Protein deficiency disorders

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Introduction

The clinical definitions of protein deficiency disorders and the terminology relating thereto still remain somewhat confused despite the recent attention the subject has received from various authors and at more than one symposium (Waterlow, Cravioto & Stephen, 1960; Viteri *et al.*, 1964; Dean, 1965). The definitions proposed by the joint FAO/WHO Expert committee (1962) are unsatisfactory: protein and calorie deficiencies are considered under a single general heading and a distinction is made between kwashiorkor and marasmus solely on the basis of the presence or absence of oedema (see also Kerpel-Fronius, 1957).

The aim of the present article is to discuss protein-deficiency syndromes on a physio-pathological basis and to illustrate some of the conclusions with examples. When studying the pathological mechanisms of protein deficiencies it is necessary not only to take into account the composition of the diet but also to distinguish between the different circumstances under which the deficiency syndrome sets in. Has the deficiency existed since birth, or at least since the very early stages of life, thus preventing the organism from developing? Or has an otherwise healthy organism suddenly been submitted to a deficient diet, and when? Studies of protein malnutrition induced during the growth period (such as a child weaned on to a protein-deficient diet) or when growth has been completed [such as an adult abruptly put on to a generally deficient and thus also protein-deficient diet, as was achieved experimentally by Keys *et al.* (1950) or observed in Europe during the Second World War (Medical Research Council, 1951; Poliakov, 1964)] will be discussed and the main characteristics of protein malnutrition that make their appearance under different circumstances described.

Disorders caused by a protein-deficient diet occurring shortly after birth and lasting a relatively long time

In such diets there is generally an overall calorie deficiency. If life continues for a prolonged period

under these conditions it is observed that the rate of growth slows down and the tissues are late in attaining biochemical maturity. Experiments on animals have enabled extreme cases to be obtained (McCance, 1960, 1968).

The phenomenon of cell growth has been studied by Cheek (1968). Growth is a combination of two processes, cell division after DNA replication and an increase in cell volume. A diet that is deficient in calories prevents the DNA replication process but allows cell volume to increase, whereas a diet that is low in protein but adequate in calories does not hamper cell division although the cells remain small.

It is important to note that growth slows down to a varying degree in different organs and the phenomenon is more marked in the muscles and bones than in the kidneys (Widdowson, Dickerson & McCance, 1960). It has been demonstrated that the resumption of a theoretically adequate diet can enable the delay in growth to be caught up, either in part or completely, depending on the type of animal and the chronological age at which the diet is corrected (Lister & McCance, 1967).

Tanner (1968) has examined the question of slow growth-rates and retarded maturity in human beings. Somatic growth-rate can only be qualified as slow by comparison with the rate observed in individuals that are assumed to be nourished in the best way. For this purpose it has become customary to refer to the growth curve established at Boston (Nelson, 1964). Garn & Rohmann (1966) have established growth curves which take account of the average size of each subject's parents, and these seem preferable to the Boston curve since they enable nutritional influence to be dissociated from hereditary factors.

The following study shows how important the genetic influence can be. Somatic growth and dietary conditions were studied in two isolated farming communities living within the same cultural zone of Central Africa. Each community lives in a closed economy, with a basic diet of beans, sweet potatoes, bananas and cassava (Vis, 1968). One of

TABLE 1. Mean weight and height during growth in males and females of two communities of Central Africa compared with American standards

Age (years)	Height (cm)				Weight (kg)		
	Nelson (1964)	Garn & Rohmann (1966)	Area II	Area III	Nelson (1964)	Area II	Area III
Males							
1	75.2	75.6	70.0	72.5	10.0		
3	96.2	94.9	86.0	93.2	14.6	12.3	13.2
6	117.5	114.1	103.4	111.2	21.9	16.1	18.6
9	135.5	130.4	117.3	128.3	29.9	21.2	24.6
12	149.6	148.0	130.1	142.5	38.3	26.8	31.4
15	167.8	168.1	146.9	157.1	54.5	38.6	43.1
18	174.5	175.0	158.2	169.3	63.0	49.2	55.2
21			162.1	173.7		54.4	56.7
24			164.3	174.1		55.5	56.9
Females							
1	74.2	73.8	69.0	71.5	9.7		
3	95.7	94.5	84.5	93.3	14.4	11.9	14.3
6	115.9	115.0	103.4	112.0	21.0	16.0	18.5
9	132.9	132.2	119.2	127.9	28.9	22.2	27.7
12	151.9	152.8	133.4	148.1	39.7	29.1	36.7
15	161.1	162.6	147.5	152.9	51.4	41.2	46.3
18	162.5	165.0	150.0	155.6	54.4	48.1	50.8
21			152.0	156.9		50.2	51.3
24			152.3	158.3		50.3	51.9

Area II: Bantus of the western shore of the Kivu lake.

Area III: Bantu/Nilotics half-breeds of the eastern shore of the Kivu lake.

Calorie intake per day and per inhabitants in % of the total amount as recommended by the FAO expert group (1957):

Area II: 1957-59: 83.2.

1965-67: 84.9.

Area III: 1966-67: 80.2.

Protein intake (as reference protein) per day and per inhabitant in % of the total amount reference protein as recommended by the joint expert group FAO/WHO (1965) and Net Dietary Protein calories per cent (NDP cal %; Platt, Heard & Stewart, 1964):

Area II: 1957-59: 112.5 (NDP cal %: 6.18).

1965-67: 110.7 (NDP cal %: 5.54).

