PROTEIN-CALORIE MALNUTRITION*

Fernando E. Viteri
and
Benjamin Torún

Large segments of the world's population live under conditions where the availability and intake of food are inadequate for their needs.[1] This is the case in many developing areas where food consumption is deficient both in quantity and quality. Insufficient food intake leads to chronic caloric deficiency, and ingestion of foods with insufficient protein concentration induces protein deficiency in vulnerable groups. This is particularly true when the protein is of poor quality, as is the case with most vegetable proteins. The problem with the latter is that the bulk of the food often imposes a limit to its intake. Also, amino acid deficiencies further limit the utilization of such protein sources, so that small children cannot satisfy their naturally elevated nitrogen and specific amino acid requirements.

These dietary factors, associated with many other health problems to be described later, lead to primary chronic protein-calorie malnutrition (PCM). In conditions conducive to primary PCM, the intakes of other essential nutrients, such as vitamins and minerals, are also generally low; however, serious manifestations of their specific clinical deficiencies are less common than might be expected because, when the calorie and protein intake is the limiting factor, the requirements for other nutrients diminish. Nevertheless, in PCM, vitamin or mineral deficiencies may become overt.

Primary PCM should be differentiated from secondary PCM, which is the consequence of a primary disease that leads either to inadequate food intake or utilization or to increased nutritional requirements. Examples of secondary PCM are psychologic disorders, obstructive gastrointestinal lesions, primary malabsorptive problems, diseases inducing cachexia of metabolic, infectious or neoplastic origin and endocrine disorders.

This chapter deals only with primary PCM, that is, the situation where energy and protein intake are apparently the most limiting factors in malnutrition.

EPIDEMIOLOGIC AND ETIOLOGIC CONSIDERATIONS

All developing areas of the world have several common characteristics, among which are low weight of newborn babies, high disease prevalence, small physical size of inhabitants, elevated mortality rates,

*Scientific articles published on this subject are much more numerous than those cited in the present chapter. However, because of limited space, the reader is often referred to some comprehensive reviews on the subject. Publications cited at the beginning or at the end of paragraphs or sections are general references for the topic dealt with. Through these, as well as through the more recent specific articles cited, many other important references may be easily located by those interested in a deeper approach to the subject.

Table 24–1. Mortality Rates of Children 0-4 Years of Age*

Age	*Guatemala (1965)*	*%*	*U.S.A. (1967)*	*%*	*Ratio Guatemala/U.S.A.*
A. Infant mortality (deaths/1000 live births)					
0–28 days	35.9	39.1	16.6	73.8	2.2
1–11 months	55.9	60.9	5.9	26.2	9.5
1 year	91.8	100.0	22.5	100.0	4.1
B. Mortality in children between 1 and 4 years of age (deaths/1000 children of the corresponding age)					
1 year	50.0		1.4		35.7
2 years	35.2		0.9		39.1
3 years	24.9		0.7		35.6
4 years	15.6		0.6		26.0
1–4 years	30.3		0.9		33.7

* Compounded from data published by the Pan American Health Organization: *Las Condiciones de Salud en l Américas 1965–1968*. Washington, Organización Panamericana de la Salud, Septiembre 1970 (Publicació Científica No. 207), and INCAP.[3]

particularly during infancy and early childhood (Table 24–1) and, as a consequence, short life expectancy. The main reasons for these characteristics are undernutrition and poor environmental health. These situations lead to decreased productivity and increased waste of human and economic capital, including food. This perpetuates and often aggravates underdevelopment, thus worsening nutrition and health and, therefore, establishing a vicious cycle. This general picture, associated with a large concentration of still unproductive young people, provides the background for underdevelopment.

The magnitude of the problem varies from area to area. As an example, we cite the figures obtained from a survey of the Central American region where, by projecting to the total population of the area the prevalence obtained from a statistically representative sample of all of the 2.5 million children below 5 years of age, 1.6 million could be categorized, on the basis of body weight, as suffering from or as having had undernutrition.[4] Nearly one-third of them had been or were moderately or severely malnourished (second- and third-degree undernutrition) at the time of the survey.[3] These findings are presented in Table 24–2.

Mild and moderate forms of adul undernutrition are more difficult to re ognize but are also prevalent in developin areas. The manifestations of chronic PC in this age group are more evident in term of performance than in symptoms or clin cal signs.

In adult males engaged in agricultur practices requiring intensive physical e fort, caloric intake is often insufficient an leads to chronically limited energy expen diture in order to maintain a delicate en ergy balance. This results in suboptim work performance, inadequate intera tions with other family members or po participation in community programs aft working hours. In adult women, chron undernutrition results in inadequate re productive performance, which include little weight gain during pregnancy, deliv ery of small-for-date babies and in adequate milk production in terms of bot quantity and quality.[5,6]

A high proportion of newborns with lo weight at birth is associated with a highe incidence of infant mortality.[7] Inadequat quantity and quality of woman's milk in groups of low socioeconomic condition ar important factors in infant malnutrition.

Protein-calorie malnutrition should ther be considered a social disease affectin

Table 24–2. Children Below 5 Years of Age in Central America, 1965–67, Presenting Growth Retardation which, by the Gómez* Classification, Could be Cataloged as Malnourished†

Country	Total Population below 5 Years of Age	1st, 2nd, and 3rd Degree Malnourished		Malnourished					
				1st Degree		2nd Degree		3rd Degree	
		No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Costa Rica	294,300	153,200	52.0	117,900	40.0	31,300	10.6	4,000	1.4
El Salvador	554,400	380,000	68.5	244,600	44.1	116,900	21.1	18,500	3.3
Guatemala	833,400	611,660	73.4	380,100	45.6	197,700	23.7	33,860	4.1
Honduras	346,900	221,300	63.7	143,000	41.2	71,200	20.5	7,100	2.0
Nicaragua	287,500	148,800	51.8	112,300	39.1	32,400	11.3	4,100	1.4
Panama	207,900	104,947	50.4	84,625	40.7	18,990	9.1	1,332	0.6
Total	2,524,400	1,619,907	64.2	1,082,525	42.9	468,490	18.6	68,892	2.7

* Gómez, et al.[2]

† Numbers are extrapolations from a statistically representative sample.

families, communities and geographic areas because of the negative effects that mild-to-moderate PCM of adults has on the well-being of the children and the development of the community.

In these settings, the few subjects who develop severe PCM with clinical manifestations must be interpreted as index cases which point at a widespread underlying nutritional problem. Thus, the fact that over 8 per cent of all adults admitted to public hospitals in countries such as Guatemala have moderate-to-severe primary PCM strengthens the concept that the poor functional performance of underprivileged populations is closely related to underlying mild-to-moderate PCM.

From the epidemiologic point of view, PCM can be conceived as the consequence of the interaction of the environment on the host through an agent which, in this case, is the deficient availability of calories and protein at the cell level. The environment, host and agent factors are interwoven.

Environment

This can be considered at two levels: (1) macroenvironment, at a regional or national level and (2) microenvironment, at the family and individual level.

In the developing areas, the macroenvironment is that of poverty, not only in the strict economic sense but also in the more important concept of human resources. Both are the cause and the consequence of lack of education, unsatisfactory health of the population, poor communications, low productivity, unfavorable economic balance and inadequate utilization of natural resources; all of these factors lead to inadequate food production, conservation, distribution and consumption.

The microenvironment constituted by the family, which is the biologic unit in terms of nutrition, receives the impact of the macroenvironment and further limits the availability of nutrients to the host. The factors operating at this level are meager purchasing power, faulty concepts of food utilization that lead to poor food consumption practices and inadequate distribution of available nutrients among the members of the family. The latter is particularly evident in the case of small children and when disease strikes a member of the family whose food intake is very often thereby drastically restricted.

Host and Agent

Maternal malnutrition and infectious episodes during pregnancy are frequently the cause of prematurity and small born-at-term infants, as well as of poor nursing performance. Children already at a nutritional disadvantage are the victims of poor feeding practices, especially in those regions where breast-feeding is being replaced early in life by artificial formulas in the face of prevailing inadequate education, hygiene and economic resources. All of these factors must be adequate to allow successful artificial feeding.

Inadequate feeding takes place at a time when nutritional requirements are high per unit of body weight. The consequence is an increasing number of infants who suffer from early protein-calorie malnutrition, particularly in urban areas. The most common type of severe malnutrition at this age is that of nonedematous PCM, due to a predominant caloric deficiency.[9]

Even when properly breast-fed, complementary feeding practices for the child are poor, and induce some degree of PCM after the first 3 or 4 months of life. When weaning occurs, most children are fed diets that provide insufficient amounts of calories and proteins. Others receive only starchy gruels or high-carbohydrate low-protein diluted cereal drinks, which accentuate protein deficiency. Table 24–3 presents the median nutrient intake of rural Central American children, expressed as per cent of the recommended allowances for each age group.

It is important to realize that, in the developing areas, children are smaller in size than those of the same age in the developed areas; consequently, their actual requirements are somewhat reduced. Nonetheless, a decreased food intake for age, even when it could be fairly satisfactory for size, perpetuates undernutrition. If, at this time, the child is forced-fed diets high in calories but low in protein, he becomes acutely protein-deficient in spite of being fat. This severe protein deficiency gives rise to edematous PCM of the "sugar-baby" type.[10] More often, infants become the victims of mild-to-moderate repeated infections[11] and, by the time they are weaned, develop a common diarrhea syndrome known as "weanling diarrhea."[12]

After weaning, children eat little or no milk and other animal products and they are fed the usual family foods, frequently in insufficient amounts, because of poor availability of food and incorrect cultural practices in child feeding. Also, after weaning, children living in these environments frequently suffer from acute infections. As a consequence, their nutritional condition rapidly deteriorates. Those children who prior to weaning were growing at a slower rate and very often were somewhat underweight for their height become frankly

Table 24–3. Median Nutrient Intake as Per Cent of Recommended Allowances of Nutrients Consumed by Preschool Children in the Rural Area of Guatemala*†

	Age Groups (years)			
Nutrients	*1 (38)‡*	*2 (43)*	*3 (34)*	*4–5 (14)*
Calories	63	66	80	48
Proteins	79	74	108	67
Calcium	72	69	101	72
Iron	56	71	103	66
Vitamin A¶	24	30	25	20
Thiamin	100	92	128	68
Riboflavin	50	46	50	31
Niacin	42	50	68	39
Vitamin C	40	60	56	20

* Over 90 per cent of preschool children consumed less calories and over 60 per cent consumed less protein than the recommended allowances. The calories and protein consumption was lower than recommended in 80 per cent and 40 per cent of the families, respectively.

† Modified from Flores, Menchú, Lara, and Guzmán: Arch. Latinoam. Nutr., *20*, 41, 1970.

‡ Figures in parentheses represent the number of children.

¶ Vitamin A intake has improved, especially in the older preschoolers, since sugar fortification with this vitamin was begun in 1976.

undernourished. Those who follow this path develop the edematous type of PCM, but at the same time are somewhat emaciated. They suffer from a predominant protein deficiency, superimposed on various degrees of caloric deficit.

