Reprinted from The Journal of the American Medical Association
June 1, 1957. Vol. 164

COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following paper was presented at the symposium, "The Relation of Proteins and Amino Acids to Human Nutrition," in Los Angeles, May 21, 1956. This symposium was sponsored by the Council on Foods and Nutrition, with the cooperation of the Los Angeles County Medical Society and the School of Medicine, University of California at Los Angeles. This report is the fourth of the series, which will be available in monograph form.

PHILIP L. WHITE, SC.D., *Secretary.*

KWASHIORKOR IN CHILDREN AND ITS RESPONSE TO PROTEIN THERAPY

Nevin S. Scrimshaw, M.D., Ph.D., Moisés Béhar, M.D., Guillermo Arroyave, Ph.D., Carlos Tejada, M.D.
and
Fernando Viteri, M.D., Guatemala, Central America

In its severe form, protein malnutrition is most frequently seen today in young children. Under the name of *síndrome pluricarencial de la infancia* (S. P. I.) in the Spanish-speaking countries, and kwashiorkor in most other parts of the world, a well-defined protein deficiency syndrome is common in children 1 to 5 years of age in most underdeveloped areas of the world. The condition begins to develop as soon as the quantity of protein contained in the mother's milk becomes inadequate for the needs of the growing child. The amount of protein obtained by the nursing infant becomes inadequate sometime after the 8th to 10th month. This inadequacy steadily increases until the time of weaning, when the child is likely to receive a diet containing a high proportion of carbohydrate and little or no protein of animal origin. During this period, the growth and maturation of the child are greatly slowed. If they are fortunate, children in the lower economic groups in underdeveloped areas pass through the pre-school period with little additional external evidence of damage and resume more normal growth and development when they reach school age. Unfortunately, many of these children with underlying protein malnutrition do not escape more serious consequences; they develop the severe protein malnutrition snydrome of kwashiorkor and die from it.

Factors Associated with Development of Clinical Kwashiorkor

Any one of several factors may precipitate the acute episode of kwashiorkor in a child already suffering from malnutrition.[1] One of the commonest is infectious diarrhea, which not only interferes greatly with the child's absorption of nutrients and increases his loss of body proteins but also may cause the mother to further restrict his diet. Frequently the child is given a starchy solution such as rice water or corn starch gruel containing essentially no protein, and strong purgatives are administered to rid him of the worms that the mother mistakenly believes are causing the diarrhea. With such treatment the child is likely to develop frank symptoms of kwashiorkor in two to four weeks.

Other precipitating causes of kwashiorkor in an already malnourished child may be an attack of some infectious disease such as measles or whooping cough, an emotional shock such as the death of a parent, or a worsening of the economic condition of the family. At times the basic diet is so poor that the child gradually develops kwashiorkor without any other identifiable precipitating cause.

Characteristics of the Acute Syndrome

Clinical Findings.—Retarded growth and development as initial clinical characteristics of the syndrome have already been mentioned. Psychic changes include profound anorexia, apathy, and, frequently, irritability. Muscle tone is decreased, and edema may often be severe. The skin changes include atrophy of the skin appendages, areas of hyperkeratosis, and altered pigmentation. The skin lesions are suggestive of those of pellagra but are not confined to areas exposed to sunlight. Secondary infections may result in the development of extensive excoriations. The hair is likely to be thin, brittle, and pale and sometimes acquires a reddish cast. It is frequently sparse and usually can be pulled out easily. Changes in the nails often parallel those in the hair. Various other clinical signs and symptoms associated with concomitant specific vitamin and mineral deficiencies may be present but vary from one region to another.

Pathology.—The pathological changes found at autopsy in fatal cases are often so severe that it is inconceivable that they have come about in the relatively short period of time after either the occurrence of a precipitating cause or the onset of the clinical signs and symptoms.[2] This is taken as further evidence for belief in the widespread existence of an underlying severe malnutrition in underdeveloped areas, even in children who do not manifest the clinical characteris-

From the Institute of Nutrition of Central America and Panama (INCAP).

tics of kwashiorkor. In addition to the lower body weights, most of the organs are grossly underweight, and a monolobular reticulosis of the liver that has taken a relatively long time to develop is seen in about 20% of the cases.

In acute kwashiorkor, the liver is enlarged and shows a fatty change that is often so severe it involves almost every cell and obliterates the lumen of the sinusoids. In some cases the pancreas may be enlarged rather than underweight, but the pancreatic acini always show moderate to severe atrophy and a reduction in the number of secretory granules. Fibrosis is likely to be present in the pancreas and may be severe. Atrophy of the intestine and stomach occurs; it may be very pronounced and associated with a gross dilatation of these organs.

The skin and skin appendages show a marked degree of atrophy, as do also the follicles of the thyroid. In the latter case, there is a loss of colloid substance and an increase in interstitial fibrosis. The skin shows hyperkeratosis and parakeratosis over the area of gross lesions. Atrophy and loss of lipids are apparent in the adrenal cortex, and fatty degeneration of the kidney tubules may be present.

Hematological Findings.—The characteristic anemia appears to be normocytic or mildly macrocytic, and the bone marrow shows relative hypoplasia of the erythroid series.[2a] When hookworm or other conditions producing iron deficiency are present, the child with kwashiorkor may have a hypochromic microcytic anemia with no hypoplasia of the marrow.

Biochemical Alterations.—The positive biochemical findings have been reviewed recently.[3] They include the low activity of the serum enzymes amylase, esterase, lipase, and alkaline phosphatase as well as of the enzymes lipase, amylase, and trypsin in the duodenum. Total serum protein and albumin levels are both greatly lowered, although the relative amounts of alpha$_1$ globulin and gamma globulin seem to be somewhat increased. The values of serum vitamin A, carotene, and vitamin E tend to be very low; those of riboflavin are within normal limits, whereas those of ascorbic acid are usually lowered in the acute disease. Blood serum calcium and phosphorus levels are little altered, but low serum levels have been reported for cholesterol, phospholipids, and urea, whereas the total serum lipid levels and the ratio of free to total cholesterol appear to be high. Kwashiorkor is also associated with low blood serum levels of potassium,[4] but this may be due primarily to the diarrhea.

