph to this problem,[29] and has stimulated surveys for goiter in all member countries. In these surveys goiter is classified as Grade 3 if the thyroid enlargement is visible at a distance, Grade 2 if it is visible on close inspection with the head in a normal position and Grade 1 if it is smaller although more than four or five times the normal size. The presence of nodules suggests fetal deprivation of iodine.

Most goiters in schoolchildren are Grade 1, but Grade 2 and even Grade 3 goiters occur in older children. Rarely is there a suggestion of thyroid dysfunction; in children, at least, enlargement of the gland seems to be a successful compensatory hypertrophy. Goiter may become progressively larger in adults to the point where it is disfiguring, interferes with respiration and becomes so fibrotic that it cannot be eliminated by iodine therapy. In children simple goiter usually disappears within a few weeks after

iodine administration, but will reappear if iodine is no longer supplied.[30]

Aside from cosmetic reasons, the increased frequency of cretinism in goitrous areas and the suspicion that goiter is responsible for some feeblemindedness and deaf-mutism require preventive action. Furthermore, thyrotoxicosis parallels endemic goiter in most goitrous regions.[31] A relation to thyroid carcinoma is less certain.

The relative contribution of primary iodine lack and of the presence of goitrogenic factors in food and water to the frequency of endemic goiter is not well defined. The thiocyanates and thiocyanate precursors present in many members of the cabbage family are the best known food goitrogens, but a wide variety of other foods, including peaches, pears, strawberries, spinach and beans, has been shown to have goitrogenic activity in laboratory animals.[32] Hardness of the water, vitamin A deficiency and polluted water supply have been reported to be goitrogenic in man.[33] The combination of environmental iodine lack and the monotonous, mainly vegetarian diet of foods with goitrogenic activity is sufficient to explain the high prevalence of endemic goiter in so many of the underdeveloped countries.

Fortunately, endemic goiter is the easiest of all deficiency diseases to prevent. The method of choice is iodized salt. Although salt is frequently consumed in a crude, moist form unsuitable for iodization with potassium iodide as practiced in Europe and North America, in the form of potassium iodate, iodine can be added to crude salt without special packaging or handling.[34] An iodine level between 1 in 10,000 and 1 in 20,000 parts of salt is recommended.

Dental Caries and Periodontal Disease

Dental caries is exceedingly prevalent in most of the underdeveloped countries. Comparatively young persons with teeth broken off at the gums or entirely absent are a common sight. Tooth decay is presumably not more active in such areas than in many highly developed countries, but because of the lack of dental care, its consequences are more serious. Indeed, some malnourished populations enjoy remarkably good teeth, particularly when the natural fluoride content of soil and water reaches prophylactic levels. A number of cities in these regions are now obtaining the benefits of fluoridated water. Periodontal disease is also a serious public-health problem, again owing more to poor dental hygiene and lack of dental care than to malnutrition.

Trace-Mineral Deficiencies

Only zinc, magnesium and copper deficiencies have been specifically identified. Recent studies in the Near East[35] report zinc deficiency to be a factor responsible for a syndrome of dwarfism and hypogonadism in male adolescents. The deficiency of zinc may result either from a low intake or from impaired absorption due to a high dietary content of phosphates and phytates as in diets predominantly of cereal grains. Similar syndromes in other areas have been attributed to anemia, to liver dysfunction caused by schistosomiasis or to general undernutrition. Since these factors do not always provide a satisfactory explanation, further studies on zinc deficiency in representative areas are widely needed.

A marked depletion of magnesium has been demonstrated in children suffering from kwashiorkor, both by metabolic balance studies and by direct analysis of muscle biopsies.[36] Some patients with low serum magnesium values and tetany have responded well to administration of magnesium.[37] This may not be a deficiency of dietary origin; it is more probably related to metabolic disturbances or impaired absorption owing to the severe protein deficiency. Nevertheless, the possible occurrence of magnesium deficiency in the general population in areas where protein-calorie malnutrition exists needs to be studied.

