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CHARACTERISTICS OF KWASHIORKOR[1] (SINDROME PLURICARENCIAL DE LA INFANCIA)

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SÍNDROME PLURICARENCIAL DE LA INFANCIA, as it is known throughout Latin America, or Kwashiorkor as it is called in most other areas of the world, is not only attracting increasing attention as a major disease entity but is also becoming much better understood. Indeed at the recent Princeton Conference on Protein Malnutrition in Children, sponsored by the Food and Agriculture Organization, the World Health Organization and the Josiah Macy Jr. Foundation, workers from seven different centers on three continents expressed a very large measure of agreement as to the characteristics of Kwashiorkor (1). After noting the clinical signs and symptoms and pathological findings generally agreed upon as characterizing the syndrome, we propose to review its known biochemical and physiological characteristics.

CLINICAL CHARACTERISTICS

Retarded growth and development are a consequence of the severe protein malnutrition characteristic of children with Kwashiorkor. It occasionally happens, however, that the process is so acute that the adverse effect on growth does not become manifest in the relatively short time before appearance of clinical symptoms. The changes of apathy and anorexia are also prominent clinical features and the rapid recovery from these symptoms is a good prognostic sign in treated cases. The child is also frequently hyperirritable. In all cases there is some degree of loss of muscle tone.

Edema is a constant finding and may often be very severe. The skin changes include atrophy, and areas of hyperkeratosis with pigmentation. Excoriations and secondary infection frequently may develop. The skin lesions are pellagroid in appearance but unlike those of pellagra are not confined principally to areas exposed to sunlight. Instead they are often severe over the trunk. Frequently acrocyanosis and a variegated pattern of erythema are observed in areas where the pellagroid lesions are not apparent.

The hair changes may include alterations of texture as well as of color. The hair is likely to be thin, dry, sparse and easily pulled out. It is usually abnormally pale and in some individuals acquires a reddish tint. The nails may be soft, irregular and show transverse lines of diminished growth.

PATHOLOGICAL CHARACTERISTICS

The liver shows fatty change which is often so severe as to involve almost every cell and obliterate the lumen of the sinusoids. A proliferation of the portal reticulum is also observed. Subsequently the proliferation increases producing a star-like pattern and, later on, a ring of reticulum fibers surrounds each lobule to produce a monolobular reticulosis. The pancreas may initially appear enlarged but is more generally found at autopsy to be atrophied. The acini always show moderate to severe atrophy and a reduction in the number of secretory granules. Fibrosis is likely to be present and may be severe.

Some degree of atrophy of the wall is found in the intestine and stomach and gross dilatation is frequent at autopsy. The skin and skin appendages show atrophy especially in the region of gross lesions. The skin is also characterized by hyper- and parakeratosis. Atrophy of the follicles of the thyroid and a decrease in colloid substance together with interstitial fibrosis appear to be particularly severe in Central American cases (2). This is probably related to the prevalence

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of endemic goiter in the same areas, but thyroid changes have also been described from Africa (3). The adrenal cortex shows atrophy and loss of lipids. Sometimes fatty degeneration of the kidney tubules is also encountered.

HEMATOLOGICAL FINDINGS

A mild to moderate degree of anemia is a constant finding in Kwashiorkor, but the type may be microcytic, normocytic or macrocytic. We believe that the basic anemia associated with the protein deficiency of this syndrome is normocytic or mildly macrocytic in type and associated with a hypoplasia of the erythroblastic series in the bone marrow. Such an anemia responds readily to the feeding of skim milk alone as determined by a marked reticulocyte response and the renewal of erythroblastic activity in the bone marrow, illustrated in figure 1.

The presence of hookworm or chronic malaria may result in the appearance of microcytic hypochromic anemia which requires supplementary iron for a satisfactory therapeutic response. Even when the anemia is normocytic or macrocytic it is probable that iron stores are also inadequate. At least we have often seen macrocytic anemias become microcytic as dietary treatment was continued without supplementary iron.