Physiological Changes.—Nitrogen retention has quite naturally received considerable attention because kwashiorkor develops as the result of a prolonged negative balance. All workers agree that the nitrogen balance becomes strongly positive whenever protein is given in the acute phase of the disease. Children with kwashiorkor also retain a higher proportion of the total nitrogen of the diet than do well-nourished children.[5] The only information on amino acid metabolism shows a reduced excretion of threonine in the urine and higher than normal ratios of isoleucine to leucine and of phenylalanine to tyrosine.[6] Fat retention is lowered,[7] and steatorrhea is usually encountered.

Altered kidney function is indicated by the frequency of oliguria, and altered cardiac function is indicated by electrocardiographic changes. The latter changes include a profound diminution in the amplitude of all deflections and occasional prolongation of the QT interval.[8] There is no information on initial endocrinological changes, unless the oliguria is considered to be caused by a failure of the liver to destroy antidiuretic hormone as is suggested by Gopalan.[8]

Effect of Protein Therapy

The foregoing review of the characteristics of kwashiorkor has been intentionally brief, since more complete recent reviews are available.[3] The principal purpose of this article is to summarize the effects of protein therapy on these initial findings.

Disappearance of Clinical Signs.—When dried skim milk or half-skim milk alone is given, most of the findings show rapid change. In the first 7 to 10 days,

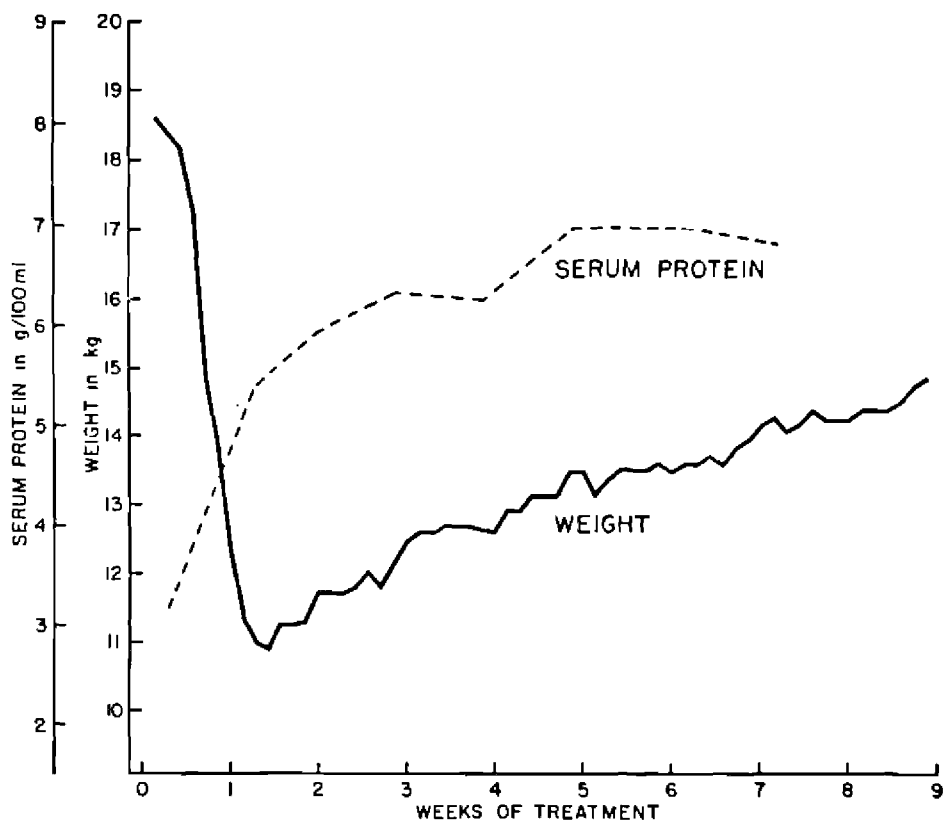

Fig. 1.—Serum protein and weight changes in recovery from kwashiorkor in girl 6 years, 6 months old.

if the child responds to therapy, the apathy and irritability largely disappear and the child's appetite returns. Edema largely or entirely disappears, the skin lesions clear up obviously, new hair and nail substance begin to grow with good color and texture, and the muscle tone improves.

Under ideal conditions, the weight drops rapidly as edema is lost but then begins to climb (fig. 1), and the diarrhea stops promptly. The remarkable change in appearance when severe edema is lost is illustrated by the child in figure 2. The boy in figure 3 shows full recovery, which occurred in 10 weeks of dietary treatment. In less favorable cases, possibly associated with cross infections caused by poor hospital conditions and lowered resistance, intermittent diarrhea continues for many weeks, and the child fails to gain in weight during this extended period.