Copper depletion severe enough to cause hypocupremia has been observed in some patients with the syndrome of iron deficiency and hypoproteinemia, kwashiorkor and sprue.[38] Anemia and bone disease due to copper depletion have been recognized in 2 Peruvian children with kwashiorkor.[39] More extensive studies may disclose a hitherto unsuspected prevalence of copper depletion in some malnourished subjects.

Synergism of Nutrition and Infection

The role of infectious diseases in precipitating kwashiorkor, marasmus and keratomalacia in children taking diets of borderline adequacy has been emphasized in preceding sections. Diarrheal diseases are especially frequent in underdeveloped countries because of poor environmental sanitation and deficient personal hygiene. Respiratory infections are also common and tend to be more severe than in more favored regions. These infectious diseases, along with the common communicable diseases of childhood, decrease appetite and cause extra metabolic loss of nitrogen and a number of other essential nutrients.[40] Equally important, attendants commonly reduce the intake of food of persons who are ill, especially children, by substituting thin carbohydrate gruels or cereal infusions for the usual solid food. The frequent administration of strong purgatives to children with diarrhea adds to the disastrous nutritional consequences.

Of equal or greater concern is the fact that malnutrition severe enough to interfere with growth and development is also able to interfere with resistance to infections. The common childhood diseases, rarely

fatal in well nourished children and scarcely requiring medical care, are major causes of death in areas where malnutrition prevails in childhood. Mortality from measles in 1959-1960, for example, was 180 times higher in Mexico, 189 times higher in Guatemala and 418 times higher in Ecuador than in the United States,[41] although the disease caused no special problems among the better nourished children of families with middle and upper incomes in the same countries.

In a two-year analysis of the deaths of children in four Guatemalan highland communities, diarrheal disease and common childhood infections were apparently responsible for nearly two thirds in the group from one to five years of age.[42] Few of these infections would have been fatal in well nourished children. Conversely, approximately two fifths of the children of this age group who died during the period of observation had the symptoms of kwashiorkor, but the syndrome appeared to have been precipitated in nearly every case by a preceding episode of diarrhea, measles or other infection. Overall mortality in children of this age in the four communities, as in the country as a whole, was over 40 times higher than in the United States and Western Europe, and the difference could be accounted for by the synergism of nutrition and infection.

In a recent five-year study by INCAP in the rural Guatemalan highland village of Santa Catarina Barahona, children under five years and all pregnant and nursing mothers were offered a supplement providing 15 gm. of protein and 450 calories five days a week. No medical care was given. Mortality decreased remarkably for children six to eighteen and eighteen to thirty-six months of age, as compared with preceding years, whereas no change occurred in the control village of Santa Cruz Balanya.

It is now increasingly recognized that the acute diarrheal disease of infants and young children so common in developing countries during and shortly after weaning is microbiologically nonspecific and yet constitutes an epidemiologic entity to which the name "weanling diarrhea" has been applied.[43] Throughout the world a known pathogenic agent can be identified in only about 20 per cent to a maximum of 40 per cent of cases of weanling diarrhea. The remainder defy expert microbiologic investigation, including a search for causative enteroviruses. Infectious agents identified are mainly various strains of enteropathogenic *Escherichia coli,* shigellas and occasional salmonellas.

The hypothesis is advanced that many weanling diarrheas are the consequence of organisms not normally pathogenic in a well nourished child. Even the various strains of *Esch. coli,* shigella and salmonella with accepted pathogenic properties are known to invade the well fed nursing infant under six months of age without necessarily causing diarrhea. The incidence is relatively low at this time, as is the mortality rate. After the mother's milk is no longer a sufficient source of protein the same organisms may then be associated with diarrheal disease. Cases and deaths increase, and rates continue high throughout the long weaning period and for the months immediately thereafter. Weanling diarrhea is spread by direct and indirect contact rather than by food or water of common origin.