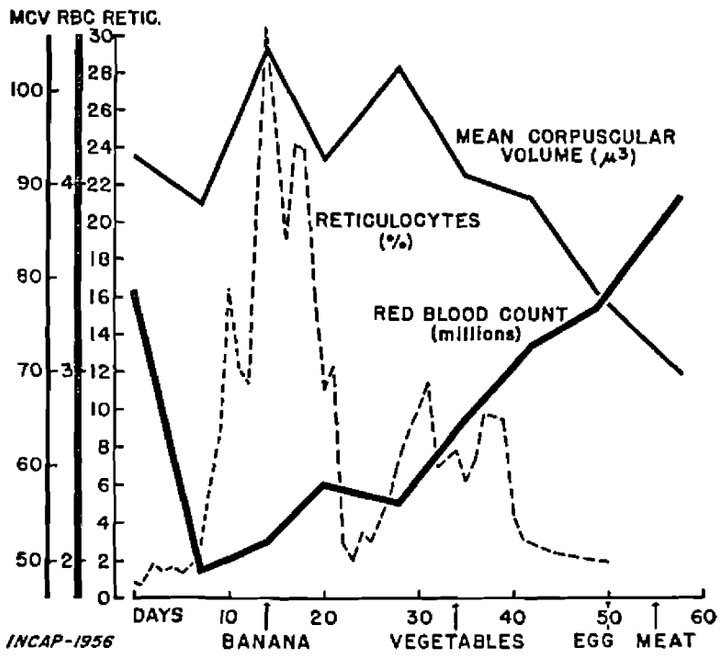

FIG. 1. Anemia in a 22-month-old girl with kwashiorkor. A prompt reticulocyte response was obtained from the administration of half skim milk alone with an accompanying increase in red blood cell count. The initial drop is due to hydration. When supplementary iron was given at the end of the period shown, a second reticulocyte response was obtained and the mean corpuscular volume returned to normal.

PARASITOLOGICAL FINDINGS

In general the intestinal parasites encountered are the same as those in children without Kwashiorkor in the same economic and social groups. Undoubtedly the parasitic infestation hastens the development of Kwashiorkor by interfering with the utilization of food, but there are no experimental studies to demonstrate this and the development of Kwashiorkor is not dependent on the presence of any particular species or combination of species of intestinal parasites.

BACTERIOLOGICAL FINDINGS

Studies in INCAP have identified Shigella organisms in 9.4% of 32 cases, but this is the same frequency with which they were recovered from non-Kwashiorkor cases hospitalized at the same time. However, since the diarrhea has usually been present for many weeks before hospitalization, the percentage of Shigella or Salmonella recoveries would be small even if the diarrhea were originally bacterial in origin.

Despite the relatively negative nature of the laboratory findings, there seems little doubt that infectious diarrhea plays an important part in the chain of events that leads a chronically malnourished child to develop frank Kwashiorkor. This has been discussed in detail in previous publications (4, 5).

BIOCHEMICAL FINDINGS

Total Protein in Blood. There is general agreement among all workers that serum total protein is low in Kwashiorkor and that if recovery is to occur the levels return to normal within two to three weeks after the initiation of good dietary treatment. The decrease is due principally to the lowering of serum albumin and hence the determination of albumin is a slightly more sensitive measurement of response to therapy. Since it has also been observed that the percentage of total globulin is increased, the albumin/globulin ratio is initially reversed and the normal ratio restored by therapy.

Electrophoretic studies (6–9) have demonstrated that the increase occurs in the alpha globulin fraction, particularly the alpha[1], as well as in the gamma globulin. The beta globulin component is little affected. Dean and Schwartz (6) have reported an unknown component mi-