Area III: 1966-67: 116.0 (NDP cal %: 5.14).

the communities composed almost entirely of Bantus lives along the western shore of the Kivu lake; the other inhabits the eastern shore and is composed of Bantu/Nilotic half-breeds and 30% are pure Nilotic subjects.

The height and weight values at different ages for the males of the two communities are compared in Table 1 and Fig. 1. The tables and graphs show that growth continues in both communities until the age of 25 years, whereas it ceases at 18 years of age among Americans. The Nilotics are genetically taller than the Bantus, and this characteristic reappears in the mixed blood population. Both communities show weight-deficits when growth is complete, but the height-deficit is most marked in the pure Bantu community. The weight-deficit in the two communities exists from the first stages of life since the average birth weight for girls is 2.80 kg and for boys 2.95 kg, although the growth curves for the first 6 months of life tend to approach the American ones (see also Gallez, 1960). Table 1 shows that food supplies

did not differ over a period of 10 years, so it may be assumed that these populations have been nourished in similar fashion for several decades and that their somatic growth has become adapted to their food intakes. Any attempts to determine, as some have proposed, the degree of malnutrition of a child on the basis of the difference between its growth curve at a given age and that of the American child would give a false idea of the situation since the rhythm of growth is not the same. Under constant dietary conditions, the difference in weight by comparison with American standards is about 30% at the age of 15 years and only 10% at 25 years of age. Without the reference growth curves it is impossible to say that the two communities are chronically under-nourished. Biological analyses at any rate furnish no evidence since, even during growth under such deficient dietary conditions as those described above, the homeostasis of extra-cellular fluid is maintained: the levels of free amino acids, albumin and haemoglobin in the blood are all normal.

FIG. 1. Growth curves in males of two communities of Central Africa as compared to an American standard. (a) American standard (for parental midpoint of 165 cm) (Garn & Rohmann, 1966). (b) Bantu/Nilotic half-breed community. (c) Bantu community.

Disorders caused by a protein-deficient diet occurring suddenly after a period of normal diet

We shall consider chiefly what happens in children, i.e. in growing subjects. A habitual distinction is made between two clinical forms of the protein-deficient state, pure kwashiorkor and marasmus. Pure kwashiorkor or 'sugar baby' (Jelliffe, Bras & Stuart, 1954) is the clinical condition attained by children, and particularly babies, when they are fed with a diet that is rich in calories, mainly of carbohydrate origin, and very poor or completely lacking

in proteins. Marasmus is a condition of general undernourishment which occurs when the diet is reduced in calories but the ratio of proteins to other nutrients remains the same (Kerpel-Fronius, 1957). These two definitions show how necessary it is to study diet composition when investigating the pathological mechanisms of protein deficiencies. The same individual deprived of proteins will develop marasmus if the total calorie intake is deficient but kwashiorkor if the diet is rich in carbohydrates. For a better understanding of these disorders, an analysis of nitrogen metabolism under protein-deficient conditions must be combined with a study of hydroelectrolytic and lipid-carbohydrate metabolism. The clinical and biological characteristics believed to be peculiar to pure kwashiorkor and to marasmus are given in Table 2.

Arrested growth

Growth comes to a distinct halt especially if the deficiency is very marked. Clinically this cessation of growth can be detected by the visible transverse lines on the radiographs of long bones in children or animals that have been cured of their conditions of malnutrition (Jones & Dean, 1956; Platt & Stewart, 1962).

For clinical reasons children suffering from protein malnutrition of the pure kwashiorkor type generally show only slightly retarded growth, since the oedema appear relatively faster than in marasmus (if the latter shows any oedema at all), and it is this symptom that induces the parents to get medical care for their children. Table 3 shows, in relation to the average growth curve for Central Africa, the weight deficits of children with the clinical characteristics of marasmus or pure kwashiorkor.

Decrease in serum proteins

Observers of protein deficiency in children (pure kwashiorkor) generally agree that there is a clear

TABLE 2

	Pure kwashiorkor	Marasmus
Retarded growth	±	++
Weight loss	- or ±	+++
Diarrhoea	+	++
Oedema	+++	- or +
Subcutaneous fat	+++	-
Skin and hair lesions	++	-
Liver	Enlargement and fatty infiltration	-
Plasma proteins and albumins	↓ ↓	N
Essential amino acids	↓ ↓	N
Pancreatic enzymes	↓ or ○	N
Urinary hydroxyproline creatinine index	↓	↓ ↓
Mental behaviour	Lack of appetite, apathy	Nervous tension, aggressive appetite

TABLE 3. Muscle composition and clinical data concerning four children with pure kwashiorkor (1, 2, 3 and 4) and four children (5, 6, 7 and 8) with marasmus complicated by protein deficiency

	Normal figures	1	2	3	4	5	6	7	8
Age (in years)		2	6/12	11/12	10/12	11/12	2	10/12	10/12
Sex		F	M	M	M	F	F	M	M
Clinical oedema		+	+	+	+	0	0	+	+
% deficit of weight in relation to height		7.3	0	17.0	0.1	22.6	26.3	27.1	20.6
Plasma proteins		5.8	5.2	4.7	3.6	3.9	4.0	3.6	5.6
Plasma albumin		2.7	1.3	1.6	1.5	1.3	1.3	0.9	2.2
Muscle									
Water	342.4	378.0	374.0	392.9	361.0	674.0	514.6	405.3	521.0
Cl	15.4	19.1	15.1	17.7	13.8	39.6	34.4	30.3	30.8
Na	25.8	18.7	20.8	28.9	23.4	38.9	43.8	32.7	35.7
K	42.2	?	39.7	41.9	37.4	39.8	30.0	40.6	49.6

The figures are expressed in g or mm/100 g fat free solid.