The majority of children, however, do not develop a severe degree of PCM and, through a series of adaptive mechanisms, remain in a state of mild-to-moderate protein-calorie malnutrition. This condition is characterized only by growth retardation and by periods wherein they have a mild weight-for-height deficit, with or without traces of edema. Children who survive the critical weaning and preschool periods continue to grow at a slower rate and their caloric and protein requirements per unit of body mass rapidly decrease. Their daily diets continue to be low in both calories and protein, but they usually can procure more food and often have already had most of the common childhood infectious diseases. Thus, these children can progress into adulthood without further serious risks of becoming severely undernourished. However, if a severe infection or diarrhea supervenes, they can still develop severe PCM, regardless of age. Among the common childhood infections, measles and whooping cough are well known to precipitate severe protein-calorie malnutrition. In children and adults, repeated acute diarrheal episodes, chronic malaria, schistosomiasis and massive infestations by hookworm, Trichiuris trichiura or Strongyloides, plus other stresses such as acute food shortage and severe physical or psychologic stresses, can induce severe PCM.

PHYSIOPATHOLOGY AND ADAPTIVE RESPONSES IN CALORIE AND IN PROTEIN DEFICIENCY

Through a series of physiologic mechanisms, the body tends to maintain a dynamic equilibrium. A typical example is the tendency toward caloric equilibrium: After the ingestion of a meal energy is stored, mostly in the form of high-energy phosphates, fat and glycogen, which are drawn upon to obtain energy during the daily regular and relatively short periods of fasting and during periods of increased energy expenditure.

With longer periods of caloric and/or protein restriction, the body progressively adapts itself in order to maintain as adequate a functional status as the limited supply of nutrients allows. Consequently, in the process leading to PCM, the body is dynamically adapting to it and continues to do so throughout, until the individual is "maximally adapted." This adaptation results in a decreased nutrient demand and in the attainment of nutritional equilibrium compatible with a lower level of cellular nutrient availability. If, at this point, the supply of nutrients becomes persistently lower than that to which the body can adapt, death supervenes. However, although in most instances the nutrient supply is low, it is not so inadequate as to cause death and the individual is thus able to live in a state adapted to the diminished intake. In this process, most functions are altered and have the following characteristics: (1) They are more susceptible to being overwhelmed by an overloading mechanism, which brings about decompensation or failure of adaptation and consequently poses a threat to the life of the host. In other words, the adapted PCM individual is a labile, functionally fragile subject. (2) Because of their dynamic nature, the degree of functional alteration generally correlates with the degree of protein depletion. This correlation is also influenced by the rate at which depletion occurs, or at which repletion takes place during nutritional rehabilitation.[13]

The adaptive metabolic processes in both caloric and protein malnutrition occur by hormonal interaction, by servomechanisms at the cellular level and by as yet poorly understood generalized body reactions. Briefly, caloric deficit induces the hormonal adaptations described in

Table 24–4. Schematic Hormonal-Adaptive Mechanisms in Malnutrition

Hormone	*Stimulus*	*Result*	*Hormonal Activities in*	
			Caloric Deprivation	*Protein-caloric Deprivation*
Insulin	↑ Glucose ↑ amino acids	↓ Protein synthesis (muscle) ↑ Growth ↑ Lipogenesis	Decreased	Decreased
Growth hormone	↓ Glucose ↑ amino acids	↑ Protein synthesis (body) ↑ Growth ↑ Lipolysis ↓ Urea synthesis	Variable, generally normal	Increased
Glucocorticoids	↓ Glucose ↓ amino acids	↑ Protein catabolism (muscle) ↑ Protein turnover (viscera) ↑ Neoglucogenesis ↑ Lipolysis	Increased	Variable, generally normal
Thyroid hormones	↑ Energy metabolism	Energy homeostasis ↑ Protein turnover	Decreased	Decreased

Table 24–4, which lead to increased fat mobilization from adipose tissue.

During the initial phases of deficiency, the individual shows decreased physical activity and a lower basal energy expenditure per unit of lean body mass. The body composition is progressively altered by decreasing adiposity at a fast rate and lean body mass at a slower rate. Muscle catabolism produces an increased efflux of amino acids, primarily as alanine. As the caloric deficit becomes severe, basal energy expenditure may be normal or even increased per unit of lean body mass, which then decreases at a faster rate.[13–15]

Protein deficit usually occurs together with caloric inadequacy and the hormonal changes are generally similar to those observed in caloric deprivation; often, fasting circulating growth hormone levels are higher in protein deprivation than in caloric deficit[16,17] and glucocorticoids are not increased in the former, although free cortisol is higher than normal, resulting in functional hypercorticism[18] (Table 24–4). Somatomedin levels are low in PCM, especially in cases with severe protein deficiency.[19] In protein deficit there are also cellular adaptation mechanisms not directly hormonally mediated but induced by the poor availability of amino acids, causing decreased protein synthesis at the ribosomal level. The result of both mechanisms of adaptation are an internal shift in protein metabolism to an increase in muscle protein catabolism and, therefore, a relative increase in amino acid availability at the visceral level. The composition of the free amino acid pool is altered. There is a decrease in both the synthesis and the catabolism of total body proteins, the latter predominating over the former.

The most significant change in protein metabolism is a marked recycling of amino acids. The end-result is a longer half-life of some proteins, such as albumin, and a generally decreased protein and amino acid turnover. In addition, the internal body distribution of protein changes. This is the case with albumin, which diminishes more in the extravascular than in the intravascular space. Urea synthesis de-

creases and simple nitrogen-containing compounds, such as urea, apparently are more efficiently utilized as sources of nitrogen. In terms of body composition, a progressive reduction in lean body mass occurs, resulting primarily from muscle, and probably also from skin, protein loss. Visceral protein is initially reduced ("labile protein") but then becomes stable or may even regain some of its total mass. As the body protein turnover and total body protein mass decrease, basal oxygen consumption also decreases.[13,20,21]

These adaptations, which lead to the sparing of body protein, are easily upset by forced calorie intake, primarily in the form of carbohydrates such as starch gruels. Hormonal adaptation mechanisms are "fooled" and, as a consequence, internal amino acid and protein shifts are impaired, thus inducing visceral amino acid depletion and a breakdown of adaptation. Infections leading to disease and other stresses also upset adaptation by causing anorexia and markedly reduced food intake in the face of increased energy and protein needs. Fever increases energy waste and is accompanied by large nitrogen losses and shifts toward amino acid utilization for energy purposes. Amino acid utilization is also diverted for increased synthesis of special proteins, such as gamma globulins (antibodies).[22,23] This probably also reflects a breakdown of the amino acid-sparing adaptive mechanisms described.

An important finding in most investigations of the hormonal status in PCM is that hypophyseal functional capacity is unimpaired. Another important concept must be kept in mind in explaining metabolic adaptations: Hormonal effects may not be wholly explained by circulating levels of hormones and metabolites. Cellular responses to hormonal stimulation, as well as hormonal metabolism, may be markedly altered in PCM.

When the adaptive mechanisms are maintained, the impact of PCM is diminished and the length of time that an individual takes to go from mild to severe protein-calorie malnutrition is prolonged. Of course, the individual has to sacrifice certain functions and some nutrient reserves and, for this reason, becomes more susceptible to injuries which a well-nourished individual can withstand with little repercussion. Total body K content is reduced.[24–26] Total circulating hemoglobin is reduced pari passu with decreased body oxygen demands. Red cell production is diminished and hemodilution takes place.[13,14,27] Cardiac work decreases, as does functional reserve,[28] and central circulation takes precedence over peripheral circulation. Cardiovascular reflexes are altered, leading to postural hypotension and diminished venous return. Hemodynamic compensation in severe PCM occurs primarily from tachycardia rather than from increased stroke volume. The renal plasma flow, glomerular filtration rate and tubular function decrease. As a consequence, in severe cases, the renal concentrating ability and acidification mechanisms are impaired.[29] Before this occurs, chronic sodium retention and increased serum and urine antidiuretic activities lead to relatively increased total and extracellular body water.[30] Intracellular water is reduced in absolute terms because of losses in lean body mass, but intracellular overhydration may be present.[24,26,31] Physical strength is diminished, further inducing a reduction in the physical working capacity.[32,33]

Other alterations not directly correlated with the degree of protein deficit, but always present in advanced protein deficiency, include impaired intestinal absorption, moderately decreased capacity to transport protein-bound substances in blood, reduced gonadal function and lowered resistance to infection. The immune systems affected in severe PCM include those mediated by cells: antibodies, phagocytes, complement and other nonspecific factors including lysozyme.[34] Moderate

PCM and fetal malnutrition, as well as other specific nutrient deficiencies, appear to have profound effects on cell-mediated immunity.

Impaired intestinal absorption of lipids and disaccharides and a decreased rate of glucose absorption occur in severe protein deficiency; the greater the protein deficit, the greater the functional impairment. A decrease in gastric, pancreatic and bile production is also observed, with normal to low enzyme and conjugated bile acid concentrations. These alterations further impair the absorptive functions. Protein-deficient individuals are diarrhea-prone because of these alterations and possibly also because of irregular intestinal motility and gastrointestinal bacterial overgrowth. Diarrhea per se aggravates the malabsorption.[35–40]

Finally, a generalized decrease in nervous system function is clearly apparent in severe PCM.[41,42] The etiology of these alterations has not been elucidated. Several explanations have been proposed, among others decreased brain potassium content and catecholamine production, reduced number of cells in the central nervous system when malnutrition occurs before 6 to 8 months of age and small cell size when it occurs at a later age.[43–45]

Decompensation from severe calorie deficiency occurs from inability to maintain internal energy supply and results in hypoglycemia, hypothermia, impaired circulatory and renal functions, acidosis, coma and death. In the case of decompensation from protein deficiency, visceral functional failure also results from unavailability of amino acids. At the same time, an accelerated tissue breakdown takes place. The resulting alterations are failure of the liver to synthesize certain proteins such as albumin, several clotting factors and transport proteins, leading to fatty liver, increased free circulating cortisol, hemorrhagic diathesis, and jaundice in extreme cases; various degrees of renal failure with acidosis, as well as water and sodium retention, frankly decreased cardiac work and tissue anoxia with pulmonary congestion occur. All of these factors lead to the development of clinical edema and, in extreme cases, skin lesions with hemorrhagic phenomena. In addition, fluid leakage into the gastrointestinal tract,