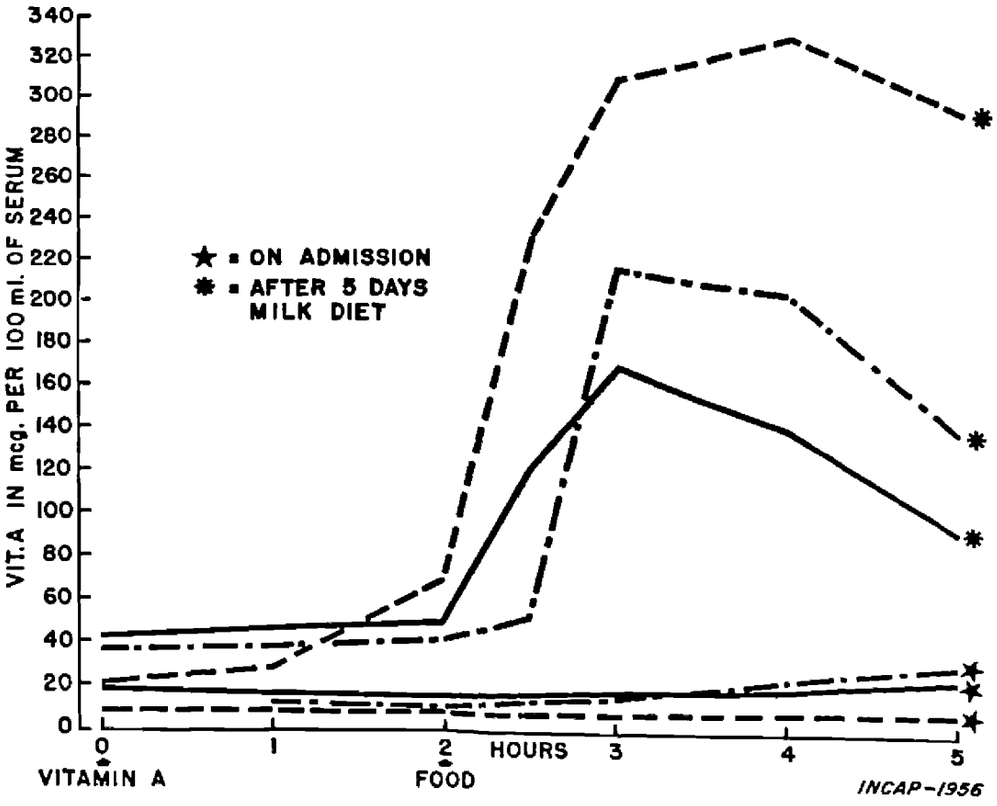

FIG. 2. Serum vitamin A in Kwashiorkor after oral administration of vitamin A palmitate. Administration of a single dose of 75,000 mcg. vitamin A palmitate by stomach tube produced no response in acute Kwashiorkor cases on admission, even when a test meal was given at the end of two hours. A marked increase in serum vitamin A was obtained in the same test following five days of treatment.

grating between the alpha[2] and beta fractions in several cases. In more detailed electrophoretic studies Close (7) reports that the curves suggest a number of additional protein fractions which may represent either normal components visible because of the low albumin values or the presence of unknown abnormal fractions.

Vitamins in Blood. *Vitamin A and carotene.* In Central America we have consistently found exceedingly low carotene and vitamin A serum levels (5, 8). The values determined by the method of Bessey *et al.* (10) are given in table 1 for nine recent cases. The values rise with good diet therapy to essentially normal limits in two to three weeks. Since vitamin A deficiency is common in Central America, but not in all areas of the world in which the syndrome occurs, it is not certain that low serum vitamin A and carotene levels will prove to be a constant finding. However, Moore and Sharman (11) and Trowell, Moore and Sharman in Uganda (12) also report very low carotene values in Kwashiorkor.

In view of the lowered duodenal enzyme activity and disturbed gastrointestinal function discussed subsequently, it is not surprising to find the absorption of fat soluble vitamins to be grossly abnormal. In our studies 75,000 micrograms of vitamin A palmitate in oil administered by stomach tube produced no detectable effect in five hours on the serum levels of children with Kwashiorkor, even when a meal was given two hours later as suggested by Mendeloff (13). As illustrated in the three cases in figure 2, a very marked and prompt response was observed to the same test following five days of treatment.

Vitamin E. The serum vitamin E levels are relatively low initially but also rise promptly and markedly with treatment as illustrated in table 1. (The method of Quaife *et al.* (14) was employed.) Trowell in Uganda (12) also reports low vitamin E values and believes that they reflect the generalized failure in intestinal absorption illustrated by the vitamin A and carotene findings.