Considerable evidence is available to suggest that, with reasonable isolation of patients and care to avoid cross infections, most children who recover will do so without the long stationary period in weight. It should be added that some children fail to respond to any kind of therapy, grow rapidly worse, and die. In these

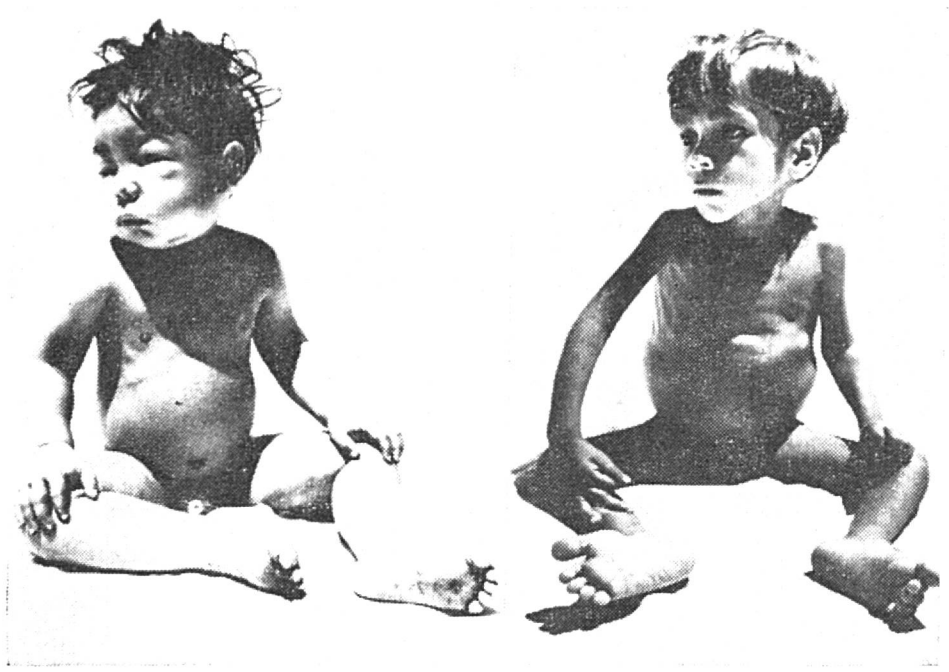

Fig. 2.—Boy 3 years, 10 months of age, showing (*left*) kwashiorkor with severe edema. Five weeks later (*right*) when edema has been lost, considerable degree of undernutrition is revealed.

patients the biochemical and pathological changes described earlier seem to have progressed too far to be reversed. Fortunately, these cases are in the minority.

Hematological Response.—When the mild macrocytic anemia of kwashiorkor is uncomplicated by

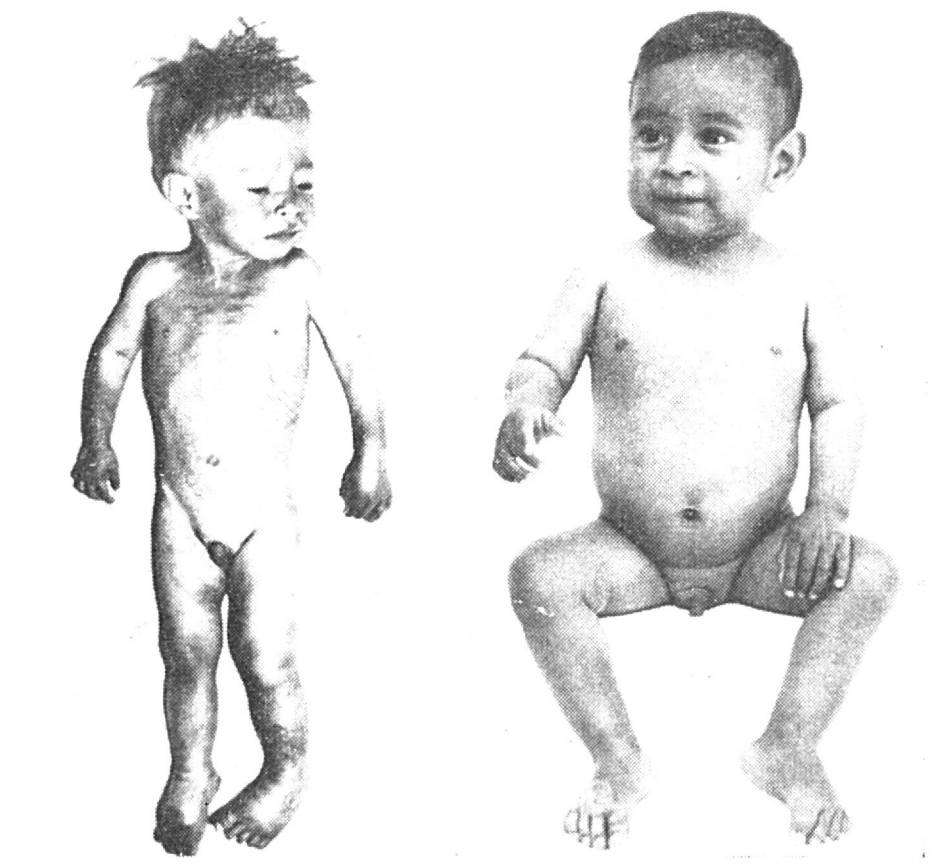

Fig. 3.—Boy 2 years, 3 months of age, showing edema, skin lesions, and other characteristics of kwashiorkor (*left*). Ten weeks later (*right*) good recovery occurred with dietary treatment alone.

hookworm or other conditions directly affecting iron metabolism, it responds rapidly to the administration of milk alone. Figure 4 illustrates the prompt reticulocyte response and rapid increase in red blood cell count. In our cases, however, if supplementary iron is not given, a microcytosis develops that can be corrected by the oral administration of iron, which will produce a second reticulocyte response. These changes are accompanied by a renewal of erythroblastic activity in the bone marrow. When microcytic anemia is present initially, supplementary iron must be given from the beginning if a satisfactory hemopoietic response is to be obtained.