Although the children with marasmus have no clinical evidence of oedema they have a higher water, chloride and sodium content in muscle than children with pure kwashiorkor. The composition of the tissue of the muscles in malnourished children is comparable to the composition of the muscles of younger children (see Dickerson & Widdowson, 1960).

The degree of weight deficit and alterations of muscle composition may indicate the importance of the marasmic component of the protein-calorie deficiency.

The absence of pitting oedema in cases 5, 6, 7 and 8 may be in relation with the loss of subcutaneous fat (Frenk *et al.*, 1957). These results indicate that in marasmic kwashiorkor the protein deficiency component must have appeared later than the marasmus processus.

decrease in the serum proteins. The drop is particularly striking for liver-synthesized proteins, i.e. albumin and lipoproteins. It has been demonstrated fairly conclusively (Munro, 1966), that protein synthesis in the liver is dependent upon the supply of alimentary amino acids after each meal. Investigations carried out on animals show that variations in endoplasmic reticulum, the increase in RNA and the synthesis of 'labile proteins' are closely related with alimentary nitrogen intakes. The catabolism of 'labile proteins' and the decrease in RNA content start very rapidly—2 or 3 hr after a meal. Later, if the protein deficiency persists, there is a drop in albumin synthesis. This will not be noticed immediately in the plasma because of compensatory mechanisms, i.e. the transfer of albumin from the extravascular compartment and the decrease in catabolism, as has been demonstrated by isotopic studies (Cohen & Hansen, 1962; Picou & Waterlow, 1962; McFarlane, 1964; Hoffenberg, Black & Brock, 1966). However, by this method of study, since the measurements are not made in a steady state, it is theoretically impossible to ascertain what should be attributed to protein synthesis and what to the transfer of albumin from the extravascular to the intravascular compartment; but it may nevertheless be assumed that, in the absence of alimentary protein intake, there is no protein synthesis in the liver (Waterlow, 1964; Hoffenberg *et al.*, 1966). Because of the compensatory mechanisms affecting the homeostasis of circulating albumin in kwashiorkor, data obtained on the relative level of plasma proteins will not reflect the absolute

decrease in albumin until a certain time has elapsed. By contrast, free amino acids, and particularly essential amino acids, decrease rapidly in the plasma (Arroyave *et al.*, 1962; Holt *et al.*, 1963; Vis, 1963; Whitehead & Dean, 1964; Edozien & Obasi, 1965; Saunders *et al.*, 1967). Their homeostasis during a protein-deficient period depend on the catabolism of 'labile proteins', i.e. proteins which have a rapid turnover (Munro, 1964). These originate mainly from the liver, pancreas and intestinal mucosa, and disappear within 2 or 3 days. Saunders *et al.* (1967) claim that only the fasting aminogram of untreated cases is characteristic of the disease. The drop in protein synthesis in the liver also results in a decrease in plasma lipoproteins, and the transport of free fatty acids in the plasma is hampered by the drop in circulating albumin. These two facts explain how, in kwashiorkor, subcutaneous fat can be preserved and fatty infiltration of the liver can occur, while total lipids and cholesterol in the plasma drop to low levels (Schwartz & Dean, 1957). The metabolism of γ -globulins does not seem to be influenced directly by alimentary intake, and the level of serum globulins decreases much later than that of the albumins. A fall in the albumin-globulin ratio is in fact typical of pure kwashiorkor.

It has been shown that when plasma albumin is reduced through wastage without alimentary deficiency (nephrotic syndrome, plasmapheresis) the rate of protein synthesis in the liver is markedly increased (Hoffenberg *et al.*, 1966). The same phenomenon occurs in children with kwashiorkor during the early stages of adequate refeeding (Cohen &

TABLE 4. Amino acid residues obtained after the analysis of the non-collagen nitrogen (soluble in 0.05 N-NaOH) and the collagen nitrogen of striated muscles from children suffering from severe marasmus complicated by protein deficiency

	Non-collagen nitrogen		Collagen nitrogen	
	Before treatment	After treatment	Before treatment	After treatment
OH proline	—	—	9.04 ± 1.42	5.66 (4.95– 6.57)
Aspartic acid	10.14 ± 0.53	9.56 (9.35–10.45)	5.35 ± 0.62	6.86 (5.96– 7.43)
Threonine	5.26 ± 0.22	5.77 (5.41– 5.95)	2.20 ± 0.40	3.48 (2.73– 4.27)
Serine	5.32 ± 0.41	5.49 (5.18– 5.93)	3.74 ± 0.56	3.99 (3.61– 4.36)
Glutamic acid	16.39 ± 0.58	15.95 (14.24–17.23)	9.05 ± 1.23	7.01 (5.56– 7.87)
Proline	4.52 ± 0.29	4.82 (4.25– 4.86)	10.64 ± 1.59	12.23 (11.62–12.80)
Glycine	7.12 ± 0.43	7.40 (7.16– 7.93)	28.54 ± 3.64	21.98 (18.64–23.86)
Alanine	9.07 ± 0.37	9.39 (9.02–10.16)	10.62 ± 1.50	11.74 (9.94–12.41)
Valine	5.64 ± 0.59	6.52 (6.45– 7.06)	2.68 ± 0.57	3.67 (3.32–4.38)
Methionine	1.13 ± 0.32	2.24 (1.45– 2.74)	0.13 ± 0.15	0.43 (0.16– 0.78)
Isoleucine	4.88 ± 0.29	4.79 (4.56– 5.46)	1.26 ± 0.39	3.45 (3.24– 3.64)
Leucine	9.38 ± 0.41	8.45 (7.93– 9.21)	3.81 ± 0.71	6.42 (5.31– 6.97)
Tyrosine	2.17 ± 0.23	2.71 (2.31– 2.90)	tr.	0.35 (0.22– 0.71)
Phenylalanine	3.50 ± 0.25	3.70 (3.38– 3.99)	1.55 ± 0.56	1.69 (1.10–2.83)
OH lysine	0.58 ± 0.20	0.31 (0.23– 0.46)	0.44 ± 0.21	0.35 (0.22– 0.71)
Lysine	7.76 ± 0.93	6.66 (6.04– 7.15)	3.45 ± 0.58	4.78 (3.17– 5.88)
Histidine	2.17 ± 0.25	2.12 (1.47– 2.74)	0.81 ± 0.29	0.96 (0.57– 1.53)
Arginine	4.42 ± 0.56	3.93 (3.36– 4.81)	3.92 ± 0.78	4.79 (4.02– 5.41)