Thiamine. No blood thiamine values have been previously reported for children with Kwashiorkor. The data presented in table 1 were obtained using the method of Burch *et al.* (15) and do not appear to be low. There is, however, a significant increase following three to five weeks of hospital treatment.

Riboflavin. Riboflavin values have been reported previously only from this laboratory (5, 8) and the average values stated to be within normal limits. Recent average values of assays

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TABLE 1. BLOOD VITAMIN LEVELS IN KWASHIORKOR

Constituent	No.	Content/100 ml	
		Upon admission	After recovery
		μg	
Carotene	9	5.0	139‡
Vitamin A	9	12.8	34.1‡
Vitamin E§	7	0.39	0.64‡
Thiamine*	4	5.23	6.83‡
Free riboflavin†	9	0.59	1.82‡
Total riboflavin	9	1.58	3.79‡

* Determined in whole blood—all other assays were made with blood serum.

† Free plus a very small amount of flavin mononucleotide.

‡ Difference is significant at the 1% level.

§ mg/100 ml.

for both total and 'free' fractions are given in table 1. The individual levels vary greatly from extremely low values to ones as high or higher than those found in normal individuals. This is true for both the 'free' or unhydrolyzed fraction (free riboflavin plus the flavin mononucleotide) and the total riboflavin (unhydrolyzed fraction plus the flavin adenine dinucleotide) as determined by the method of Burch *et al.* (16). The increase with treatment is significant, probably due to the high riboflavin content of the large amount of milk given.

Ascorbic acid. Although serum ascorbic acid values have been previously reported from this laboratory as lying within normal limits (5, 8), they are omitted from table 1 because the situation is proving to be more complex than at first realized. In many cases very high ascorbic acid values, as determined by the method of Lowry *et. al.*(17), employing the modification suggested by Goodland *et al.* (18), are obtained. It now appears probable that these high values in certain Kwashiorkor cases are an artifact due to some as yet unidentified substance. Whatever the cause, the apparent ascorbic acid values of those cases which are initially high drop markedly in the first few days of treatment before rising to the essentially normal levels found on discharge. No ascorbic acid values in Kwashiorkor have as yet been reported from other laboratories.

Vitamins in Tissues. We have determined vitamin A in the livers of nine cases of Kwashiorkor by an adaptation of the methods of Sobel and Werbin (19) and Ames *et al.* (20). The results, shown in table 2, are exceedingly low in comparison with the one excellently nourished case and the one in fairly good nutritional state which we have thus far been able to obtain.

TABLE 2. LEVELS OF SOME LIVER CONSTITUENTS IN KWASHIORKOR (per 100 gm of fresh tissue)

Constituent	Kwashiorkor 9 cases		Moderately well nourished 1 case	Excellently nourished 1 case
	m	*s*		
Thiamine, mg	0.09	0.06	0.08	0.12
Riboflavin, mg	0.68	0.14	0.82	0.56
Niacin, mg	5.84	2.18	7.89	13.23
Vitamin A, mg	3.50	2.63	13.23	95.65
Protein, gm	10.9	1.4	15.2	18.7
Fat, gm	24.7	11.7*	2.6	4.4

* The large standard deviation is due to an unusually low value of 9.0%. All other values ranged between 18.6 and 37.1.

Niacin values obtained by the microbiological method of the United States Pharmacopeia (21), thiamine by the method of Hennessey and Cerecedo (22) and riboflavin by the method of Hodson and Norris (23) all closely resembled those in the child considered to be in fairly good nutritional state. They differed significantly from the excellently nourished case only in lower niacin values. Until more information is available on the range of values in normal children, caution is necessary for the interpretation of these data.

Minerals in Blood. The average values for blood serum calcium in 13 acute cases of Kwashiorkor recently studied by us was 10.1 mg/100 ml (s 2.0)[3]. For 11 of these cases the value for serum phosphorus was found to be 3.74 mg/100 ml (s 0.7). Both averages are similar to those found in the Belgian Congo (24). Although these values are considered to be within normal limits, slightly lower levels for calcium have been reported from Brazil (25) and Egypt (26).