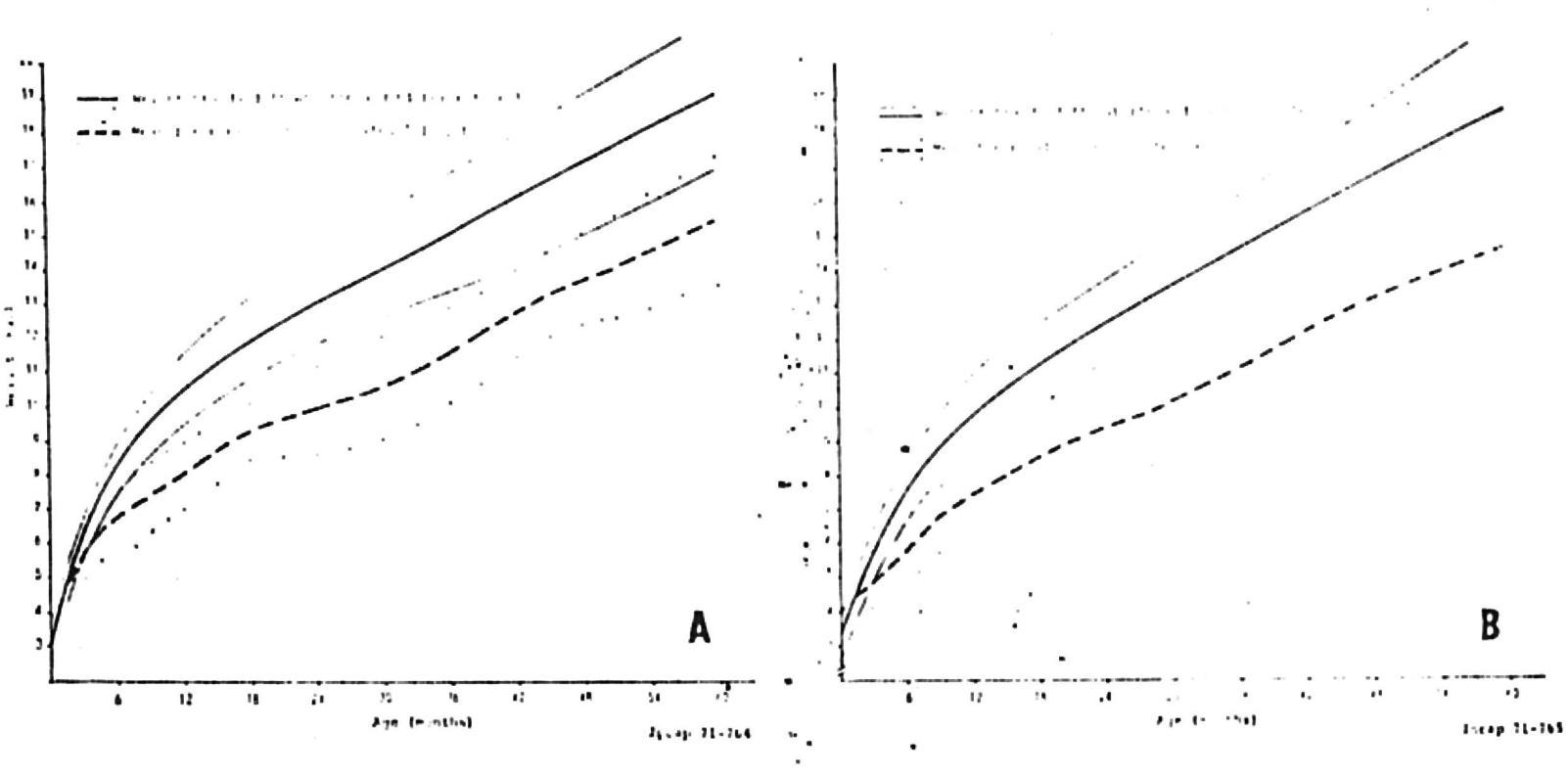

Fig. 24–1. Weight of rural Guatemalan male and female children below 5 years of age, in relation to that of U.S.A. children. Number of Guatemalan children in the sample: 431 males and 436 females. (From INCAP.[3])

increased susceptibility to pulmonary infections, water and electrolyte disturbances with hypokalemia and hypomagnesemia, frank central nervous system depression and death can result.[46–48]

DIAGNOSTIC CHARACTERISTICS OF PROTEIN-CALORIE MALNUTRITION

The clinical and biochemical picture of PCM varies according to its severity and to the characteristics of the host, the environment and the agent.

Chronic Mild-to-moderate PCM[49]

Clinical. It is obvious that the severe syndromes of edematous and nonedematous PCM, recognized as kwashiorkor and marasmus, respectively, represent the critical end of a spectrum of varying degrees of deficiency.

However, before these severe stages are reached, children survive with insufficient calories, protein or both, a situation which does not allow them to grow and develop at the rate to be expected from their genetic potential. A long-standing restriction would be clearly manifested by a retardation in height and weight gain (Figs. 24–1 and 24–2). This reduced size may be a life-saving device to allow the children to survive on the restricted food available to them.

Fig. 24–2. Appearance of two 10-year-old children in the rural Central American region. The one at the left has always been well nourished. The one at the right has been mild-to-moderately malnourished.

Under these chronic conditions, it is generally observed that body mass, although markedly retarded for the chronologic age of the child, is adequate for its height. However, these children may be chronically affected by temporary periods of weight-for-height deficits. As judged by body composition studies, bone maturation and biochemical measurements, the malnourished child is not a small version of his well-nourished counterpart of equivalent chronologic age. He shows an immaturity in biologic development compatible with his retarded physical size. This includes deficits in lean body mass and adiposity, with relative overhydration affecting primarily the extracellular space. Without knowing the actual age of the subject, it is often difficult or even impossible to determine the presence or extent of malnutrition.

Other characteristics of such cases, which are more difficult to attribute exclusively to nutrition, are reduced physical activity, mental apathy, frequent episodes of ill-defined sickness, anorexia and diarrhea and a higher fatality rate from common infectious diseases.

It has been shown that an association exists between retarded physical growth and development and some tests of psychomotor and mental development.[30–32] The isolated effect of malnutrition as a cause of this phenomenon is strongly suggested by data derived from animal experimental work. Direct proof does not exist in humans, although studies are now under way from which an answer to this question is expected. Nevertheless, it is beyond doubt that the responsible factor is the complex of social deprivation, of which nutrition is one of the most important components.[33]

Chronic PCM in adults generally results in marked leanness (Fig. 24–3), which, in severe cases, can reach a state resembling cachexia. Because their protein requirements per unit of body mass are much smaller than those of children, the main

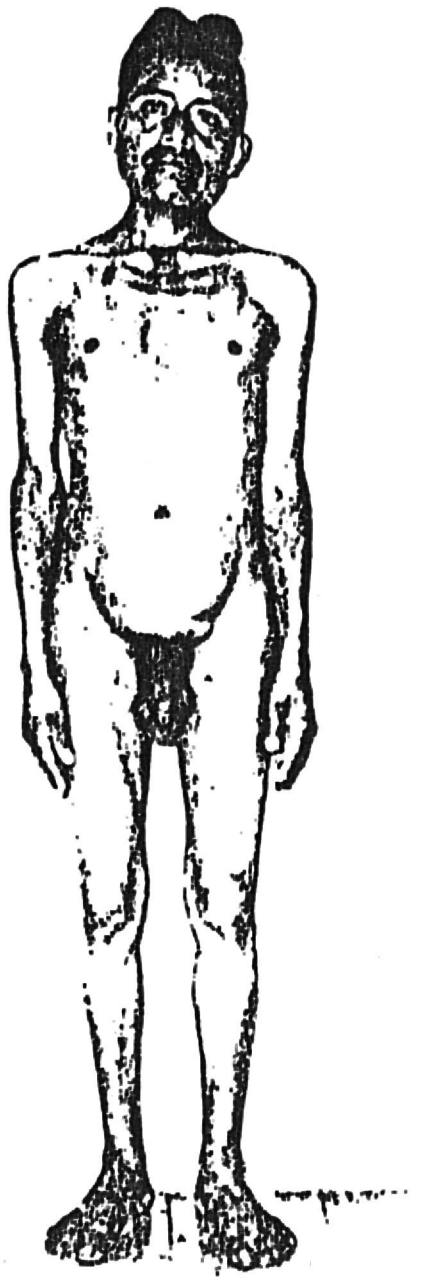

Fig. 24–3. Mild-to-moderate malnourished 36-year-old man.

manifestations are of primary calorie deficiency. Thus, physical activity and capacity for prolonged physical work are reduced, perhaps as a mechanism to maintain caloric equilibrium on low food intake. Changes in body composition similar to those described for children can also be observed.[32,33]

Biochemical. Because of the characteristically low protein intake, subjects have a low excretion of urea N per unit of creatinine[34] and a somewhat abnormal plasma free amino acid pattern with a decrease of the branched essential amino acids.[35,36] It has been reported also that

they excrete a lower amount of hydroxyproline in the urine, in good agreement with the slow growth rate.[57] Slight decreases in transferrin and albumin serum levels have been reported.[58,59] If lean body mass is reduced for height, this is manifested by a decreased creatinine/height index.[60]

Severe Protein-calorie Malnutrition

Clinical. ***Nonedematous PCM.*** Severe calorie deficiency is clinically recognized in children by the syndrome identified as marasmus in most parts of the world, or nonedematous severe PCM (Fig. 24–4). The child is frankly small for his age, looks emaciated and, in extreme conditions, reduced to "skin and bones" because of an essentially total absence of adipose tissue. His skin is usually dry and "baggy," wrinkles easily and has lost its turgor. The hair is sparse, thin and dry, and can be pulled out easily; it loses its normal sheen and acquires a dull brown or reddish yellow color, giving it a lifeless appearance. The face resembles that of a monkey, with sunken cheeks in extreme cases, because of the disappearance of the Bichat fat-pad. The child is weak and looks hypotonic, and his pulse, blood pressure and temperature may be low. He is sensitive to cold temperature, cries easily and is often found retracted from his environment, sucking one or more fingers. His viscera are small and lymph nodes are easily felt. Soon after therapy is initiated the child becomes alert and interested in his environment. In adults, extreme emaciation is characteristic of calorie deficit (Fig. 24–5).

Common complicating features are eye lesions, due to hypovitaminosis A, and skin infections. The classical cases suffer from constipation and are ravenously hungry, but diarrhea, anorexia and vomiting, with

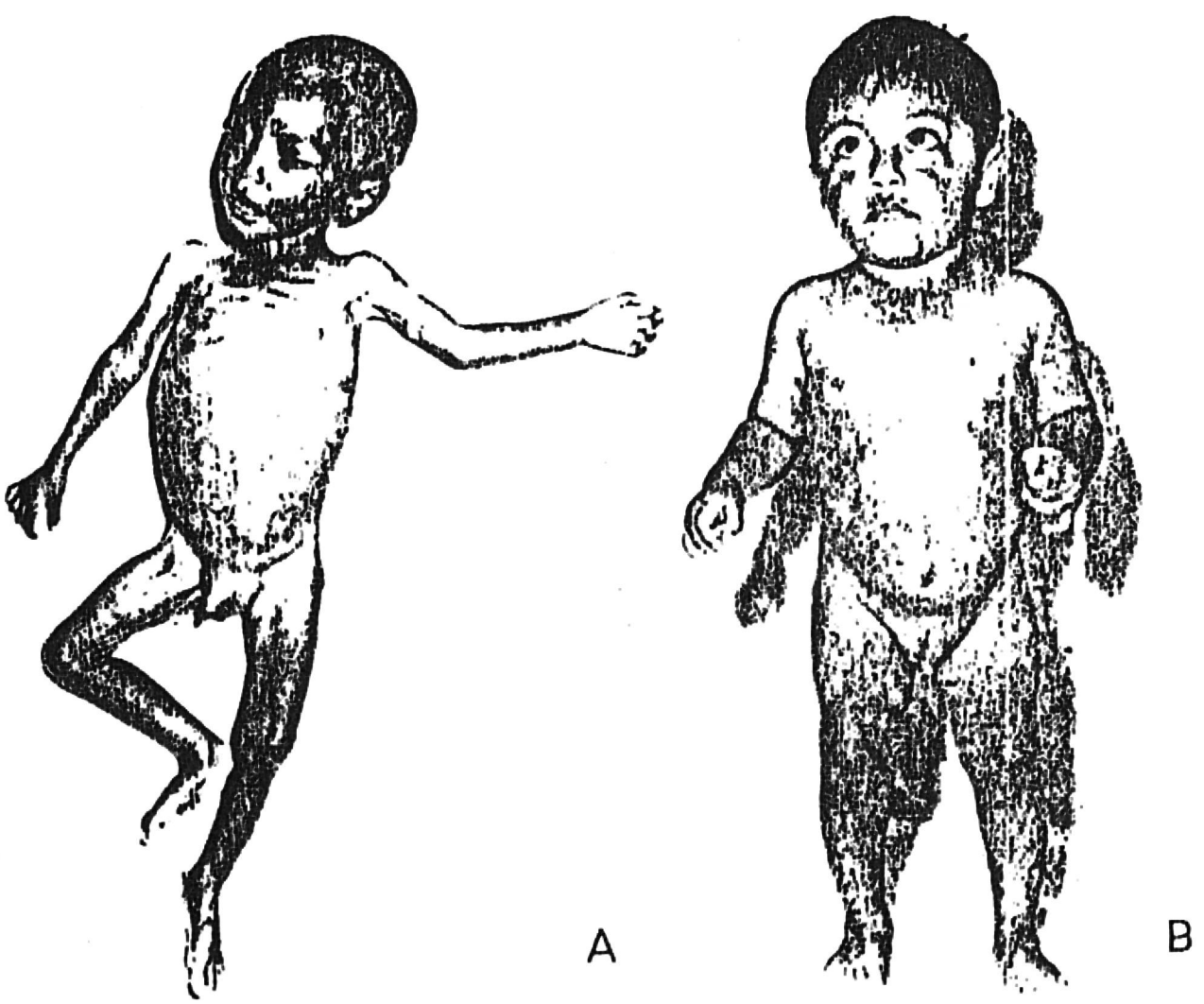

Fig. 24–4. Twenty-one-month-old child with severe nonedematous PCM (marasmus) on admission to the hospital and 4 months later, when fully recovered.