For this reason latrine construction and improvement of central water supplies has little influence on the incidence of weanling diarrhea without increased availability and use of water for personal cleanliness. Supplementary feeding, however, can be expected to reduce both morbidity and mortality from weanling diarrhea, and this was reported in the five-year study in Guatemala referred to above.

It should be emphasized that weanling diarrhea is exceedingly common and contributes importantly to the retarded growth and development of children during the sixth to thirty-sixth months of life and to the occurrence of kwashiorkor and marasmus. It accounts for much of the mortality attributed to gastroenteritis in the national and international vital statistics. Feeding and rehydration are the important elements of its treatment and will materially reduce the number of deaths. Laboratory studies of specific agents are of theoretical interest but of little help in guiding therapy or control activities.[44] Antibiotics or sulfonamides are useful in the treatment of secondary complications but have little effect on the diarrhea itself.

Progress in identifying the mechanism whereby malnutrition exaggerates infection has been slow. It is well known from studies in laboratory animals that a variety of nutritional deficiencies will interfere with antibody formation and with leukocyte response and activity. In kwashiorkor the antibody response is inhibited.[45,46] This has also been observed in malnourished patients with chronic infections[47] and in experimental pantothenic acid and pyridoxine deficiency in human volunteers.[48,49] Children with kwashiorkor may show no febrile or leukocytic reaction to infection. Nothing is known, however, of the extent of involvement of any of these mechanisms in the lowered resistance of subclinical deficiency states.

Alterations in tissue integrity, especially of mucous membranes and other epithelial structures so characteristic of kwashiorkor, vitamin A deficiency, scurvy, pellagra, ariboflavinosis and some other deficiencies, also are partly responsible for increased susceptibility to some infections. Other potential but unproved means by which resistance is decreased in malnourished inhabitants of underdeveloped countries include interference with general resistance factors such as lysozymes, interferon and properdin,

decreased nonspecific resistance to bacterial toxins, endocrine imbalances and altered intestinal flora.

Because developed countries with the greatest potential in medical research have so little malnutrition severe enough to interfere with resistance to infection the problems of synergism between malnutrition and infection have not received the attention they merit. For a large proportion of the world's populations they are critically important.

Concluding Remarks

Clinical malnutrition and the synergism between nutrition and infection represent only part of the influence of malnutrition on morbidity and mortality in underdeveloped areas. Food influences the frequency of many pathogenic conditions other than classic nutritional disease. For example, remarkable variations in the frequency of liver, stomach and bladder cancers, renal and hepatic calculi and atherosclerosis among populations have been related to differences in dietary habits. Whether these are caused by dietary deficiencies or excesses, naturally occurring toxic substances in foods, unintentional food additives, mold-induced toxins, dietary imbalances, nutritional interference with endocrine function, reduced resistance to carcinogenic factors or some combination of these is largely unknown. The consumption of large quantities of a single staple, as in many underdeveloped countries, is likely to make important very low levels of toxicity that are of no significance in foods eaten in moderate quantities.

The prevention of malnutrition requires intensive and co-ordinated programs to correct the inadequate food consumption due to ignorance, poverty and lack of available food, as well as to control diseases interfering with nutritional status. Most supplementary feeding programs for vulnerable groups are emergency measures and not substitutes for permanent prevention. No country can afford to accept as a long-range solution the utilization of surpluses of other countries unless it is in the position of having sufficient foreign exchange from its own resources for their continued purchase.

The scientific and technologic knowledge to correct the shortage of food in most of the underdeveloped countries is now available. With application of improved agricultural technics, scientific methods of animal raising, better food processing and modern methods of food preservation, the availability of food can be tremendously increased in most areas where it is now scarce. New food crops can be introduced, and unexploited land resources utilized, although irrigation may be required.