Pathological Changes.—Of the reversible pathological changes, only those in the liver can be studied conveniently. From both autopsy and biopsy specimens we know that nearly all the liver cells contain excessive fat in the acute stage of the disease and that the sinusoids are obliterated by the swelling of the cells. Within 3 to 14 days of optimal dietary treatment, this extra fat disappeared in our cases. Figure 5 shows the microscopic appearance of a biopsy specimen of the liver, with partial disappearance of fat, obtained five days after admission in a child with an acute

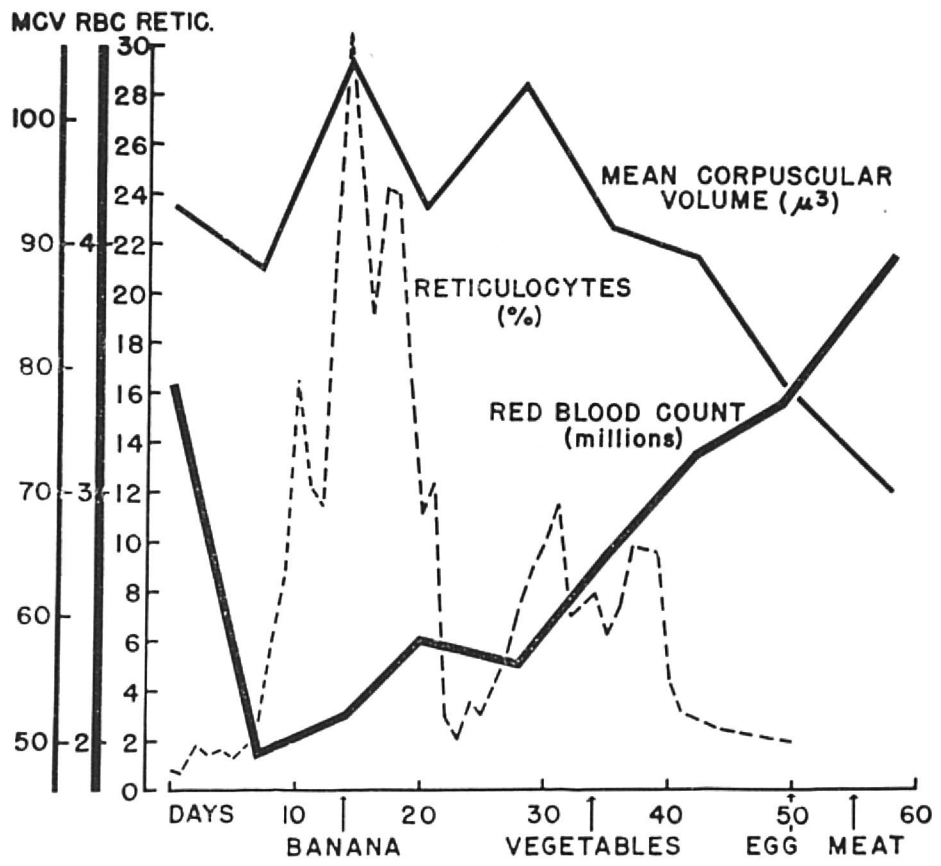

Fig. 4.—Anemia in kwashiorkor. Findings in girl 22 months old given half-skim milk.

case of kwashiorkor. Since fat disappears in the opposite order in which it is laid down, the cells in the center of the lobules are the first to lose their fat. In most cases, when stained with a reticulum stain such as Gömöri, the liver shows a mild to moderate reticulum fiber proliferation. This persists for as long a period of time as we have been able to follow cases, at present a maximum of 15 weeks (fig. 6).

Associated with this reticulum fiber proliferation is an increase in the number of histiocytes in the portal spaces. In some cases a thickening of the walls of the central veins that stains for reticulum and sometimes for collagen is noted. The thickening is different in type from that described by Bras [9] under the name of veno-occlusive disease. In none of our cases has a true hepatic cirrhosis been found. The possible relationship of the reticulum fiber proliferation to fibrosis in the adult is unknown.

Biochemical Recovery.—Changes in levels of certain biochemical substances occur during recovery.

Serum Protein: The prompt response in most cases of kwashiorkor to a diet rich in protein is illustrated for one individual case in figure 1. The average increase in serum protein and albumin levels with adequate treatment is shown in figure 7. A rise in serum albumin from 1.7 to 3.1% and in total serum protein from 3.8 to 6.3% in only two weeks illustrates well the rapid recovery that can take place.

Serum Vitamin Changes: As might be expected, changes in some of the serum vitamin levels are profound. Figure 8 shows the very low levels of vitamin A found in patients upon admission and the gradual rise that occurred as treatment proceeded. This rise was greater when 5,000 units of vitamin A were given daily for the first two to three weeks in addition to the 800 to 900 units contained in the daily diet. The