The results are expressed in % of the total amount of amino acid residues found. Before treatment: twenty-two cases (mean ± interval of confidence of the mean). After treatment: seven cases (range of the figures).

There is a relative increase of proline, hydroxyproline and glycine before treatment. On the other hand, there is no alteration of the intracellular pattern.

In marasmus the increase of the extracellular space (Table 3) indicates that the total cellular volume has decreased although the intracellular protein pattern remains constant (Table 4).

Hansen, 1962): the level of plasma albumin increases and reaches normal values after 10 or 12 days (Edozien & Obasi, 1965) and there is a temporary excess of cholesterol and lipids in the blood, whereas fatty infiltration of the liver takes 1–2 weeks to disappear.

In marasmus, whether in children or adults, there is no relative or absolute decrease of serum albumin. Nitrogen catabolism is nevertheless very considerable but it takes place mainly in striated muscles, which lose appreciable amounts of nitrogen. During the first days, labile proteins are used as a precarious reserve. The amino acids released by peripheral tissues in marasmus are recycled in the liver, and as the activity of the urea-cycle enzymes is reduced the amino acids are used in preference in the process of protein synthesis (Waterlow, 1964). Since the synthesis of plasma albumin and lipoproteins is normal, fatty acids may be conveyed from the adipose tissues, and there is no reason for fatty liver to occur. The longer nitrogen catabolism lasts in the muscles, the more we must expect to find slow-turnover proteins being preserved, especially collagen. This explains the relatively increased level of hydroxyproline in the muscle.

Table 4 gives the results of the analyses of intra- and extra-cellular proteins performed on striated muscle samples taken from marasmic children during the disease and after it has been cured. The proportion of glycine, proline and hydroxyproline (i.e.

collagen) is much higher in relation to the other amino residues of extracellular proteins before treatment than afterwards. But no significant difference can be shown in the patterns of amino residues from intracellular tissues.

The rate of catabolism of collagen is greatly reduced in the malnourished infant (Picou, Alleyne & Seakins, 1965). The urinary excretion of hydroxyproline peptides depends on the rate of growth. Whitehead (1965) described an index urinary hydroxyproline × body weight/creatinine which is low in both marasmus and kwashiorkor.

Subcutaneous adipose tissues

Lipolysis in the adipose tissues is normally continuous, which would lead to the accumulation of free fatty acids if these were not constantly reforming triglycerides from the L α -glycerophosphate coming from the glycolysis. This synthesis of triglycerides is encouraged by the action of insulin and inhibited by epinephrine, ACTH and growth hormone. Not only α -glycerophosphate but also fatty acids can be formed from glucose. The accumulation of free fatty acids inhibits new synthesis by a feedback mechanism, slowing down the conversion of fructose-6-phosphate into fructose 1-6-diphosphate and the acetyl-CoA carboxylase reaction (see Shapiro, 1965).

An individual whose diet is quantitatively deficient loses his subcutaneous fat more or less rapidly.

Since the supply in glucose is insufficient, little glycerophosphate is formed and free fatty acids accumulate. These can be carried in the plasma since the level of plasma proteins is normal in conditions of undernourishment resulting from low-calorie but otherwise balanced diets. These free fatty acids will serve as a source of energy for the other tissues or will reach the liver and be esterified into triglycerides or serve to synthesize phospholipids and lipoproteins.

In marasmus there is thus a wasting of the subcutaneous fatty tissues and there is no reason for fat to accumulate in the liver. In the child suffering from kwashiorkor, however, the situation is quite different. The subcutaneous adipose tissue is preserved and fatty infiltration of the liver develops (Behar *et al.*, 1957). The cause of this essential difference between the two syndromes lies in the excess supply of carbohydrates in the diet that characteristically gives rise to kwashiorkor. The latter causes secondary hyperinsulinism, and some authors such as Dupin (1958) have described a hypertrophy of the islets of Langerhans caused by the β cells in the pancreas. The presence of sizeable quantities of glucose and insulin encourages the formation and esterification of free fatty acids and the accumulation of triglycerides in the subcutaneous adipose tissue. The low levels of plasma albumin and the drop in lipoprotein synthesis in the liver explain the necessary fat storage, and thus the hepatic infiltration which is characteristic of protein malnutrition (Waterlow, 1948; Waterlow & Weisz, 1956; Mendez & Tejada, 1962). In its turn, the above described hyperinsulinism stimulates protein synthesis in the striated muscles, and inhibits this process in the liver (Munro, 1964).