The problems of supplying protein to the growing populations of underdeveloped areas will be aided by resources not now in common food use. Although protein from marine resources, particularly fish-protein concentrate, has received more popular attention, the greatest promise is in the oilseed meals. In temperate zones soya flour is a practical protein source, but cottonseed flour is more available in the tropical areas, where conventional animal sources of protein of high biologic value are often scarce and costly.

The Institute of Nutrition of Central America and Panama (INCAP) has developed a low-cost all-vegetable mixture containing 27 per cent protein of high biologic value and a balanced complement of the other essential nutrients. Already successfully marketed in Guatemala and Colombia under the name of "Incaparina," it is composed of cottonseed, corn and sorghum flours, supplemented with torula yeast as a source of components of the vitamin B complex, synthetic vitamin A and calcium carbonate. Incaparina is cooked with water and served as a thin, sweetened gruel flavored to taste. Its chief advantages are high nutritive value, local availability of principal ingredients, low cost and cultural acceptability. There is sufficient knowledge to develop such foods for any country of the world.

Permanent correction of malnutrition in underdeveloped areas requires fundamental education in the importance of adequate nutrition and the relation between poor diets and ill-health. Not only must the low educational level and lack of technical skill and understanding among the common people be overcome, but also governmental officials and leaders in these countries must acquire greater awareness and understanding of nutrition and other health problems. At present, malnutrition, as such, is often unrecognized, and even severe malnutrition syndromes are commonly attributed to some unrelated agent such as magic or worms. Efforts to improve dietary habits must take into consideration available resources, economic possibilities, food habits and prejudices.

Good results can be expected only when the dietary recommendations and education in nutrition are adapted to the cultural pattern of the populations. Even then, education alone will fail if there is not enough good food within the purchasing power of the people educated. In many countries the rapid population rise is outstripping whatever increases are achieved in food production. A more rational rate of population increase in these countries is imperative if food production is to catch up with food need.

The trained workers and material resources required are far greater than those available in the underdeveloped countries. Supplying these cannot be the responsibility of the United States alone. A major effort is required on the part of all the more privileged nations.

In spite of the difficulties, the correction of nutritional deficiencies is indispensable to the stability, progress and peace of the world.