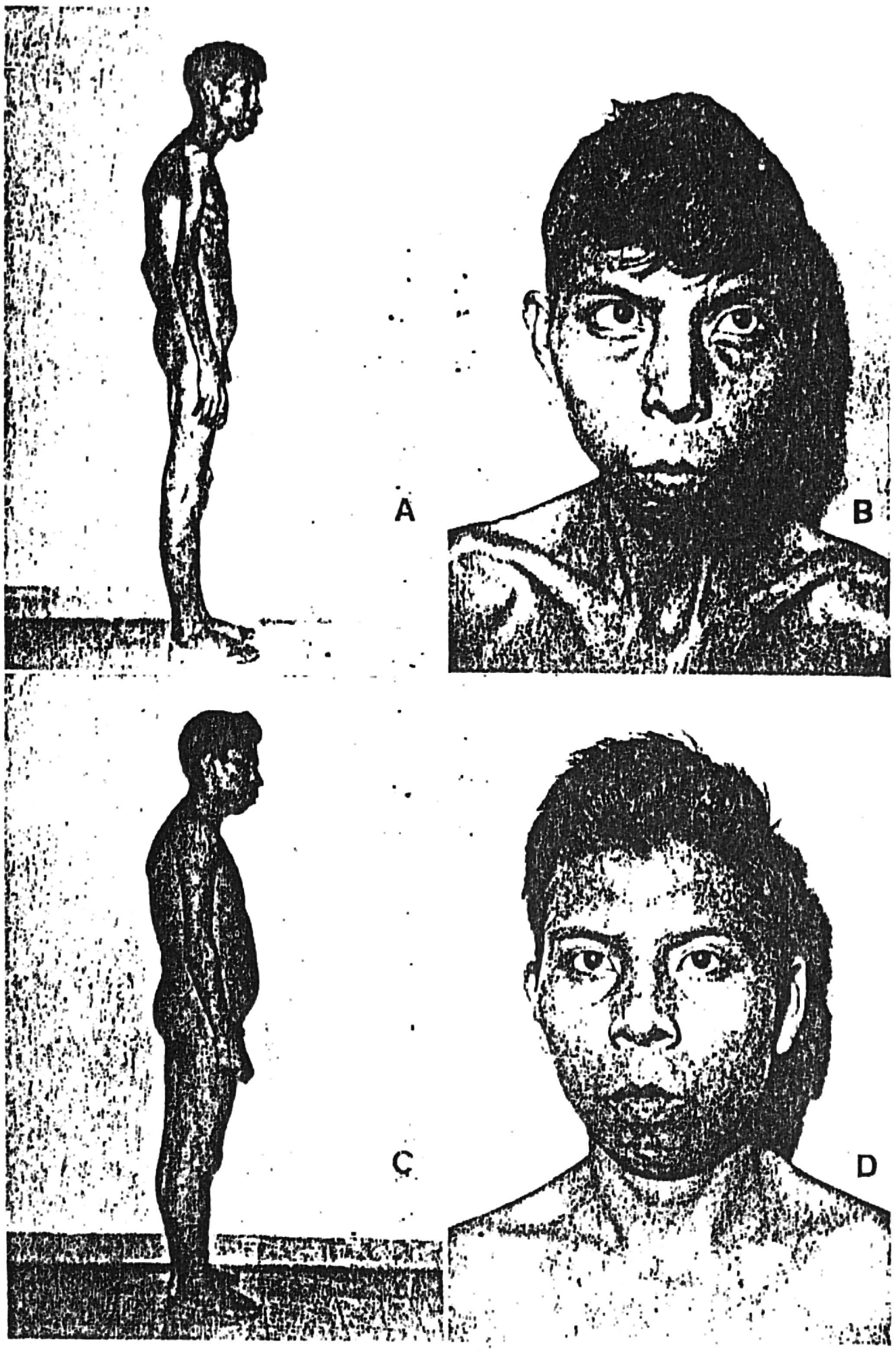

Fig. 24–5. Twenty-nine-year-old man with severe nonedematous PCM on admission to the hospital and 3 months later, when fully recovered.

dehydration, are not rare; dehydration, acidosis and electrolyte imbalances may, in fact, cause death. Postmortem examination shows only generalized atrophy, without fatty liver. Clinically and post mortem, the child has no edema, although his total body water is increased for his size.[15,24]

Edematous PCM. The child with acute severe protein deficiency of the sugar-baby type (Fig. 24–6) is usually almost normal in height for age; his body fat is normal or increased, but flabby, and he is clinically edematous. The edema may be located only in the lower segments of the body, through the action of gravity, but generally his face is swollen, his cheeks look heavy and his eyelids are swollen shut. He is pale and the skin shines in the edematous areas. In other parts of his body the skin may be dry and atrophic or have large asymmetric confluent areas of hyperpigmentation and hyperkeratosis. A peeling type of desquamation occurs in these areas, leaving underneath a fine, atrophic pinkish skin. Hair is atrophic, dry, depigmented and has a reddish tint, falls off easily and breaks upon rolling between the fingers. Often, zones of alopecia are noted. The nails are brittle and have horizontal grooves. The general appearance is that of a hypotonic, miserable-looking child. He is apathetic and irritable at the same time. In the severest cases his apathy is profound. Anorexia is almost universal. Hepatomegaly is frequent, as are a swollen stomach and intestinal loops. Diarrhea is almost always present. Frequent complications are eye lesions due to vitamin A deficiency, cheilitis and cheilosis, as well as other manifestations of deficiencies of the vitamin B complex. Upper respiratory infections and dehydration, even in the presence of edema, are common and often lead to death. Intestinal motility is irregular, and these children often become dehydrated before they pass a huge liquid stool. As the child begins to recover he loses his edema and remains fat and flabby. This appearance often misleads the clinician who may consider him recovered because his weight may be normal. In fact, he is still severely protein deficient in terms of lean body mass.

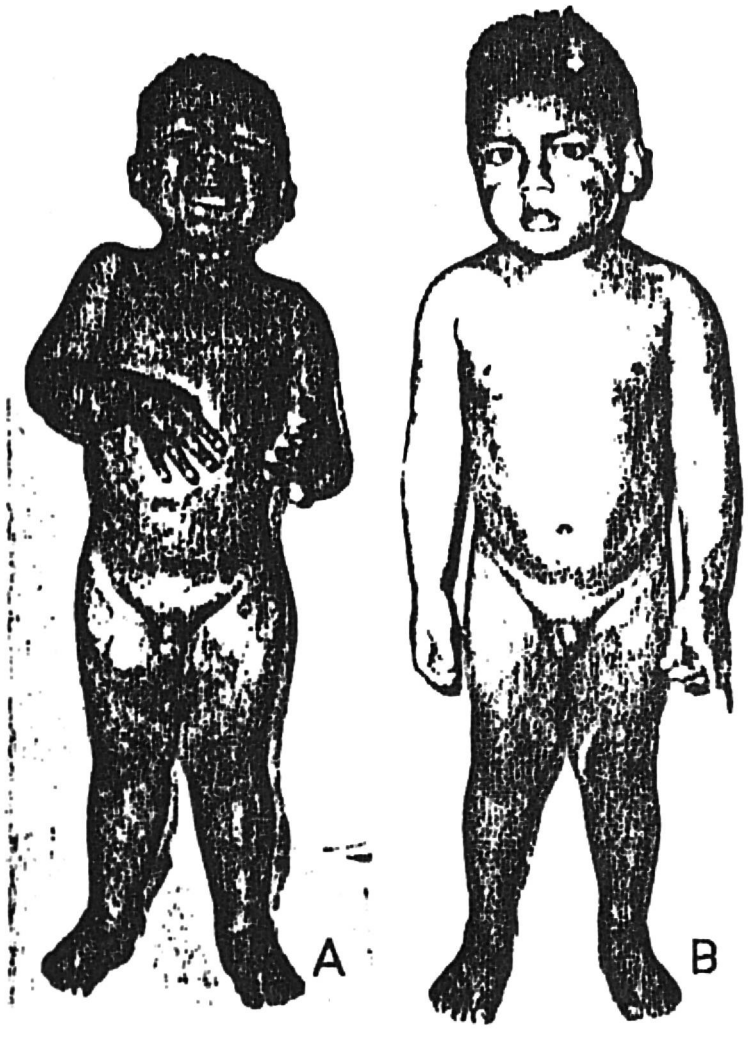

Fig. 24–6. Thirty-six-month-old child with severe edematous PCM and preservations of adiposity (kwashiorkor) on admission to the hospital and 4 months later, when fully recovered.

Pulmonary edema with bronchopneumonia, septicemia, gastroenteritis and water and electrolyte imbalances are the most common causes of death. At autopsy, generalized edema, visceral and muscle atrophy and severe fatty liver are found. Red bone marrow is centripetally retracted.

Most cases of severe malnutrition, both in children and adults, fall between these two extremes of pure caloric and pure protein deficiency. In these cases, a moderate-to-severe protein deficit may be superimposed on a severe degree of caloric deficiency, and vice versa (Fig. 24–7). These subjects, suffering from severe PCM with edema, together with pure

Fig. 24–7. Twenty-five-month-old child with severe edematous PCM superimposed on chronic caloric deficit. In addition to being edematous, he appears wasted (marasmus-kwashiorkor). Pictures were taken on admission to the hospital and 4 months later, when fully recovered.

protein deficiency, have been identified with kwashiorkor. Clinical edema constitutes the main characteristic for diagnosis.[1] The mixed PCM cases have also been identified with a variety of terms, among which are pluricarential syndrome in Central America, undernutrition in other Latin American regions, and protein malnutrition in certain African and Asian countries.[1,48,49] In adults, a predominant protein deficiency can also lead to edematous PCM (Fig. 24–8).

Biochemical. In severe protein-caloric malnutrition several biochemical alterations can be observed. Many of these distinguish between the *edematous* and the *nonedematous* types.