Oedema—water and electrolyte metabolism

The presence of an abnormally high quantity of water in the organism depends on several factors: the osmotic pressure of the proteins, the hydrostatic pressure in the veins, the state of the capillaries, the balance of water and sodium chloride, the secretion of aldosterone, the secretion of the antidiuretic hormone and finally the quantity of fat and collagen in the cutaneous and subcutaneous tissues.

In marasmic children there is intense nitrogen catabolism in the muscles, accompanied by a depletion in potassium. The nitrogen loss seems to take place mainly at the expense of the intracellular substance although eventually certain extracellular proteins also tend to disappear (Table 4). But on the whole, the extracellular space (chloride space) becomes relatively larger without there necessarily being more water in absolute terms (isohydric oedema). Keys *et al.* (1950) have revealed definite cases of haemodilution in adults suffering from

famine oedema (which are really cases of marasmus): thus, in addition to isohydric oedema, there is retention of water and sodium chloride. It will not be forgotten that during fat combustion there is a perceptible endogenous water supply since the combustion of fat in the presence of oxygen produces a higher weight in water than the original weight in fat.

Since the myocardium undergoes the same changes as the striated muscle in the marasmic process, there will, therefore, be a tendency towards heart failure (Wharton, Howells & McCance, 1967) and an increase in hydrostatic pressure. The pitting oedema appearing on the feet and legs of undernourished adults during or after the last war could not always be explained by increased hydrostatic pressure or by a fall in the osmotic pressure due to the proteins (Medical Research Council, 1951). Although the marasmic organism has a high water content in the active tissues (expressed per unit of non-fatty dry solids) and although this water is mainly extracellular, clinical oedema does not usually occur.

Although oedema formation in pure kwashiorkor is chiefly dependent on the drop in intravascular osmotic pressure, other factors are nevertheless important, namely the intake of water and sodium chloride, and possible secondary hyperaldosteronism (Lurie & Jackson, 1962). The presence of oedema is detected clinically by examining the cutaneous tissue. Frenk *et al.* (1957) have stressed that the cutaneous and subcutaneous tissues (fat and collagen) play an important role in the possible formation of oedema; so there is not necessarily a good correlation between the size of the clinical oedema and the abnormally high accumulation of water in the organism.

Most authors who have investigated protein-calorie malnutrition in children have noted a considerable depletion of the potassium stores (Hansen, 1956; Pille, 1957), attaining a 30% drop in certain cases. There also seems to be a drop in the magnesium stores (Linder, Hansen & Karabus, 1963; Montgomery, 1961; Garrow, 1965). Vis *et al.* (1965) did not find such a considerable fall in potassium stores; the balance tests showed that each gram of nitrogen lost was accompanied by only 3–4 mm of potassium. It seems that the absolute depletion in potassium is an additional factor in protein-deficient conditions which does not depend so much on nitrogen catabolism as on the potassium supply in the food and on the severity of the diarrhoea. This does not mean that the problem might not be more complex since Garrow, Fletcher & Halliday (1965) have shown that certain tissues, such as the brain, can suffer an appreciable drop in their potassium stores while the rest of the organism shows little or no depletion.

The main blood buffers are represented by bicarbonate, proteins and haemoglobin. In acquired marasmus, the level of circulating haemoglobin is low because the blood tissue wastes away in the same proportion as the active tissue (Keys *et al.*, 1950), but this drop is insufficient to disturb the blood pH. The marasmic child often suffers phases of diarrhoea with an absolute drop in bicarbonate with a consequent compensated or non-compensated hyperchloraemic acidosis (Dubois, Van der Borgh & Vis, 1968). In pure kwashiorkor diarrhoea is less frequent, but there is a decrease in haemoglobin and protein buffers in the blood although in most cases the pH is normal.

Since the buffer reserves are low in either case, the pH will fall more easily than under normal conditions. Furthermore, the use of the classical nomogram is not possible in cases of undernourishment and it is still difficult to determine the various disturbances exactly (Moon, 1967).

Enzyme activities

Veghelyi (1950) has drawn attention to the fact that in protein-deprived children, of the kwashiorkor type, there is a diminution and even cessation of the activity of enzymes of pancreatic origin in the duodenal fluid. For the liver enzymes, however, the situation is more complex: Waterlow & Patrick (1954) have shown that the activity of a great number of enzymes remains unchanged, notably that of enzymes from the oxidation-reduction chain (DPN-cytochrome C-reductase, succinic dehydrogenase and cytochrome oxidase). The same seems to be true for liver transaminase (Burch *et al.*, 1957). In addition, the activity of other pancreas-originating enzymes has been found to be decreased in the plasma, notably that of amylase and lipase.

The drop in lactase activity of the jejunum is very marked in African children suffering from pure kwashiorkor or marasmus (Cook & Lee, 1966), and this fact is confirmed by the difficulties experienced when trying to feed milk. The problem has in fact proved to be more complex than was originally supposed since Cook & Kajubi (1966) have shown that the lactase deficiency must be considered congenital and not acquired in certain African tribes. The enzyme disorders encountered in protein-deficient conditions of the pure kwashiorkor type make the interpretation of anaemia difficult. Temporary metabolic blockages during histidine catabolism, which have been observed in several regions, very often conceal a folic acid deficiency because the urinary elimination of formiminoglutamic acid increases only after the administration of a protein-rich diet (Velez *et al.*, 1963; Ghitis *et al.*, 1963; Allen & Whitehead, 1965).