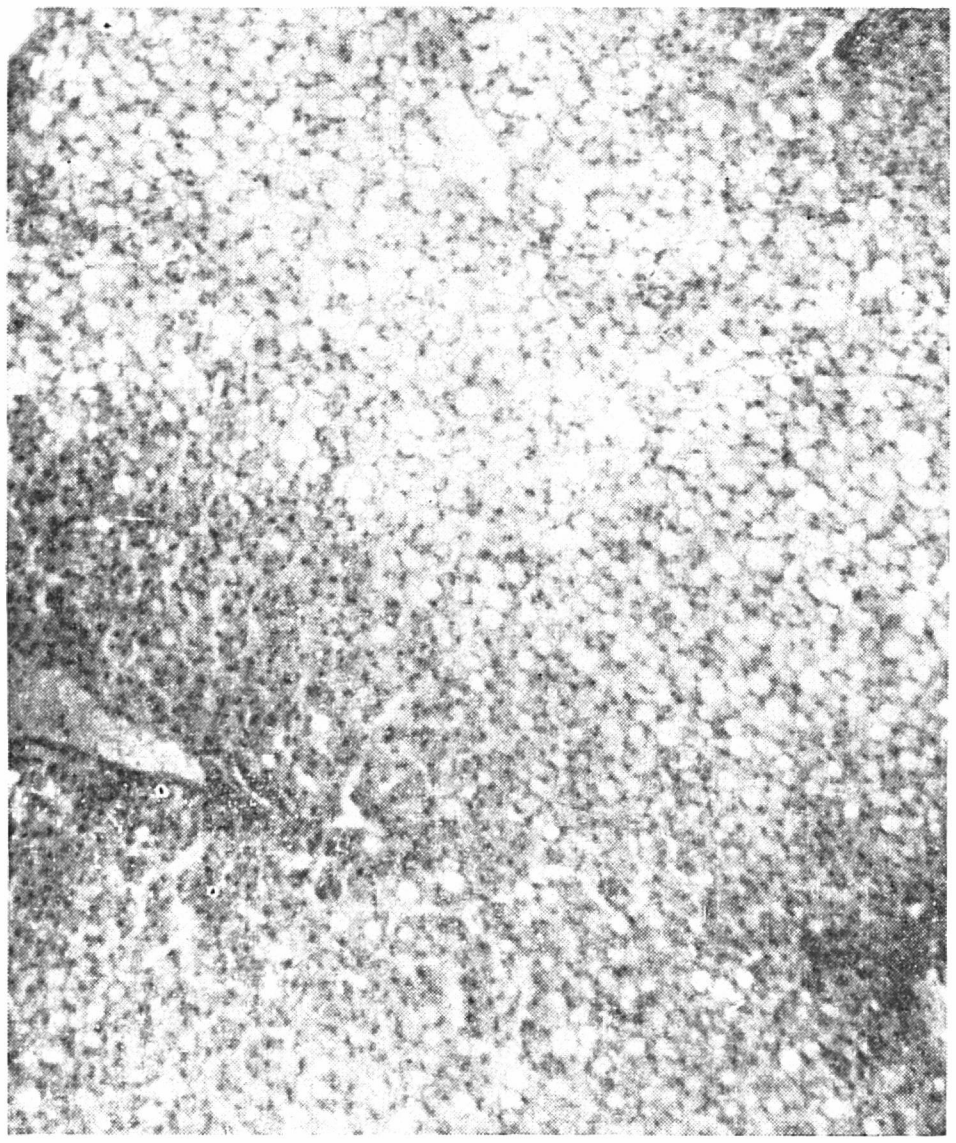

Fig. 5.—Microscopic appearance of liver in boy 3 years of age with acute kwashiorkor after five days of dietary treatment. This section shows disappearance of fat droplets in cells of central portion of lobules. On patient's admission, all of liver cells appeared to contain fat (hematoxylin and eosin stain).

oral administration of a single dose of 75 mg. of vitamin A produced no effect on serum vitamin A levels in children admitted with kwashiorkor.[2a] However, only five days after milk therapy was begun, this oral dose produced a prompt and significant increase in the serum levels of vitamin A. The serum carotene and vitamin E levels, also initially low, rose with treatment.

In general, we have not found the amount of water-soluble vitamins to be greatly lowered in serum. The data summarized in figure 9 show a rise with treatment in the values for both total riboflavin and the so-called free riboflavin fraction. We find that ascorbic acid values also rise with treatment.

Serum and Tissue Enzymes: The rapid rise in the activity of serum enzymes with the feeding of good quality protein is striking. Figure 10 illustrates the increase in serum amylase level that takes place with treatment. Esterase and lipase show similar responses.[3a] All three enzymes have their principal origin

Fig. 6.—Microscopic appearance of liver in boy 5 years of age admitted to hospital with acute kwashiorkor and given four weeks of dietary treatment. This section shows extensive reticulum fiber proliferation commonly seen after clinical recovery (Gömöri stain).

in the pancreas and therefore are useful indicators of the altered pancreatic function in the syndrome and of the recovery in response to treatment.

Figure 10 also shows the rise in levels of alkaline phosphatase and pseudocholinesterase (a nonspecific enzyme that hydrolyzes not only esters of choline but a variety of noncholine esters as well). We have found

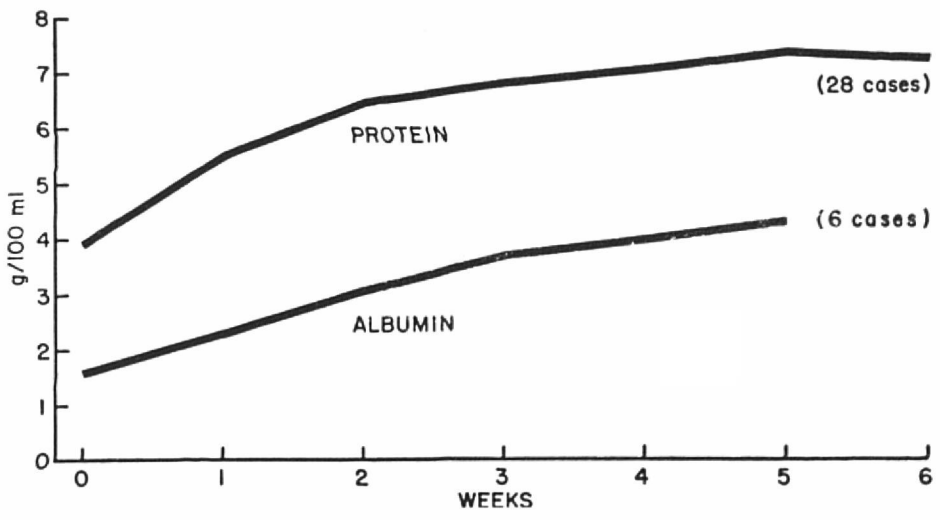

Fig. 7.—Response of serum protein and albumin levels to diet therapy in kwashiorkor.

the latter to be the most sensitive indication of satisfactory response. After an initial drop, alkaline phosphatase level shows a similar rise with treatment.[2a]

Just as this syndrome of protein malnutrition is associated with a widespread decrease in the activity of other enzymes, so is there an equally widespread

and rapid recovery. Waterlow [10] has shown, through a study of liver biopsy specimens from malnourished children in Gambia, British West Africa, that the pseudocholinesterase activity increases more than 100% when a milk diet is given. Although cytochrome