Proteins and Nitrogenous Compounds. The child who has reached the severe stage of edematous PCM has been submitted to a severe negative protein balance.[61,62] Consequently, his total body nitrogen is markedly reduced. Different organs share this protein loss to different extents.[63–65] The liver rapidly loses a fraction of proteins, while the loss of muscle protein is progressive and, because of the large muscle mass, accounts for the major protein loss. Kidney, brain and endocrine organs seem to retain their protein more efficiently. However, the importance of these different losses in terms of organ function cannot be derived from their relative magnitudes. A low ratio of protein to DNA is found in muscle, liver and brain, indicative of intracellular protein loss.[44,66] In nonedematous PCM these changes are moderate, becoming severe only in the most advanced stages.

The concentration of several protein fractions in the body fluids is low. (Although present in both types of PCM, edematous and nonedematous, the changes to be described are more pronounced in the first type. In the second, they may be totally absent.) The concentration of total proteins is reduced, mainly due to a decreased albumin concentration. The concentration of beta-globulins is also decreased. The gamma-globulin fraction concentration is either normal or increased; therefore, the per cent contribution to the total plasma proteins is always high.[48] Some plasma proteins with very specific functions may also be decreased. Among them, those associated with the transport of other nutrients and hormones are particularly important: transferrin,[58,67] ceruloplasmin,[67] retinol-binding protein (RBP),[68] alpha- and beta-lipoproteins,[69] thyroxin,[70,71] and cortisol-[72,73] and aldosterone-binding proteins.[71] Impaired blood transport may attain significance in the development of secondary metabolic abnormalities, as has been shown in the case of lipids and vitamin A.[75] The blood concentration of urea nitrogen is low, as is its excretion in the urine. This reflects the

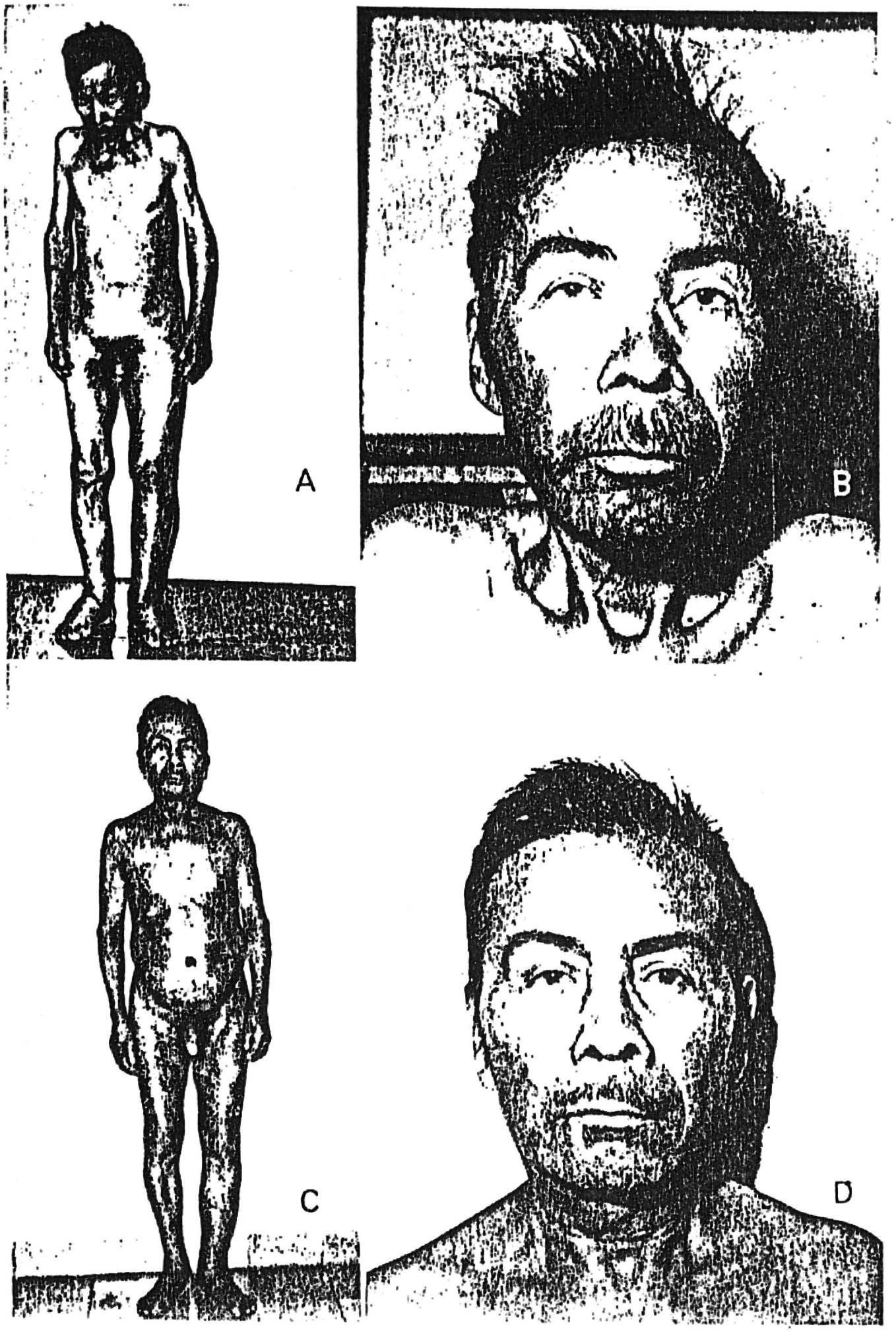

Fig. 24–8. Forty-six-year-old man with severe edematous PCM on admission to the hospital and 3 months later, when fully recovered.

low catabolic rate of body proteins and decreased urea synthesis, which are characteristic of primary protein deficiency.[20,76,77] When calories are the most limiting factor, urea production is increased because body protein catabolism is elevated.[78]

The excretion of urinary creatinine is decreased,[79,80] a consequence of the decrease in muscle tissue and lean body mass.[81,82]

The plasma free-amino acid pattern is abnormal in edematous PCM. A lowered concentration of valine, leucine, and isoleucine is characteristic, as is also a very low tyrosine concentration.[83,84] The ratio of the branched essential to nonessential amino acids is low. Another finding, which is very characteristic, is a low tyrosine/phenylalanine ratio, as a result of a deficiency in phenylalanine hydroxylase.[85] In nonedematous PCM, plasma amino acid alterations may be absent.[55]

Hemoglobin concentration is variable, but often it is around 8 to 10 gm per 100 ml because of hemodilution. Generally, the cells are normochromic and normocytic. Hypochromia can be present if a severe iron deficiency exists from other causes. Mild to overt megaloblastosis can occur because of folate deficiency.[86] The great majority of subjects are not anemic but physiologically adapted to the decreased oxygen demands.[14,27] Leukocytosis can occur if infection is present. Leukopenia and thrombocytopenia generally indicate the presence of gram-negative septicemia.

Although it has been observed that urinary amino acid excretion is abnormal, no consistent pattern seems to be evident. The abnormal metabolites ethanolamine and beta-aminoisobutyric acid have been detected, suggesting a defect in transmethylation.[87] Excretion of urocanic acid has been shown to be abnormal after a histidine load.[88]

Carbohydrates. Usually blood glucose is normal. However, there is an increased tendency to hypoglycemia upon fasting. This is compatible with the finding that liver and muscle glycogen stores are normal or low.[89] Some alterations revealed by clinical laboratory studies suggest abnormal metabolic handling of glucose. Glucose tolerance tests give a diabetic type of curve, and insulin secretion is low.[90,91] Impaired glucose utilization, glycogenolysis and glycolysis have also been demonstrated. In addition, there are isolated pieces of evidence of impaired enzymatic steps along the glucose oxidation, the Krebs cycle and the galactose-to-glucose conversion paths.[89,92,93]

Lipids. Steatorrhea is a characteristic of edematous PCM, even when the diet is practically devoid of fat.[94] Lipid absorption is reduced.[95] Low levels of many serum lipid fractions; neutral fat, cholesterol, particularly its esters, vitamins A and E and phospholipids have been demonstrated. These findings suggest that the changes in specific plasma proteins and physical chemical structure of the lipid-protein complexes account for impaired blood transport.[75,96,97] In fact, there is direct evidence for decreased lipoproteins as well as for decreased RBP, the specific vitamin A-binding protein.[68] A great part of the fatty liver may well be the consequence of inability to mobilize fat.[97]

Vitamins.[98] Signs of water-soluble vitamin deficiencies vary with the local dietary patterns, but, even when intakes are low, serum concentrations of thiamin, riboflavin, vitamin C, niacin metabolites and folates may well be within the normal range, and overt clinical signs of deficiency of these factors are rarely seen. Vitamin B_{12} serum levels are often found to be high. All of the above findings suggest that, although the supply of these vitamins may be low, tissue demands are also decreased.

In the edematous type of PCM (kwashiorkor), serum levels of vitamins A and E are consistently lower than normal. In the case of vitamin A, poor vitamin intake and defective absorption and transport explain these alterations. This expla-

nation may well apply also to vitamin E. All levels rise rapidly with therapy.

Water and Electrolytes.[47,99–101] Hypoosmolarity is a common finding. Serum sodium levels are from normal to low. Potassium and magnesium serum levels are not decreased, except when excessive losses of the cations occur through diarrhea and vomiting. In such cases, hypokalemia is accompanied by a loss of potassium from specific tissues such as muscle and brain.[26,102] This results in a decreased cellular potassium/nitrogen ratio. Mild acidosis is also common, on account of a decrease in the renal acidification mechanisms. Total serum calcium is somewhat low, primarily because of the protein-bound fraction.

Enzymes. The activity of several serum enzymes such as amylase, pseudocholinesterase and alkaline phosphatase is reduced. Their drop is consistent with and quite parallel to that of albumin, so that they may be normal in nonedematous PCM.[48,103] Serum transaminases are elevated and reflect increased tissue transaminase activity and leakage from the cells.[104] Around 15 hepatic enzymes have been studied,[105,106] including dehydrogenases, oxidases and esterases. Of these, 4 are clearly decreased in the edematous type of PCM—xanthine oxidase, glycolic acid oxidase, d-amino acid oxidase and cholinesterase. It has been pointed out that these enzymes are not involved in fundamental physiologic functions and seem to be of relatively little importance. On the other hand, cytochrome c reductase, a key enzyme in electron transport, is well preserved.

More complex systems, which depend on the integrity of the mitochondria, have been studied. Oxidative phosphorylation is somewhat reduced, and phosphate uptake into phosphatides is about half the value seen in recovered children.[61]

Enzymatic changes in liver and PMN leukocytes have been studied comparatively.[107] It has been found that not only are changes in both tissues similar but that they are characteristically different in the edematous and nonedematous types. In summary, these changes are: increased activity of fumarase and aconitase, decreased activity of isocitric dehydrogenase, glutamic dehydrogenase and aldolase in the edematous malnourished child with the reverse being true of the nonedematous patients. Muscle creatine phosphokinase activity has been found to be consistently low in children with the edematous type, while in those suffering from the marasmic type low or normal values can be observed.[108]

It is impossible to separate the effects of protein deficiency per se on enzymes from changes in activity, which may reflect changes in functional pattern in response to adaptation. In general, the latter interpretation seems more plausible. Measurements done in vitro with reconstructed systems tell nothing about subcellular structure changes, which may alter linking of enzymes with their substrates and cofactors. These could well involve alterations in membrane structure at the cellular and subcellular level.