Conclusion

Marasmus and pure protein malnutrition, as defined at the beginning of this study, are two quite distinct conditions of dietary deficiency in children, the first characterized by retarded growth and modifications in the biochemical structure of the bones, the second by changes in the internal organs (liver, pancreas and intestine) and in the skin and hair.

Marasmus is either the effect of an extremely slow growth-rate or the consequence of a previously normal subject being submitted suddenly to a globally deficient diet. In either case the organism is adapting itself to insufficient food intake. Kerpel-Fronius (1957) stressed the drop in basic metabolism and oxygen consumption in marasmic children. More recently, Haxhe (1967a, b) has observed that dogs submitted to a starvation diet show signs of anaemia in proportion to tissue wasting, thus confirming the findings of Keys *et al.* (1950). For Haxhe (1967a, b), anaemia under conditions of starvation should be considered as an adaptation to the reduced oxygen demand, since it is not accompanied by a rise in cardiac output. McCance (1960), on the other hand, found no anaemia in pigs submitted to a deficient diet shortly after birth, but in such cases the organism adapts to deficient intakes by an extremely slow growth-rate, without any tissue wasting. In marasmus, whatever its cause, protein synthesis continues in the liver, pancreas and digestive tract: the level of proteins in the blood remains normal and there are no changes in the enzymatic activities of these tissues. All this is markedly different from the condition of children suffering from protein malnutrition. The size of the carbohydrate intake in the protein-deficient diet decides whether the undernourished child will eventually develop symptoms of kwashiorkor or marasmus, i.e. whether the liver or the muscles suffer the most from nitrogen catabolism.

One essential fact in kwashiorkor is that clinical symptoms such as oedema appear rapidly after the child's subjection to the deficient diet (Viteri *et al.*, 1964; Garrow, 1966). Metabolic changes such as the decrease in essential amino acids and plasma albumin, the cessation of certain enzyme activities, the impossibility of mobilizing fat, all bear witness to the severely disturbed state of the organism. Anaemia is also present, but is no longer the consequence of adaptation but rather a reflection of the enzyme disorders affecting histidine metabolism or of the reduction in the synthesis of erythropoietin and haemoglobin.

In practice, so long as an infective disease or an additional electrolyte or vitamin deficiency does not combine with the patient's protein-deficient condition, it should normally be possible to define the

exact form of malnutrition fairly accurately, provided that data are available on age, previous diet, height and weight deficits by comparison with an average local curve, the proportion of subcutaneous adipose tissue that is maintained, the presence or absence of liver fatty infiltration, the ratio between essential and non-essential amino acids in the plasma, the level of albumin in the plasma and the urinary hydroxyproline/creatinine index. In communities where malnutrition prevails, it is often impossible to know the exact age of a subject and thus to draw a local growth-curve. It is because of these difficulties that more simple means for defining malnutrition have been proposed, for instance by the FAO/WHO Joint Expert Group in 1962, by Gomez *et al.* (1955) (a method based solely on weight deficit by comparison with the Boston curve), or by McLaren, Pellett & Read (1967). Since many investigators define their cases according to these classifications, the data in different articles are often not only confused but also contradictory.