References

1. Jelliffe, D. B. *Infant Nutrition in Subtropics and Tropics.* 237 pp. Geneva: World Health Organization, 1955. *(Monograph Series,* No. 29.)
2. Cravioto, J. Application of newer knowledge of nutrition on physical and mental growth and development. *Am. J. Pub. Health* **53**:1803-1809. 1963.
3. Viteri, F., Béhar, M., Arroyave, G., and Scrimshaw, N. S. Clinical aspects of protein malnutrition. In *Mammalian Protein Metabolism.* Edited by H. N. Munro and J. B. Allison. 2 vol. Vol. 2. New York: Academic Press, 1964. Chapter 22. Pp. 523-568.
4. Hansen, J. D. L. Protein malnutrition and its prevention and treatment with special reference to kwashiorkor and marasmus. In Brock, J. F. *Recent Advances in Human Nutrition: With special reference to clinical medicine: With a number of invited contributions on special subjects.* 454 pp. London: Churchill, 1961. Chapter 23. Pp. 267-281.
5. Castellanos, H., and Arroyave, G. Role of adrenal cortical system in response of children to severe protein malnutrition. *Am. J. Clin. Nutrition* **9**:186-195, 1961.
6. Scrimshaw, N. S., and Béhar, M. Protein malnutrition in young children. *Science* **133**:2039-2047, 1961.
7. Trowell, H. C., Davies, J. N. P., and Dean, R. F. A. *Kwashiorkor.* 308 pp. London: Arnold, 1954.
8. Waterlow, J. C., Cravioto, J., and Stephen, J. M. L. Protein malnutrition in man. *Advances in Protein Chem.* **15**:131-238, 1960.
9. Holt, L. E., Jr., Snyderman, S. E., Norton, P. M., Roitman, E., and Finch, J. Plasma aminogram in kwashiorkor. *Lancet* **2**:1343-1348, 1963.
10. Béhar, M., Viteri, F., and Scrimshaw, N. S. Treatment of severe protein deficiency in children (kwashiorkor). *Am. J. Clin. Nutrition* **5**:506-515. 1957.
11. Béhar, M., Bressani, R., and Scrimshaw, N. S. Treatment and prevention of kwashiorkor. In *World Review of Nutrition and Dietetics.* Edited by G. H. Bourne. Vol. 1. 272 pp. London: Pitman Medical, 1960. Pp. 73-101.
12. Scrimshaw, N. S. Protein deficiency and infective disease. In *Mammalian Protein Metabolism.* Edited by H. N. Munro and J. B. Allison. 2 vol. Vol. 2. New York: Academic Press, 1964. Chapter 23. Pp. 569-592.
13. Majaj, A. S., Dinning, J. S., Azzam, S. A., and Darby, W. J. Vitamin E responsive megaloblastic anemia in infants with protein-calorie malnutrition. *Am. J. Clin. Nutrition* **12**:374-379, 1963.
14. McLaren, D. S. Xerophthalmia. *Am. J. Clin. Nutrition* **11**: 603-609, 1962.
15. *Idem.* Vitamin A in human nutritional eye disease. In McLaren, D. S. *Malnutrition and the Eye.* 390 pp. New York: Academic Press, 1963. Chapter 12. Pp. 162-231.
16. Oomen, H. A. P. C. Discussion of proceedings of conference on beriberi, endemic goiter and hypovitaminosis A: held at Princeton, N. J., June 1-5, 1958. *Federation Proc.* **17** (Supp. 2): 111-124, 1958.
17. Beaver, D. L. Vitamin A deficiency in germ-free rat. *Am. J. Path.* **38**:335-357, 1961.
18. Roels, O. A., et al. Effect of protein and fat supplements on vitamin A-deficient Indonesian children. *Am. J. Clin. Nutrition* **12**:380-387, 1963.
19. Guzman, M. A., Arroyave, G., and Scrimshaw, N. S. Serum ascorbic acid, riboflavin, carotene, vitamin A, vitamin E and alkaline phosphatase values in Central American school children. *Am. J. Clin. Nutrition* **9**:164-169, 1961.
20. Burgess, R. C.[16] Pp. 3-7.
21. Platt, B. S.[16] Pp. 8-20.
22. Ramalingaswami, V.[16] Pp. 43-46.
23. Burgess, R. C.[16] Pp. 39-43.
24. Bressani, R., Marcucci, E., Robles, C. E., and Scrimshaw, N. S. Nutritive value of Central American beans. I. Variation in nitrogen, tryptophane and niacin content of 10 Guatemalan black beans (*Phaseolus vulgaris,* L.), and retention of niacin after cooking. *Food Research* **19**:263-268, 1954.
25. Bressani, R., and Navarrete, D. A. Niacin content of coffee in Central America. *Food Research* **24**:344-351, 1959.
26. Joint FAO/WHO Expert Committee on Nutrition: sixth report. *Tech. Rep. World Health Organ.* No. 245. 65 pp., 1962.