TREATMENT

Chronic Mild-to-moderate Protein-calorie Malnutrition in Children

Because the children are not only physically retarded but also proportionally immature, their protein and calorie intake should be calculated on the basis of their height, that is, as if the child were well-fed but younger, of an age for which his height would correspond to the 50th percentile. This means a higher calorie and protein intake per kg of body weight than that of children of the same chronologic age. These intakes, therefore, will promote a retention of energy and protein to permit catch-up in growth and development. Of course, they should contain the appropriate concentrations of all the other essential nutrients. When marked deficiencies of

other nutrients are also prevalent, administration of specific supplements is called for.

Severe Protein-calorie Malnutrition

The severe, uncompensated forms of PCM require medical guidance during the initial phases of treatment.[109,110] Whenever possible, children with noncomplicated PCM should be treated on an outpatient basis.[111,112] Hospitalization in pediatric wards increases the risk of cross-infections. The presence of the mother or another close relative in the hospital is highly desirable.

Mortality in severe, uncompensated PCM is high even with hospitalization, ranging from 11 to 50 per cent depending on the center where treated and on certain characteristics of the patients, such as those listed on Table 24–5. In most cases the cause of death is a complication rather than PCM per se, but such complications do not have such high mortality in well-nourished patients.

Table 24–5. Characteristics of Severely Protein-calorie Malnourished Children which Carry a Poor Prognosis

Stupor or coma.
Age less than 6 months.
Weight-for-height deficit greater than 40 per cent.
Severe, protracted diarrhea.
Infection, primarily bronchopneumonia or measles.
Hemorrhagic tendency. Purpura is usually associated with septicemia.
Severe eye lesions.
Extensive exudative or exfoliative dermal lesions.
Extensive and deep decubitus ulcers.
Dehydration and electrolyte disturbances, particularly hyponatremia, hypokalemia and probably hypomagnesemia.
Clinical jaundice or increased serum bilirubin and/or frankly elevated serum glutamic-oxaloacetic, and glutamic-pyruvic transaminases.
Hypoglycemia and/or hypothermia.
Total serum proteins below 3 gm per 100 ml.
Severe anemia with clinical signs of hypoxia.
Severe tachycardia, signs of heart failure and/or respiratory distress.

The treatment of severe PCM may be divided into two phases:

1. That oriented toward saving the patient's life by bringing him back to his adapted stage.
2. The rehabilitation or "consolidation of cure" phase. At this stage, body protein and energy repletion for the patient's height should be achieved.

The main objectives of the initial treatment are: therapy of infection and correction of water and electrolyte imbalances as well as of other factors which lead to decompensation.

Maintenance of adequate urinary output is of primary importance. Preferably this is accomplished by oral therapy, keeping in mind the fact that the severely PCM individual is hypo-osmolar.[99] In addition to hypo-osmolarity, other peculiarities of the severely malnourished patient that must be taken into account to correct and/or maintain his electrolyte balance are: (1) total body potassium depletion, frequently without hypokalemia, because of intracellular potassium depletion, (2) mild-to-moderate metabolic acidosis, which tends to disappear when electrolyte balance is reestablished and the patient receives dietary or parenteral energy and (3) increased tolerance to hypocalcemia, partly because of the acidosis, which produces a relative increment in ionized Ca^{++}, and partly because of hypoproteinemia (when present), which makes less protein available to bind Ca^{++}.

As plasma proteins increase, hypocalcemia and even tetany may appear if calcium intake is inadequate.

If there is adequate diuresis, the diet should also provide from 6 to 8 mEq per kg body weight per day of K. If needed, the potassium concentration can be increased to supply 10 mEq per kg per day body weight to replace actual K losses from diarrhea or vomiting, which are usually 40 mEq per liter. Sodium intake should be sufficient to replace losses (about 35 mEq/L from diarrhea and 12 mEq/L from emesis),

but otherwise it should be relatively low (3 to 5 mEq per kg per day) because PCM patients have an excess of body sodium. Diets very low in sodium, however, hamper both renal function and normalization of intracellular electrolyte composition.[113] An excess of sodium and osmolar overloads can easily induce cardiac failure. Magnesium should also be administered, particularly when diarrhea and vomiting occur. Usually 1 ml of $MgSO_4 \cdot 7H_2O$, 50 per cent solution IM every 12 to 24 hours, is adequate. This therapy is important if tetany, oculogyric crises, tremor and bizarre neurologic signs occur in the initial phases of realimentation. In patients with tetany, calcium gluconate should also be administered intravenously, 0.5 to 1 gm slowly in 1 hour. Unless severe, acidosis should not be treated. Usually, renal function will handle acid-base balance efficiently.

If needed, intravenous therapy can and should be used, following the general outline described for oral rehydration, except that K therapy should not exceed 6 mEq per kg per day. Osmolarity should be kept at around 280 mOs per liter, and sodium must be kept low. Administration of plasma or other "protein-rich" fluids is contraindicated, except when severe intravascular dehydration (hypovolemia) with shock is present. Shock due to severe dehydration or gram-negative septicemia should be treated as if the individual were not malnourished. In some of these cases blood transfusions are indicated, but hemoglobin concentrations should be brought only to 10 gm per 100 ml or less, which are commonly the hemoglobin levels these children achieve from adaptation. Transfusions of packed red cells are indicated only when severe anemia is present and cardiorespiratory failure is imminent. Again, hemoglobin concentrations should be brought only to about 10 gm per 100 ml.

Infection should be treated vigorously and, if possible, with the help of a laboratory, so that the infective organisms can be isolated and their sensitivity to antibacterial agents determined. When there is a choice, the use of antibiotics that inhibit protein synthesis should be avoided.

A free airway with adequate lung ventilation is essential. When pneumonia is present, oxygen therapy and even tracheostomy may have to be undertaken, because it often happens that these patients are weak and cannot clear their airways satisfactorily.

When severe hepatic failure occurs it should be treated accordingly, as is done when cardiac failure supervenes. Diarrhea is treated mainly by diet. No anticholinergic drugs are used. Another general rule is to protect the PCM patient from exposure to cold and hypothermia, and from hypoglycemia. Hypoglycemia is prevented by avoiding prolonged periods of fasting. If a patient cannot be fed by mouth, intravenous infusions should provide 20 to 30 kcal per kg per day body weight as glucose.

During this initial phase of therapy a diet based on high-quality protein, such as milk-casein mixtures (to reduce lactose loads), casein alone, egg or fish protein, is recommended. During this phase a cautious handling of the nutrition aspect is essential. This demands patience, and personnel must be conscious of the fact that the most common causes of death are the complications and not malnutrition per se. Drastic therapeutic nutritional measures, such as high protein or calorie load from the start, may precipitate death by posing an "iatrogenic" overload on enzymatic and various physiologic functions which had reached maximal adaptation in several weeks or even months in the process of progressive malnutrition. This cautious dietary approach should provide initially, in children, around 1 gm protein and 80 to 100 kcal per kg per day; 20 per cent of the calories should be derived from fat. After 2 to 4 days, the protein and energy contents of the diet should increase gradually, as shown in Table 24–6, until they provide

Table 24–6. Example of a Dietary Therapeutic Regimen for Children Based on Dry Skim Milk, Sugar and Vegetable Oil*

Days from Beginning of Treatment	*Protein (gm)*	*Energy (kcal)*	*Milk (gm)*	*Sugar (gm)*	*Oil (ml)*	*Water (ml)*
1	0.8–1‡	80–100	3	17	2	100
3	1.5–2.5	110–120	6	20	2	130
5	2.5–3.5	140–150	9	20	4	150
7	3.5–4.5	150–160	12	20	4	160
12 (marasmus‡)		175‡			6‡	
17		195‡			8	
22		215			11	
	3.5–4.5	‡	12	20	‡	160

* All amounts per kg body weight per day. The liquid formula must be supplemented with adequate levels of vitamins, minerals and electrolytes.

‡ Marasmic patients may require more than 150 to 160 kcal per kg per day. Vegetable oil 2 to 3 ml per kg per day at 5-day intervals should be added until the rate of weight gain becomes adequate.

3 to 4 gm protein and 120 to 160 kcal per kg per day. Twenty to 40 per cent of the energy then should come from fat, preferably of vegetable origin with a high content of polyunsaturated fatty acids (e.g. corn or cottonseed oils). Marasmic patients may need a higher energy intake to recover. In these cases, 20 to 25 kcal per kg per day should be added to the diet as vegetable oil at 5-day intervals, until weight gain becomes adequate. In a few instances this may require 200 or more kcal per kg per day and, even though a mild steatorrhea may develop, this regimen should be maintained. The example shown in Table 24–6 is based on a liquid diet. Children who can eat solids should receive a varied diet, aiming at the same levels of protein and energy intakes.

In the adult, the therapeutic scheme is the same but the diet should initially provide around 0.6 gm protein and 50 kcal per kg per day and eventually reach 3 to 4 gm protein and 80 to 100 kcal.

Vitamins, including folate, should be administered from the beginning, to meet recommended allowances. On admission, the routine administration of a single high dose (20,000 μg) of water-dispersible vitamin A is recommended to avoid acute eye lesions resulting from vitamin A deficiency, when high calorie and protein diets are initiated and there is greater physiologic demand for the vitamin. This is followed by a daily oral dose of 1500 μg.

The diet should also provide from 4 to 5 mEq per kg body weight per day of K, 3 to 5 mEq per kg per day of Na and adequate amounts of magnesium, calcium and phosphorus. Iron, in amounts from 16 to 32 mg, as $FeSO_4$, is routinely administered by mouth as soon as increased protein-calorie intakes are begun, in order to supply the excess requirements for this mineral produced by the rapid increase in total circulating hemoglobin.

With this regimen, the severely malnourished subjects begin a smooth recovery: They start to lose edema and to gain body mass; their general state shows the first signs of improvement and anorexia is replaced by an increased appetite; then the patient may begin to eat a more varied diet. Serum and urine values also start a trend toward normal and the hematologic status initiates recovery. All of these changes are accompanied by a rise in nitrogen and energy retention. Except for sodium, mineral retention also increases. Rapid changes in weight should be avoided, particularly a rapid loss of edema. Usually within 2 to 3 weeks of therapy

serum composition returns to normal limits, and consolidation of cure begins.

The second phase of therapy is accomplished only by dietary means. The patients should by then be receiving a complete mixed diet, providing the protein and calorie levels reached in the later phase of the initiation of therapy. A systematic program of psychosocial stimulation and progressive physical activity should be undertaken.[114,115] In children this can be accomplished through games that require frequent walking, preferably uphill, running, jumping and climbing. In adults it can be accomplished through exercise that imposes a gradual increment in cardiorespiratory work load. Complete calorie and protein repletion generally is accomplished in a 6- to 12-week period, depending on the deficits at the start of treatment. Calorie repletion is judged by weight for height, and is considered achieved when this index is 0.90 or more, based on the 50th percentile of normal well-nourished populations. It is a mistake to use weight for age as an indicator of nutritional recovery. A child who is stunted in height would have to become obese in order to reach a normal weight for age. Generally, in nonedematous PCM, normalization of weight for height is reached later than normalization of the creatinine/height index an indicator of protein repletion.[60] In edematous PCM the opposite occurs. These changes are illustrated in Figures 24–9 and 24–10. Some children, however, stabilize at a creatinine/height index lower than 0.9, though fully recovered from PCM according to other indicators.