References

- ALLEN, D.M. & WHITEHEAD, R. (1965) The excretion of urocanic acid and formimino glutamic acid in megaloblastosis accompanying kwashiorkor. *Blood*, **25**, 283.
- ARROYAVE, G., WILSON, D., DE FUNES, C. & BEHAR, M. (1962) The free amino acids in blood plasma of children with kwashiorkor and marasmus. *Amer. J. clin. Nutr.* **11**, 517.
- BEHAR, M., ARROYAVE, G., TEJADA, C., VITERI, F., & SCRIMSHAW, N.S. (1957) *Desnutricion Severa en la Infancia*. Publicaciones Cientificas del INCAP, Guatemala. Monographia No. 3.
- BURCH, H.B., ARROYAVE, G., SCHWARTZ, R., PADILLA, A.M., BEHAR, M., VITERI, F. & SCRIMSHAW, N.S. (1957) Biochemical changes in liver associated with kwashiorkor. *J. clin. Invest.* **36**, 1579.
- CHEEK, D.B. (1968) Cellular growth—hormones, nutrition and time. *Pediatrics*, **41**, 30.
- COHEN, S. & HANSEN, J.D.L. (1962) Metabolism of albumin and globulin in kwashiorkor. *Clin. Sci.* **23**, 351.
- COOK, G.C. & KAJUBI, S.K. (1966) Tribal incidence of lactase deficiency in Uganda. *Lancet*, **i**, 725.
- COOK, G.C. & LEE, F.D. (1966) The jejunum after kwashiorkor. *Lancet*, **ii**, 1263.
- DEAN, R.F.A. (1965) Kwashiorkor. *Recent Advances in Pediatrics* (Ed. by D. Gairdner) 3rd edn, p. 234. Churchill, London.
- DICKERSON, J.W.T. & WIDDOWSON, E.M. (1960) Chemical changes in skeletal muscle during development. *Biochem. J.* **74**, 247.
- DUBOIS, J., VAN DER BORGH, H. & VIS, H.L. (1968) Etude des troubles électrolytiques accompagnant le kwashiorkor marastique. II. Perturbation de l'équilibre acide-base. *Rev. franç. Étud. clin. Biol.* **13**, 153.
- DUPIN, H. (1958) *Etude des Carences Protidiques Observées Chez l'Enfant en Pays Tropical (Kwashiorkor)*. Librairie Arnette, Paris.
- EDOZIEN, J.C. & OBASI, M.E. (1965) Protein and amino acid metabolism in kwashiorkor. *Clin. Sci.* **29**, 1.
- FRENK, S., METCOFF, J., GOMEZ, F., RAMOS-GALVAN, R., CRAVIOTO, J. & ANTONOWICZ, I. (1957) Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition. II. Composition of tissues. *Pediatrics*, **20**, 105.
- GALLEZ, A. (1960) Contribution à l'étude des populations indigènes congolaises en milieu sous-développé. *Ann. Soc. belge Méd. Trop.* **40**, 481.
- GARN, S.M. & ROHMANN, C.G. (1966) Interaction of nutrition and genetics in the timing of growth and development. *Pediat. Clin. N. Amer.* **13**, 353.
- GARROW, J.S. (1965) Total body-potassium in kwashiorkor and marasmus. *Lancet*, **ii**, 455.
- GARROW, J.S. (1966) 'Kwashiorkor' and 'marasmus' in Jamaican infants. *Arch. Lat. Amer. Nutr.* **16**, 145.
- GARROW, J.S., FLETCHER, K. & HALLIDAY, D. (1965) Body composition in severe infantile malnutrition. *J. clin. Invest.* **44**, 417.
- GHITIS, J., VELEZ, H., LINARES, F., SINISTERRA, L. & VITALE, J.J. (1963) Cali-Harvard nutrition project. II. The erythroid atrophy of kwashiorkor and marasmus. *Amer. J. clin. Nutr.* **12**, 445.
- GOMEZ, F., RAMOS-GALVAN, R., CRAVIOTO, J. & FRENK, S. (1955) Malnutrition in infancy and childhood with special reference to kwashiorkor. *Advanc. Pediat.* **7**, 131.
- HANSEN, J.D.L. (1956) Electrolyte and nitrogen metabolism in kwashiorkor. *S. Afr. Lab. clin. Med.* **2**, 206.
- HAXHE, J.J. (1967a) Experimental undernutrition. I. Its effects on cardiac output. *Metabolism*, **16**, 1086.
- HAXHE, J.J. (1967b) Experimental undernutrition. II. The fate of transfused red blood cells. *Metabolism*, **16**, 1092.
- HOLT, L.E., Jr, SNYDERMAN, S.E., NORTON, P.M., ROITMAN, E. & FINCH, J. (1963) The plasma aminogram in kwashiorkor. *Lancet*, **ii**, 1343.
- HOFFENBERG, R., BLACK, E. & BROCK, J.F. (1966) Albumin and γ -globulin tracer studies in protein depletion states. *J. clin. Invest.* **45**, 143.
- JELLIFFE, D.B., BRAS, G. & STUART, K.L. (1954) Kwashiorkor and marasmus in Jamaican infants. *West Ind. med. J.* **3**, 43.
- JONES, P.R.M. & DEAN, R.F.A. (1956) The effects of kwashiorkor on the development of the bones of the hand. *J. trop. Pediat.* **2**, 51.
- KERPEL-FRONIUS, E. (1957) Metabolic disturbances in infantile malnutrition. *Mod. Probl. Paed.* **2**, 146.
- KEYS, A., BROZEK, J., HENSCHEL, A., MICKELSEN, O. & TAYLOR, T. (1950) *The Biology of Human Starvation*, Vols. I and II. The University of Minnesota Press, Minneapolis.
- LINDER, G.C., HANSEN, J.D.L. & KARABUS, C.D. (1963) Metabolism of magnesium and other inorganic cations and of nitrogen in acute kwashiorkor. *Pediatrics*, **31**, 552.
- LISTER, D. & MCCANCE, R.A. (1967) Severe undernutrition in growing and adult animals. XVII. The ultimate results of rehabilitation: Pigs. *Brit. J. Nutr.* **21**, 787.
- LURIE, A.O. & JACKSON, W.P.U. (1962) Aldosteronuria and the edema of kwashiorkor. *Amer. J. clin. Nutr.* **11**, 115.
- MCCANCE, R.A. (1960) Severe undernutrition in growing and adult animals. I. Production and general effects. *Brit. J. Nutr.* **14**, 59.
- MCCANCE, R.A. (1968) The effect of calorie deficiencies and protein deficiencies early in life on final weight and stature. *Calorie Deficiencies and Protein Deficiencies* (Ed. by R.A. McCance and E.M. Widdowson). p. 319. Churchill, London.
- McFARLANE, A.S. (1964) *Metabolism of Plasma Proteins in Mammalian Protein Metabolism* (Ed. by H. N. Munro and J. B. Allison), Vol. I, p. 297. Academic Press, New York.
- McLAREN, D.S., PELLETT, P.L. & READ, W.W.C. (1967) A simple scoring system for classifying the severe forms of protein-calorie malnutrition of early childhood. *Lancet*, **i**, 533.
- MEDICAL RESEARCH COUNCIL (1951) *Studies of Undernutrition-Wuppertal 1946-49*. Special report series No. 275.