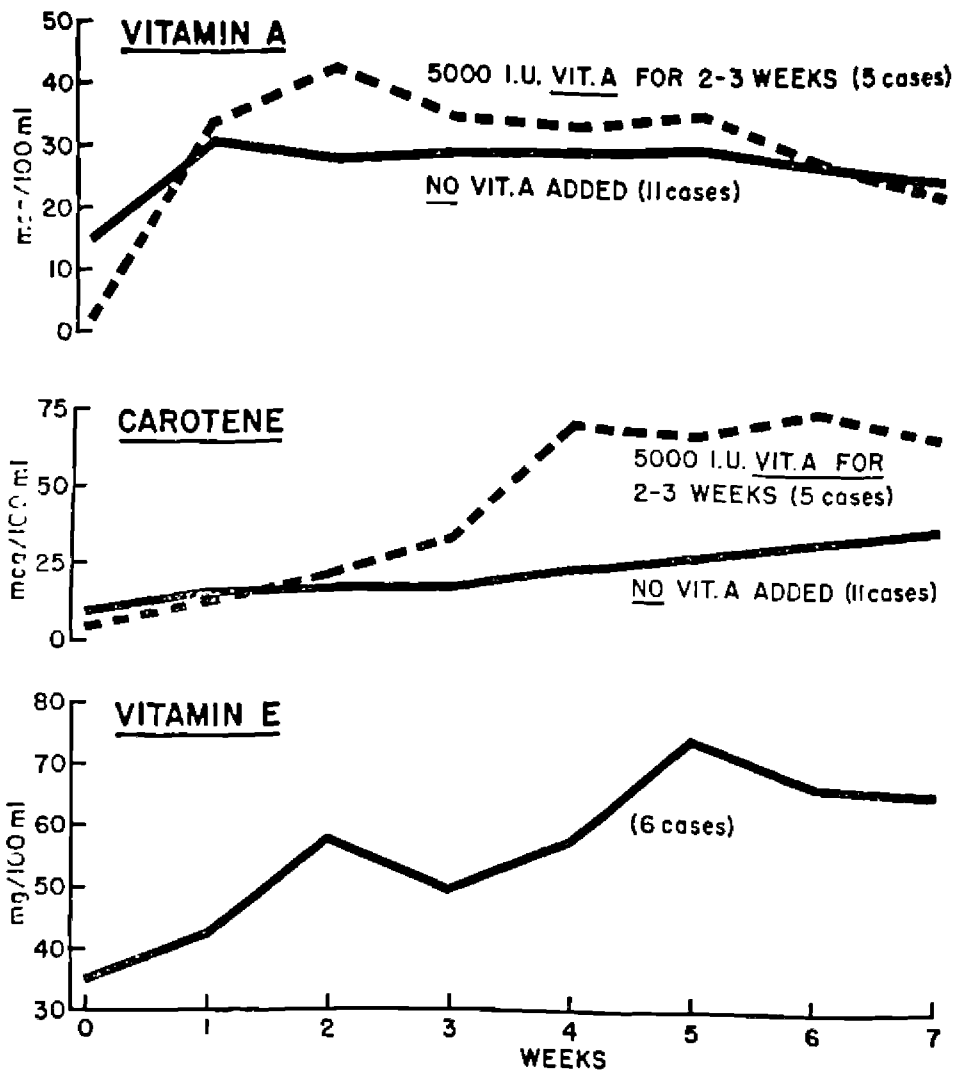

Fig. 8.—Response of serum carotene and vitamins A and E levels to diet therapy in kwashiorkor.

oxidase and lactic dehydrogenase levels are not affected, the level of transaminase in the liver also rises.[10] The alkaline phosphatase activity of liver biopsy tissue increases in kwashiorkor and decreases

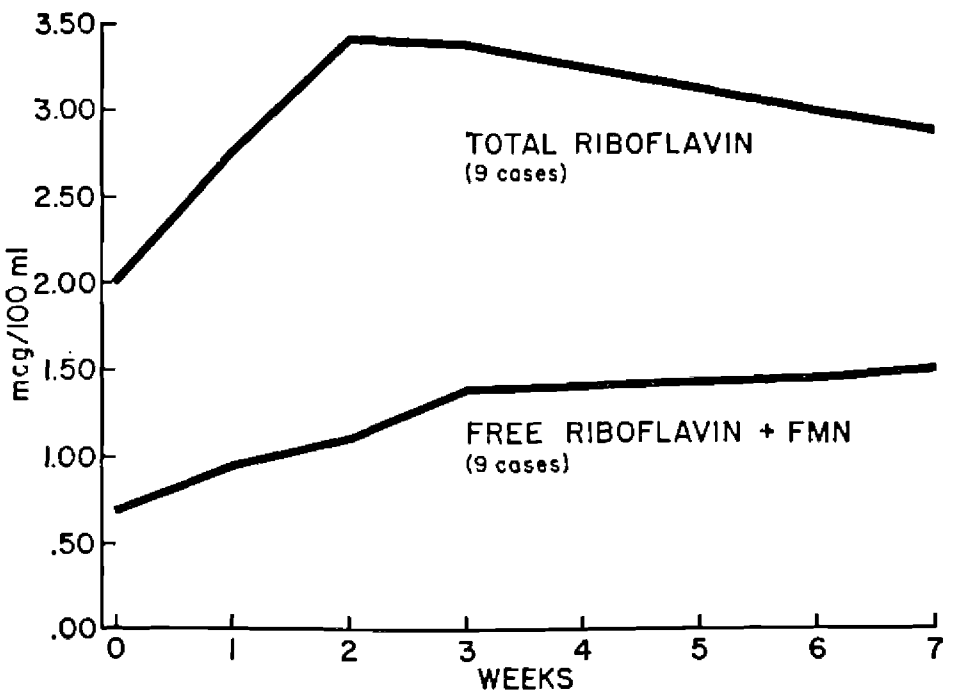

Fig. 9.—Response of serum riboflavin level to diet therapy in kwashiorkor.