PREVENTION

Prevention can be approached by (1) measures to decrease the risk of individuals reaching severe PCM and (2) improvement of the general nutritional status of

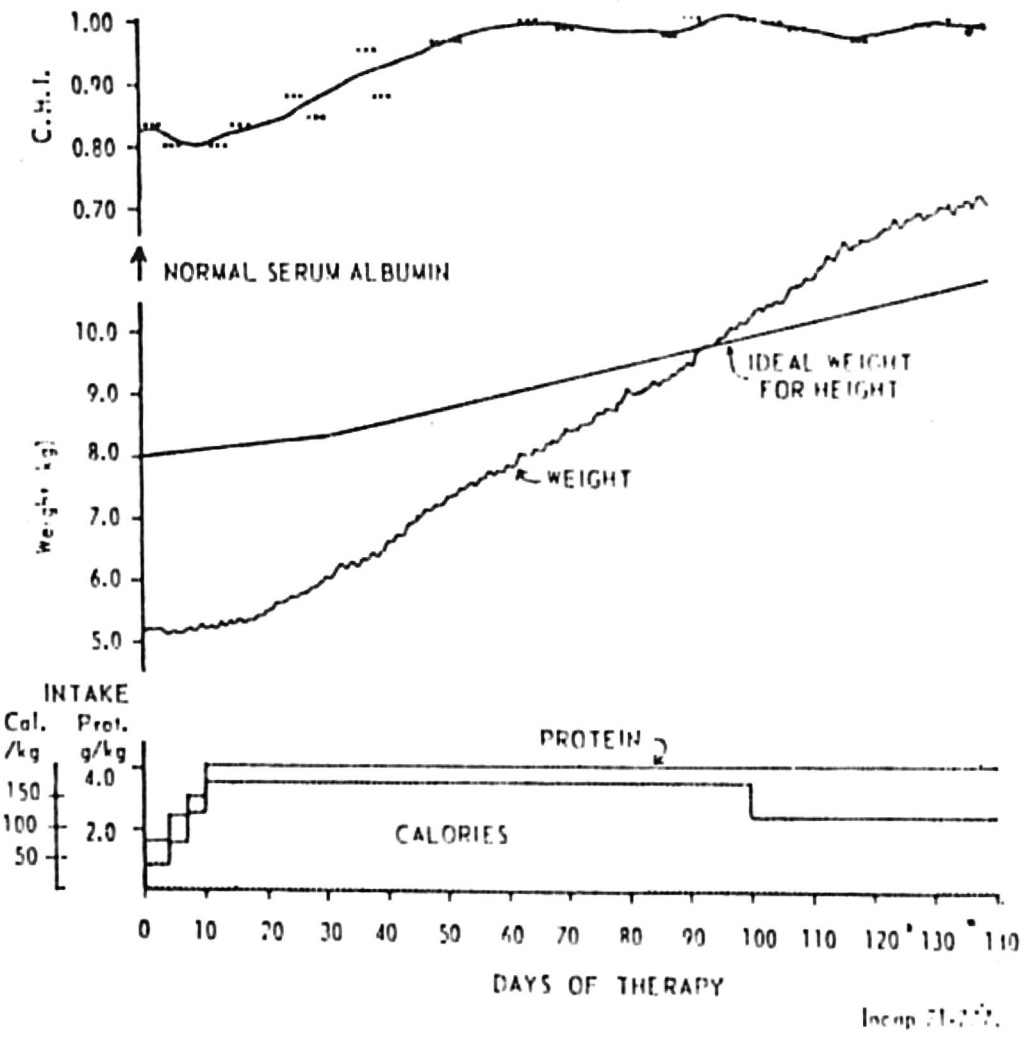

Fig. 24–9. Clinical record of a 16-month-old child during recovery from nonedematous PCM. His lean body mass (CHI) reached normal levels before his weight for height was normal.

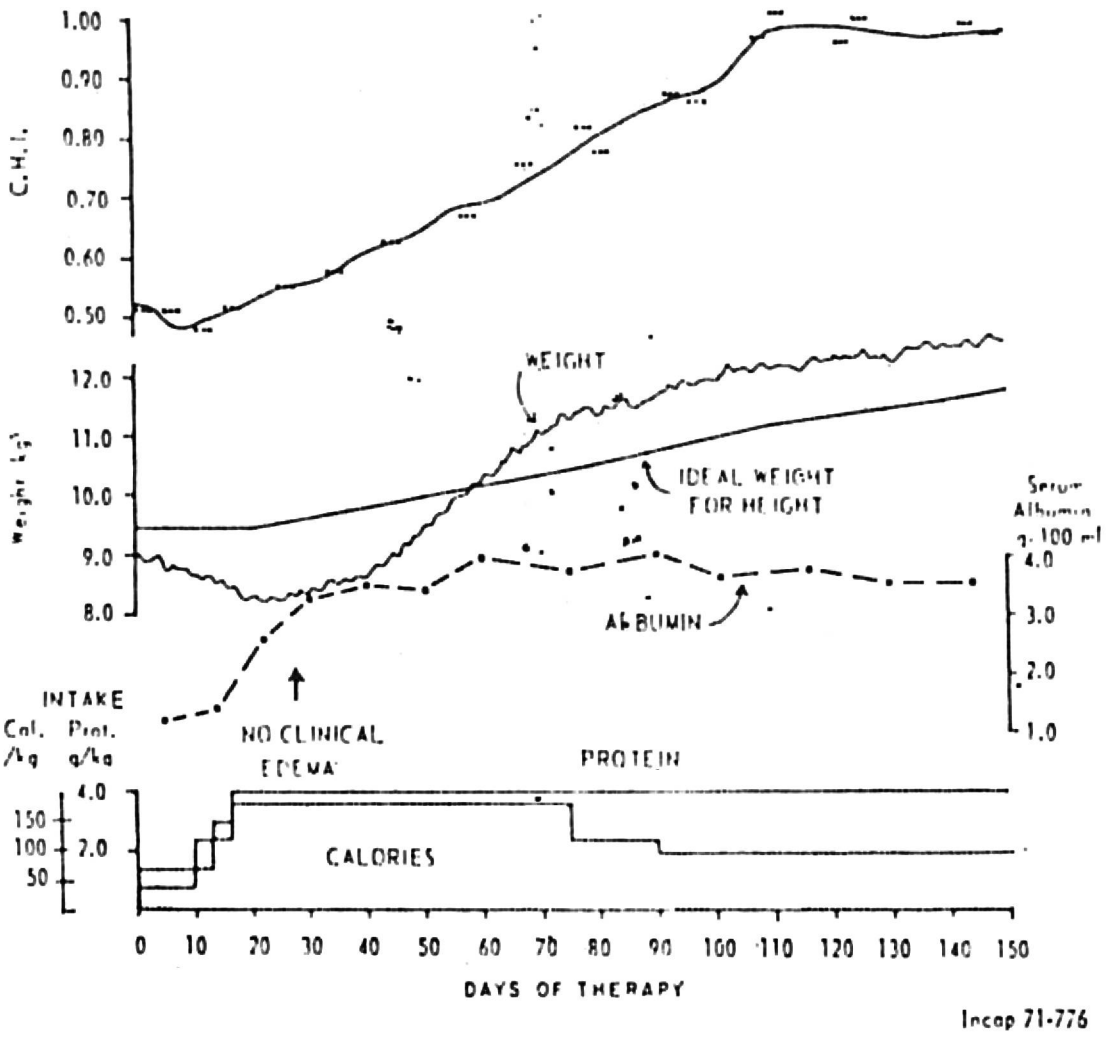

Fig. 24–10. Clinical record of a 20-month-old child during recovery from edematous PCM. His lean body mass (CHI) reached normal levels after his weight for height was normal.

the population, so that even chronic mild-to-moderate PCM cases become rare.

The first is amenable to some direct actions: (1) fostering of maternal lactation and adequate supplementation practices during infancy, (2) food supplementation programs of vulnerable groups, such as pregnant and lactating women, children up to school age and above, if possible, and physically hard-working men, (3) improvement of sanitary conditions and (4) specific nutrition education. For this last objective, nutrition education and recuperation centers have been instituted in several countries.[116] Their main objective is to educate the parents of chronic mild-to-moderate PCM children by having them participate actively in the nutrition rehabilitation of their own children. These centers must (1) be located in the community and be adapted to the local environment, (2) be supported by each community, (3) see that children are rehabilitated by the proper feeding of locally available foods and (4) see that mothers are rotated in the care of the children, so as to have direct experience of the benefits that adequate nutrition brings to their children. Experience is accumulating on the effects of these specific preventive measures, indicating that they appear to fulfill their goals.[117]

Improvement of the general nutritional status of the population, so that malnutrition is eradicated, requires a complex approach.[118] This is inseparable from the acceleration of socioeconomic development; the actions to bring it about are beyond the scope of this chapter.