27. Roche, M., Perez-Gimenez, M. E., Layrisse, M., and di Prisco, E. Study of urinary and fecal excretion of radioactive chromium Cr^{51} in man: its use in measurement of intestinal blood loss associated with hookworm infection. *J. Clin. Investigation* **36**:1183-1192, 1957.
28. Kelly, F. C., and Snedden, W. W. *Prevalence and Geographical Distribution of Endemic Goitre.* 471 pp. Geneva: World Health Organization, 1960.
29. *Endemic Goiter.* Geneva: World Health Organization, 1960. (*Monograph Series,* No. 44.) Pp. 27-233.
30. Scrimshaw, N. S., Cabezas, A., Castillo, F., and Mendez, J. Effect of potassium iodate on endemic goiter and protein-bound iodine levels in school-children. *Lancet* **2**:166-168, 1953.
31. Clements, F. W. Relationship of thyrotoxicosis and carcinoma of thyroid to endemic goitre. *M. J. Australia* **2**:894-897, 1954.
32. Greer, M. A., and Astwood, E. B. Antithyroid effect of certain foods in man as determined with radioactive iodine. *Endocrinology* **43**:105-119, 1948.
33. McCarrison, R., Newcomb, C., Viswanath, B., and Norris, R. V. Relation of endemic goitre to iodine-content of soil and drinking-water. *Indian J. M. Research* **15**:207-246, 1927.
34. Arroyave, G., Pineda, O., and Scrimshaw, N. S. Stability of potassium iodate in crude table salt. *Bull. World Health Organ.* **14**:183-185. 1956.
35. Prasad, A. S., Schulert, A. R., Miale, A., Jr., Farid, Z., and Sandstead, H. H. Zinc and iron deficiencies in male subjects with dwarfism and hypogonadism but without ancylostomiasis, schistosomiasis or severe anemia. *Am. J. Clin. Nutrition* **12**:437-444, 1963.
36. Metcoff, J., Frenk, S., Antonowicz, M. S., Gordillo, G., and Lopez, E. Relations of intracellular ions to metabolite sequences in muscle in kwashiorkor: new reference for assessing significance of intracellular concentrations of ions. *Pediatrics* **20**:960-972, 1960.
37. Back, E. H., Mongomery, R. D., and Ward, E. E. Neurological manifestations of magnesium deficiency in infantile gastroenteritis and malnutrition. *Arch. Dis. Childhood* **37**:106-109, 1962.
38. Cartwright, G. E., and Wintrobe, M. M. Perspectives in nutrition: question of copper deficiency in man. *Am. J. Clin. Nutrition* **15**:94-110, 1964.
39. Graham, G. Personal communication.
40. Scrimshaw, N. S., Taylor, C. E., and Gordon, J. E. Interactions of nutrition and infection. *Am. J. M. Sc.* **237**:367-403, 1959.
41. Pan American Health Organization. *Summary of Four-Year Reports on Health Conditions in the Americas 1957-1960.* 111 pp. Washington, D. C.: 1962. (Publication No. 64.)
42. Béhar, M., Ascoli, W., and Scrimshaw, N. S. Investigation into causes of death in children in four rural communities in Guatemala. *Bull. World Health Organ.* **19**:1093-1102, 1958.
43. Gordon, J. E., Chitkara, I. D., and Wyon, J. B. Weanling diarrhea. *Am. J. M. Sc.* **245**:345-377, 1963.
44. Health in relation to social improvement and economic development in Americas. In Pan American Health Organization, World Health Organization. *FACTS on Health Problems.* 54 pp. Washington, D. C.: Pan American Health Organization, July, 1961.
45. Olarte, J., Cravioto, J., and Campos, B. Inmunidad en el niño desnutrido. I. Produción de antitoxina difteria. *Bol. méd. d. Hosp. infant.* **13**:467-472, 1956.
46. Budiansky, E., and Da Silva, N. N. Formacao de anticorpos no distrofia pluricarencial hydropigenica. *Hospital, Rio de Janeiro* **52**:251-264, 1957.
47. Wohl, M. C., Reinhold, J. G., and Rose, S. B. Antibody response in patients with hypoproteinemia, with special reference to effect of supplementation with protein or protein hydrolysate. *Arch. Int. Med.* **83**:402-415, 1949.
48. Hodges, R. E., Bean, W. B., Ohlson, M. A., and Bleiler, R. E. Factors affecting human antibody response. IV. Pyridoxine deficiency. *Am. J. Clin. Nutrition* **11**:180-186, 1962.
49. *Idem.* Factors affecting human antibody response. V. Combined deficiencies of pantothenic acid and pyridoxine. *Am. J. Clin. Nutrition* **11**:187-199, 1962.