with treatment. The duodenal amylase, lipase, and trypsin levels rapidly return to normal in the first 10 days of treatment.[2a]

Other Biochemical Changes: Serum cholesterol values rise rapidly with treatment,[11] and the ratio of free to total cholesterol falls rapidly in the first two weeks. The low-average serum blood urea levels rise to values that exceed the normal level.[10]

Physiological Changes.—It has already been mentioned that nitrogen balance is strongly positive in the early phases of recovery and nitrogen retention is high. In the four children we studied for such data, we found that retentions range between 14.0 and 52.9% even relatively late in recovery. When the child reaches normal weight for height, however, the retention of nitrogen drops sharply regardless of the amount absorbed. The percentage of dietary fat retained decreases in the acute phase of the protein deficiency but rises with treatment.[7a] In our own studies fat retention is variable but does not return to normal even late in the recovery period.[5d] The electrocardiographic changes of the acute phase referred to before also disappear early in recovery.[8] We have recently noted that, when a patient is admitted, the size of his heart is decreased relative to the size of his chest; the heart increases in size with treatment (fig. 11).

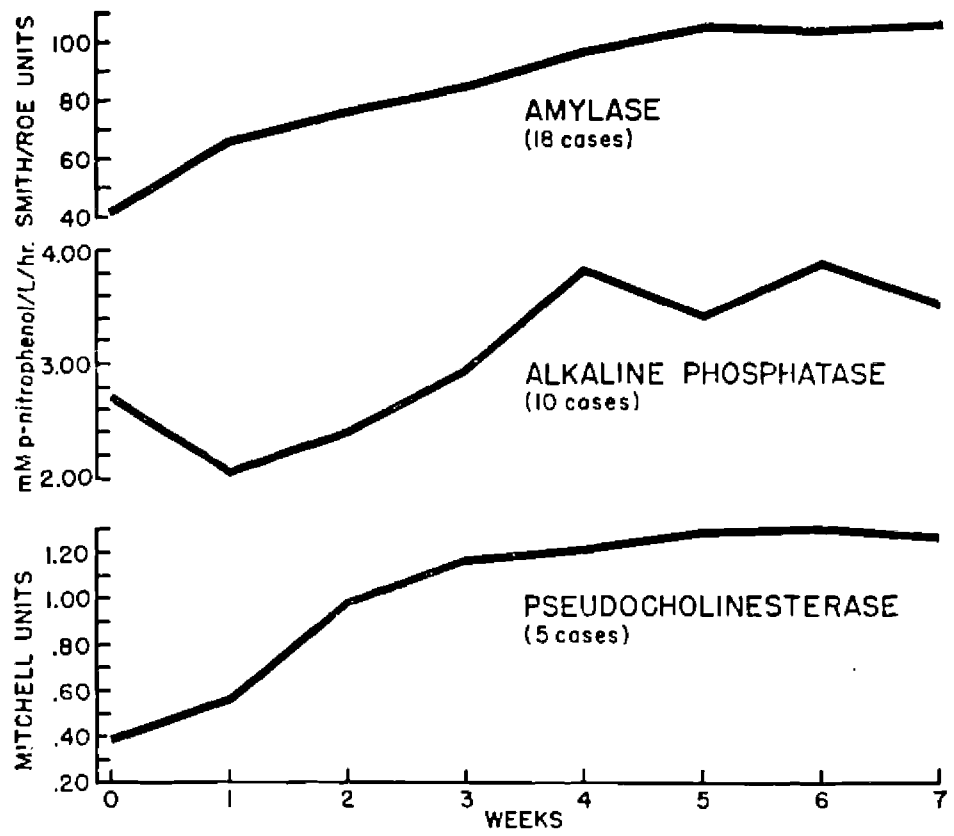

Fig. 10.—Response of three serum enzyme levels to diet therapy in kwashiorkor.

A curious set of findings is occasionally encountered relatively late in recovery. These findings were originally described by Gómez and his group in Mexico under the name of the "recovery syndrome." [12] The liver increases in size, and collateral circulation often is plainly evident, suggesting cirrhosis. An increase in eosinophil count is observed, and hypertrichosis also may develop. It has been suggested that this syndrome is caused by a recovery of pituitary function prior to the recovery of other endocrine organs, with a resulting imbalance. We have occasionally seen this in mild form in Central America, and scattered cases have been reported from other parts of the world. We suspect that this recovery syndrome is aggravated by a high caloric intake with a relatively low proportion of protein.

Relation to Caloric Deficiency

A discussion of protein malnutrition would not be complete without pointing out that it is usually associated with a recent or long-standing deficiency of calories. The cases in which there is a loss of subcutaneous fat and muscular wasting, initially obscured by the edema, are spoken of as the marasmic type of kwashiorkor because they combine degrees of both marasmus or starvation and protein deficiency. In general, these cases are clinically more severe and require longer hospitalization. Since most of the cases of kwashiorkor occurring in Mexico, Central and South America, India, South Africa, and the Belgian Congo are of this type, it is sometimes difficult to separate the effects of protein and calorie deficiency. However, in Jamaica and Uganda, where children may develop kwashiorkor without the loss of subcutaneous fat and muscular wasting, and despite the consumption of an abundance of calories, the changes that have been described as characteristic of kwashiorkor also occur.