- MENDEZ, J. & TEJADA, C. (1962) Liver composition in kwashiorkor and marasmus. *Exp. molec. Pathol.* **1**, 344.
- MONTGOMERY, R.D. (1961) Magnesium balance studies in marasmic kwashiorkor. *J. Pediat.* **59**, 119.
- MOON, J.B. (1967) Abnormal base excess curves. *Pediat Res.* **1**, 333.
- MUNRO, H.N. (1964) The regulation of protein metabolism by diet and by hormones. *Mammalian Protein Metabolism* (Ed. by H. N. Munro and J. B. Allison), Vol. I, p. 381. Academic Press, New York.
- MUNRO, H.N. (1966) Relationship between body protein synthesis and protein intake. *Nutr. Dieta.* **8**, 179.
- NELSON, W.E. (1964) *Textbook of Pediatrics*, 8th edn, p. 48. Saunders, Philadelphia.
- PICOU, D. & WATERLOW, J.C. (1962) The effect of malnutrition on the metabolism of plasma albumin. *Clin. Sci.* **22**, 459.
- PICOU, D., ALLEYNE, G.A.O. & SEAKINS, A. (1965) Hydroxyproline and creatinine excretion in infantile protein malnutrition. *Clin. Sci.* **29**, 517.
- PILLE, G. (1957) *Le Controle du traitement du Kwashiorkor au Laboratoire de Biochimie Clinique*, 1 volume. O.R.A.N.A., Dakar.
- PLATT, B.S. & STEWART, R.J.C. (1962) Transverse trabeculae and osteoporosis in bones in experimental protein-calorie deficiency. *Brit. J. Nutr.* **16**, 483.
- PLATT, B.S., HEARD, C.R.C. & STEWART, R.J.C. (1964) Experimental protein-calorie deficiency. *Mammalian Protein Metabolism* (Ed. by H. N. Munro and J. B. Allison), Vol. II, p. 445. Academic Press, New York.
- POLIAKOV, L. (1946) Auschwitz. *Collection Archives*, p. 202. Julliard, France.
- SAUNDERS, S.J., TRUSWELL, A.S., BARBEZAT, G.O., WITTMAN, W. & HANSEN, J.D.L. (1967) Plasma free amino-acid pattern in protein-calorie malnutrition. Reappraisal of its diagnostic value. *Lancet*, **ii**, 795.
- SHAPIRO, B. (1965) Regulations of lipid metabolism. *Israël J. med. Sci.* **1**, 1244.
- SCHWARTZ, R. & DEAN, R.F.A. (1957) The serum lipids in kwashiorkor. I. Neutral fats, phospholipids and cholesterol. *J. trop. Pediat.* **3**, 23.
- TANNER, J.M. (1968) Earlier maturation in man. *Scient. Amer.* **218**, 21.
- VEGHELY, P.V. (1950) Nutritional edema. *Ann. Paediat.* **175**, 349.
- VELEZ, H., GHITIS, J., PRADILLA, A. & VITALE, J.J. (1963) Cali-Harvard nutrition project. I. Megaloblastic anemia in kwashiorkor. *Amer. J. clin. Nutr.* **12**, 54.
- Vis, H.L. (1963) *Aspects et Mechanismes des Hyperaminoaciduries de l'Enfance*. Arsacia, Bruxelles and Maloine, Paris.
- Vis, H.L. (1968) General and specific metabolic patterns of marasmic kwashiorkor in the Kivu area. *Calorie Deficiencies and Protein Deficiencies* (Ed. by R. A. McCance and E. M. Widdowson), p. 119. Churchill, London.
- Vis, H.L., DUBOIS, R., VAN DER BORGH, H. & DE MAEYER, E. (1965) Etude des troubles électrolytiques accompagnant le kwashiorkor marastique. *Rev. franç. Étud. clin. Biol.* **10**, 729.
- VITERI, F., BEHAR, M., ARROYAVE G. and SCRIMSHAW, N.S. (1964) Clinical aspects of protein malnutrition. *Mammalian Protein Metabolism* (Ed. by H. N. Munro and J. B. Allison), p. 523. Academic Press, New York.
- WATERLOW, J.C. (1948) *Fatty Liver Disease in Infants in the British West Indies*. Medical Research Council, Special Report Series No. 263.
- WATERLOW, J.C. (1964) Observations on protein metabolism in relation to nutrition. *Panel on Radio-Isotope Techniques in the Study of Protein Metabolism*. PL 120/32. International Atomic Energy Agency, Vienna.
- WATERLOW, J.C. & PATRICK, S.J. (1954) Enzyme activity in fatty liver in human infants. *Ann. N.Y. Acad. Sci.* **57**, 750.
- WATERLOW, J.C. & WEISZ, T. (1956) The fat, protein and nucleic acid content of the liver in malnourished human infants. *J. clin. Invest.* **35**, 346.
- WATERLOW, J.C., CRAVIOTO, J. & STEPHEN, J.M.L. (1960) Protein malnutrition in man. *Advanc. Protein Chem.* **15**, 131.
- WHARTON, B.A., HOWELLS, G.R. & MCCANCE, R.A. (1967) Cardiac failure in kwashiorkor. *Lancet*, **ii**, 384.
- WHITEHEAD, R.G. (1965) Hydroxyproline creatinine ratio as an index of nutritional status and rate of growth. *Lancet*, **ii**, 567.
- WHITEHEAD, R.G. & DEAN, R.F.A. (1964) Serum amino acids in kwashiorkor. I. Relationship to clinical condition. *Amer. J. clin. Nutr.* **14**, 313.
- WIDDOWSON, E.M., DICKERSON, J.W.T. & MCCANCE, R.A. (1960) Severe undernutrition in growing and adult animals. VI. The impact of severe undernutrition on the chemical composition of the soft tissues of the pig. *Brit. J. Nutr.* **14**, 457.