BIBLIOGRAPHY

1 Scrimshaw and Béhar: Fed. Proc., *18* (Suppl. 3), 82, 1959.

2 Gomez, Ramos Galván, Frenk, Cravioto-Muñoz, Chávez and Vásquez: J. Trop. Pediatr., 2, 77, 1956.

3. Evaluación Nutricional de la Población de Centro América y Panamá. Guatemala, Instituto de Nutrición de Centro América y Panamá (INCAP): Oficina de Investigaciones Internacionales de los Institutos Nacionales de Salud (EEUU); Ministerio de Salud Pública y Asistencia Social. Guatemala, Instituto de Nutrición de Centro América y Panamá, 1969.
4. Viteri and Torún: Bol. Of. Sanit. Panam., *78*, 58, 1975.
5. Lechtig, Delgado, Martorell, Yarbrough and Klein: In *Perinatal Medicine* (Rooth and Bratterby, Eds.). Stockholm, Almqvist and Wiksell, 1976, p. 208.
6. Lindblad and Rahimtoola: Acta Paediatr. Scand., *63*, 125, 1974.
7. Mata, Urrutia, Kronmal and Joplin: Am. J. Dis. Child., *129*, 561, 1975.
8. Viteri, Béhar and Alvarado: Rev. Col. Med. (Guatemala), *21*, 137, 1970.
9. Soriano: Rev. Chil. Pediatr., *39*, 475, 1968.
10. Waterlow: *Fatty Liver Disease in Infants in the British West Indies* (Medical Research Council Special Report Series No. 263). London, Her Majesty's Stationery Office, 1948.
11. Mata, Urrutia and Gordon: Trop. Geogr. Med., *19*, 247, 1967.
12. Gordon, Chitkara and Wyon: Am. J. Med. Sci., *245*, 345, 1963.
13. Viteri and Alvarado: Rev. Col. Med. (Guatemala), *21*, 175, 1970.
14. Viteri and Pineda: In *Famine. A Symposium Dealing with Nutrition and Relief Operations in Times of Disaster* (Blix, Hofvander and Vahlquist, Eds.). Uppsala, Almqvist and Wiksells, 1971.
15. Kerpel-Fronius, Varga and Kun: Ann. Pediatr. (Switzerland), *183*, 1, 1954.
16. Parra, Garza, Garza, Saravia, Hazlewood and Nichols: J. Pediatr., *82*, 133, 1973.
17. Parra, Klish, Cuellar, Serrano, García, Argote, Canseco and Nichols: J. Pediatr., *87*, 307, 1975.
18. Alleyne and Young: Clin. Sci., *33*, 189, 1967.
19. Grant, Hambley, Becker and Pimstone: Arch. Dis. Child., *48*, 596, 1973.
20. Waterlow, Alleyne, Chan, Garrow, Hay, James, Picou and Stephen: Arch. Latinoam. Nutr., *16*, 175, 1966.
21. Waterlow and Alleyne: Adv. Protein Chem., *25*, 117, 1971.
22. Beisel: Annu. Rev. Med., *26*, 9, 1975.
23. Cohen and Hansen: Clin. Sci., *23*, 351, 1962.
24. Frenk, Metcoff, Gómez, Ramos-Galván, Gravioto and Antonowicz: Pediatrics, *20*, 105, 1957.
25. Alleyne: Clin. Sci., *34*, 199, 1968.
26. Nichols, Alvarado, Hazlewood and Viteri: J. Pediatr., *80*, 319, 1972.
27. Viteri, Alvarado, Luthringer and Wood: Vitam. Horm., *26*, 573, 1968.
28. Viart: Am. J. Clin. Nutr., *30*, 334, 1977.
29. Gordillo, Soto, Metcoff, López and García Antillón: Pediatrics, *20*, 303, 1957.
30. Srikantia: In *Calorie Deficiencies and Protein Deficiencies* (McCance and Widdowson, Eds.). London, J. & A. Churchill, 1968, p. 2033.
31. Brinkman, Bowie, Friss-Hansen and Hansen: Pediatrics, *36*, 94, 1965.
32. Keys, Brozek, Hanschel, Mickelsen and Taylor: *The Biology of Human Starvation*, Vol. II. Minneapolis, University of Minnesota Press, 1950, p. 1002.
33. Viteri: In *Amino Acid Fortification of Protein Foods*. Report of an International Conference Held at the Massachusetts Institute of Technology, September 16 to 18, 1969 (Scrimshaw and Altschul, Eds.). Cambridge, MIT Press, 1971, p. 350.
34. Suskind (Ed.): *Malnutrition and the Immune Response*. New York, Raven Press, 1977.
35. Viteri, Flores, Alvarado and Behar: Am. J. Dig. Dis., *18*, 201, 1973.
36. Bowie, Barbezat and Hansen: Am. J. Clin. Nutr., *20*, 89, 1967.
37. Barbezat and Hansen: Pediatrics, *42*, 77, 1968.
38. Schneider and Viteri: Am. J. Clin. Nutr., *27*, 777, 1974.
39. Schneider and Viteri: Am. J. Clin. Nutr., *27*, 788, 1974.
40. Viteri and Schneider: Med. Clin. North Am., *58*, 1487, 1974.
41. Geber and Dean: Courrier (Paris), *6*, 3, 1956.
42. Scrimshaw and Gordon (Eds.): *Malnutrition, Learning and Behavior*. Cambridge, MIT Press, 1968.
43. Hoeldtke and Wurtman: Fed. Proc., *30*, 459, 1971.
44. Winick and Rosso: In *Protein-Calorie Malnutrition* (Olson, Ed.). New York, Academic Press, 1975, p. 93.
45. Dobbing: Pediatrics, *53*, 2, 1974.
46. Wayburne: In *Calorie Deficiencies and Protein Deficiencies* (McCance and Widdowson, Eds.). London, J. & A. Churchill, 1968, p. 7.
47. Garrow, Smith and Ward: *Electrolyte Metabolism in Severe Infantile Malnutrition*. London, Pergamon Press, 1968.
48. Trowell, Davies and Dean: *Kwashiorkor*. London, Edward Arnold Ltd., 1954.
49. Viteri, Béhar, Arroyave and Scrimshaw: In *Mammalian Protein Metabolism*, Vol. II (Munro and Allison, Eds.). New York, Academic Press, 1964, p. 523.
50. Gravioto, DeLicardie and Birch: Pediatrics, *38* (Suppl., II), 319, 1966.
51. Klein, et al.: Bol. Of. San. Panam., *10*, 301, 1976.
52. Tizard: Br. Med. Bull., *30*:164-169, 1974.
53. Canosa: In *Malnutrition, Learning, and Behavior*. Proceedings of an International Conference Cosponsored by the Nutrition Foundation Inc. and the Massachusetts Institute of Technology, Held at Cambridge, Massachusetts, March 1–3, 1967 (Scrimshaw and Gordon, Eds.). Cambridge, MIT Press, 1968, p. 389.
54. Arroyave: In *Mild-Moderate Forms of Protein-Calorie Malnutrition*. Symposia of the Swedish Nutrition Foundation I, Bastad, August 29–31, 1962 (Blix, Ed.). Uppsala, Almqvist and Wiksells, 1963, p. 32.
55. Whitehead: In *Calorie Deficiencies and Protein Deficiencies* (McCance and Widdowson, Eds.). London, J. & A. Churchill, 1968, p. 109.
56. Arroyave: In *Protein Calorie Malnutrition* (von Muralt, Ed.). Berlin, Springer-Verlag, 1969, p. 48.

57. Whitehead: Lancet, *2*, 567, 1965.
58. McFarlane, Ogbeide, Reddy, Adcock, Adeshina, Gurney, Cooke Taylor and Mordie: Lancet, *1*, 392, 1969.
59. Hansen: In *Calorie Deficiencies and Protein Deficiencies* (McCance and Widdowson, Eds.). London, J. & A. Churchill, 1968, p. 33.
60. Viteri and Alvarado: Pediatrics, *46*, 696, 1970.
61. Waterlow, Cravioto and Stephen: Adv. Protein Chem., *15*, 131, 1960.
62. Waterlow: In *Protein-Calorie Malnutrition* (Olson, Ed.). New York, Academic Press, 1975, p. 23.
63. Garrow, Fletcher and Halliday: J. Clin. Invest., *44*, 417; 1965.
64. Halliday: Clin. Sci., *33*, 365, 1967.
65. Milward: Clin. Sci., *39*, 591, 1970.
66. Mendes and Waterlow: Br. J. Nutr., *12*, 74, 1958.
67. Lahey, Béhar, Viteri and Scrimshaw: Pediatrics, *22*, 1958.
68. Smith, Goodman, Arroyave and Viteri: Am. J. Clin. Nutr., *26*, 982, 1973.
69. Cravioto: Bol. Med. Hosp. Infant. Mex., *15*, 805, 1958.
70. Graham and Blizzard: In *Endocrine Aspects of Malnutrition* (Gardner and Amacher, Eds.). Sta. Ynez (California), Kroc Foundation, 1973, p. 205.
71. Graham, Baertl, Claeyssen, Suskind Greenberg, Thompson and Blizzard: J. Pediatr., *83*, 321, 1973.
72. Alleyne and Young: Clin. Sci., *33*, 189, 1967.
73. Leonard and MacWilliam: J. Endocrinol., *29*, 273, 1964.
74. Leonard and MacWilliam: Am. J. Clin. Nutr., *16*, 360, 1965.
75. Arroyave, Wilson, Méndez, Béhar and Scrimshaw: Am. J. Clin. Nutr., *9*, 180, 1961.
76. Picou and Taylor-Roberts: Clin. Sci., *36*, 283, 1969.
77. Picou and Phillips: Am. J. Clin. Nutr., *25*, 1261, 1972.
78. Reddy, Belavady and Srikantia: Indian J. Med. Res., *51*, 952, 1963.
79. Standard, Wills and Waterlow: Am. J. Clin. Nutr., *7*, 271, 1959.
80. Arroyave, Wilson, Béhar and Scrimshaw: Am. J. Clin. Nutr., *9*, 176, 1961.
81. Alleyne, Viteri and Alvarado: Am. J. Clin. Nutr., *23*, 875, 1970.
82. Picou, Reeds and Jackson: Pediatr. Res., *10*, 184, 1976.
83. Holtz, Snyderman, Norton, Roitman and Finch: Lancet, *2*, 1343, 1963.
84. Arroyave, Wilson, Funes and Béhar: Am. J. Clin. Nutr., *11*, 517, 1962.
85. Cravioto: Am. J. Clin. Nutr., *11*, 484, 1962.,
86. Adams and Scragg: J. Pediatr., *60*, 580, 1962.
87. Edozien and Phillips: Nature, *191*, 47, 1961.
88. Whitehead and Arnstein: Nature, *190*, 1105, 1961.
89. Alleyne and Scullard: Clin. Sci., *37*, 631, 1969.
90. James and Coore: Am. J. Clin. Nutr., *23*, 386, 1970.
91. Becker, Pimstone, Hansen, Buchanan-Lee and MacHutchon: S. Afr. Med. J., *43*, 1154, 1969.
92. Gillman, Gillman, Scragg, Savage, Gilbert, Trout and Levy: S. Afr. J. Med. Sci., *26*, 31, 1961.
93. Metcoff, Frenk, Yoshida, Torres-Pinedo, Kaiser and Hansen: Medicine, *45*, 365, 1966.
94. Van der Sar: Dos. Neerl. Indones. Morb. Trop., *3*, 25, 1951.
95. Jayasekera, De Mel and Collumbine: Ceylon J. Med. Sci., *8*, 1, 1951.
96. Schwartz and Dean: J. Trop. Pediatr., *3*, 23, 1957.
97. Flores, Sierralta and Mönckeberg: J. Nutr., *100*, 375, 1970.
98. Olson (Ed.): *Protein-Calorie Malnutrition*. New York, Academic Press, 1975.
99. Metcoff, Frenk, Gordillo, Gómez, Ramos Galván, Cravioto, Jeneway and Gamble: Pediatrics, *20*, 317, 1957.
100. Caddell and Goddard: N. Engl. J. Med., *276*, 533, 1967.
101. Nichols, Alvarado, Rodriguez, Hazlewood and Viteri: J. Pediatr., *84*, 759, 1974.
102. Garrow: Lancet, *2*, 643, 1967.
103. Arroyave, Feldman and Scrimshaw: Am. J. Clin. Nutr., *6*, 164, 1958.
104. McLean: Clin. Sci., *30*, 129, 1966
105. Waterlow: Fed. Proc., *18*, 1143, 1959
106. Bruch, Arroyave, Schwartz, Padilla, Béhar, Viteri and Scrimshaw: J. Clin. Invest., *36*, 1579, 1957.
107. Pineda: In *Calorie Deficiencies and Protein Deficiencies* (McCance and Widdowson, Eds.). London, J. & A. Churchill, 1968, p. 75.
108. Contreras, Pineda, Viteri and Arroyave: Fed. Proc., *30*, 231, 1971
109. Garrow, Picou and Waterlow: West Indian Med. J., *11*, 217, 1962.
110. Torún and Viteri: Rev. Col. Med. (Guatemala), *27*, 43, 1976.
111. Jelliffe and Jelliffe: J. Pediatr., *77*, 895, 1970.
112. Cook: J. Trop. Pediatr., *17*, 15, 1971
113. Nichols, Alvarado, Kimsey, Hazlewood and Viteri. In *Endocrine Aspects of Malnutrition* (Gardner and Amacher, Eds.) Sta. Ynez (California), Kroc Foundation, 1973, p. 363.
114. Viteri: Am. J. Clin. Nutr., in press.
115. Torún and Viteri: Am. J. Clin. Nutr., in press.
116. Bengoa: J. Trop. Pediatr., *10*, 63, 1964.
117. Beghin and Viteri: J. Trop. Pediatr., *19*, 404, 1973.
118. Bengoa. In *Protein Calorie Malnutrition* (Olson, Ed.). New York, Academic Press, 1975, p. 435.