Comment

A relative deficiency of protein of high biological value is the outstanding common finding in the diets of children in whom kwashiorkor develops. Furthermore, the principal characteristics of this disease dis-

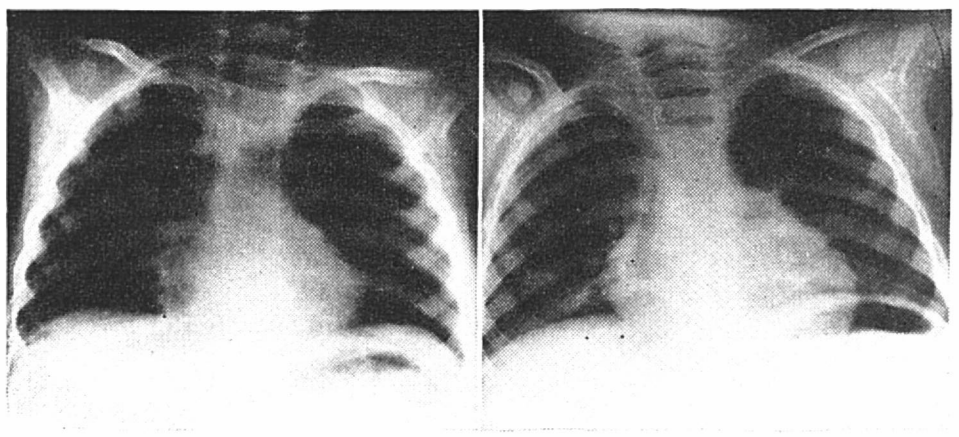

Fig. 11.—Anterior-posterior roentgenogram of thorax in boy 2 years, 7 months of age upon admission (*left*) and with initial recovery well advanced after 14 days of dietary therapy (*right*). Photographs indicate an increase in relative size of heart with treatment.

appear promptly when skim milk alone is given. It is given initially in a dilute form to provide a relatively low level of protein until it is easily tolerated by the patient. The concentration of milk is gradually increased until 4 to 8 Gm. of protein per kilogram of body weight is given by the fifth day, followed by gradual addition of other foods to supply a balanced diet rich in protein. Parenteral therapy is usually unnecessary.

These observations form the basis for considering kwashiorkor to be primarily a manifestation of severe protein deficiency. Further support has been given to this concept by the work of Brock and others,[13b] who have demonstrated that vitamin-free casein alone will bring about an "initiation of cure" including disappearance or improvement of all of the major signs and symptoms. A mixture of 18 amino acids, as in casein, with the addition of glucose, a mineral mixture, and all known vitamins was also effective. Removal of the vitamins did not seriously affect the rate of initiation of cure. Hansen and co-workers [13b] have also reported satisfactory initiation of cure with a mixture containing the 10 essential amino acids plus tyrosine, minerals, vitamins, and glucose. When the vitamins were omitted from this mixture, the rate of initiation of cure was distinctly retarded.

A remarkable thing about kwashiorkor is the dramatic rapidity with which it usually responds to a diet rich in protein. It would be suspected, a priori, that children with atrophied gastrointestinal walls, whose duodenal enzyme activity is reduced to negligible levels, would be unable to use large quantities of protein at the time of admission to the hospital with acute kwashiorkor. Nevertheless, the response to protein administration is so rapid that a few days later enzyme activities have returned to normal [14] and the absorption and retention of protein given in relatively large quantities is high.[15] The response of serum vitamin A levels to vitamin A administered orally, on admission and after four days of treatment, indicates that the ability of the child to absorb fat-soluble vitamins shows a similarly rapid recovery.[2a]

Our own experience in Central America and that of workers in other parts of the world demonstrates conclusively that the preferred treatment of kwashiorkor is not the parenteral administration of protein hydrolysates, vitamins, or other medical preparations but rather the oral administration, by stomach tube if necessary, of adequate quantities of milk or other sources of protein of good quality. There is reason to believe, from our work and that done in Coonoor, South India, and in Kampala, Uganda, that suitable vegetable protein mixtures are also satisfactory for this purpose.[16]

Occasionally, whole blood transfusion may be deemed necessary to save the life of the child, but it is our experience that, as confidence in simple feeding is gained, the decision to resort to blood transfusion is rarely made. Hansen and Brock [4] have emphasized the importance of fluid and electrolyte depletion, particularly of potassium, in diarrheic children with kwashiorkor. They recommend routine oral administration of an electrolyte solution containing potassium (Darrow's solution) with glucose for the first 24 hours, before starting to feed protein.

The prevention of kwashiorkor must be a goal of public health services and international health agencies, but the detailed study of the characteristics of the syndrome and its response to protein therapy has been enormously helpful in emphasizing the need for prophylaxis. This advancement should also serve to lessen the initial cost of hospital treatment of the condition, by eliminating costly parenteral therapy from the procedures routinely employed, and to shorten the hospital stay, by protecting the malnourished child from the cross infections of the general pediatric ward.

Summary

The characteristics of severe protein malnutrition (kwashiorkor) in children include retarded growth and development, edema, anorexia, apathy and sometimes irritability, hair and nail changes, skin lesions, diarrhea, anemia, lowered serum protein and albumin, lowered serum levels and absorption of fat-soluble vitamins, lowered serum levels of pseudocholinesterase, amylase, lipase and alkaline phosphatase, reduced duodenal enzyme activity, fatty liver, reduced heart size, and lowered electrocardiographic voltages. All of these return to normal or improve greatly within the first 7 to 10 days of protein therapy, apparently even when this therapy is given in the form of vitamin-free casein. Suitable vegetable protein mixtures may also be used.

Children exposed to cross infection in open pediatric wards require longer hospitalization for satisfactory recovery. The associated deficiency of other nutrients can be corrected by diet alone except when severe iron deficiency caused by malaria or hookworm is present; in that case, supplementary iron should be given orally. There is no convincing evidence that vitamin B_{12}, lipotropic substances, or enzyme preparations have a place in the treatment of kwashiorkor.

This investigation was supported in part by a research grant from the National Institute of Arthritis and Metabolic Diseases, Public Health Service, and by funds from the Nutrition Foundation, Inc., the Williams-Waterman Fund of the Research Corporation, and the World Health Organization. This paper is INCAP Scientific Publication I-65.

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