Enzymes in Blood. *Alkaline phosphatase.* Average alkaline phosphatase values are low in Kwashiorkor cases on admission and rise rapidly with treatment (5, 6, 8). This is illustrated by the values in table 3, obtained by the method of Bessey *et al.* (27). Dean (28) has shown that in some cases there is actually a slightly further drop in alkaline phosphatase at the beginning of treatment, a decrease which is also seen in most Central American cases. He attributes

[3] These analyses were carried out in the Instituto Agropecuario Nacional, Guatemala, through the cooperation of Dr. Robert L. Squibb, Chief of the Department of Animal Husbandry and Nutrition.

this to two fractions, one activated by magnesium and the other inhibited by cyanide, which are relatively high while the principal alkaline phosphatase of blood serum is low. These drop rapidly on treatment while the latter is rising.

Amylase, lipase and esterase. Although measured in the blood, amylase, lipase and esterase have their principal origin in the pancreas, and therefore are useful indicators of altered pancreatic function in the syndrome.

Workers in Uganda (6), the Belgian Congo (29) and ourselves in Central America (8) find serum amylase low in Kwashiorkor and agree that its prompt rise is one of the best indicators of initial recovery. Representative values obtained by the method of Smith and Roe (30) are given in table 3. In our experience the amylase is very low in most fatal cases and fails to rise with treatment.

Serum lipase and esterase have been studied in India by Srinivasan and Patwardhan (31) and shown to be low in acute Kwashiorkor and to rise with treatment. Serum esterase has also been determined by Dean in Uganda (6) and the same results obtained.

Pseudo-choline esterase. The initial pseudo-choline esterase values and their rise following treatment are also shown in table 3. A micro adaptation of the method of Reingold *et al.* was used (32). These findings are the same as those in Gambia (33), Jamaica (34, 35) and Uganda (6).

Duodenal Enzymes. Authors in Brazil (36), Hungary (37), Africa (38), India (39) and Mexico (40) have described the drastic decrease in the activity of duodenal enzymes in acute Kwashiorkor. Amylase, lipase and trypsin are all affected with values dropping nearly to zero and returning rapidly to normal in the first 10 days of treatment.

TABLE 3. BLOOD SERUM ENZYME LEVELS IN KWASHIORKOR

Enzyme	No.	Units/100 ml of serum	
		On admission	At discharge
Amylase*	15	41	114§
Alkaline phosphatase†	22	2.66	5.16§
Pseudo-cholinesterase‡	4	0.36	1.28§

* Smith and Roe Units (30).
† mM/1/hr. of *p*-nitrophenol (27).
‡ Mitchell Units (32).
§ Difference significant at the 1% level.

Enzymes in Tissues. Waterlow has studied the pseudo-choline esterase activity of liver biopsy tissue from malnourished children in Gambia (33). He found it to be low initially but to increase more than 100% when a milk diet was given to the child. In a subsequent paper he reported that cytochrome oxidase and lactic dehydrogenase were not affected but that transaminase in liver may rise (34). Sriramachari and Ramalingaswami (41) in India determined histochemically the alkaline phosphatase activity of liver biopsy tissue and found it to be increased in Kwashiorkor and to fall with treatment.

Other Biochemical Findings in Blood. *Cholesterol.* In both Uganda (6) and the Belgian Congo (29) the level of cholesterol in Kwashiorkor is very low, averaging approximately 88 mg/100 ml and increasing markedly with treatment. The ratio of free to total cholesterol fell rapidly in the first two weeks and remained more or less constant thereafter. Low cholesterol values in Kwashiorkor have also been reported from Brazil (25) and Morocco (42).

Lipids. 'Total' serum lipids were reported high in children with Kwashiorkor by Van Der Sar working in Curaçao (43). On the other hand the phospholipid levels reported by Carvalho in Brazil were low (36).

Urea. Dean and Schwartz in Uganda (6) report a low average blood serum urea of 16.2 mg/100 ml at the beginning of treatment succeeded by a rise to values which exceeded the normal level of 20 to 25 mg/100 ml

Other Biochemical Findings in Tissue. Preliminary findings for protein and fat in livers of children with Kwashiorkor are also given in table 2. The high fat contents are in agreement with those found in Gambia (44), Uganda (45), French West Africa (46) and India (47). Increased amounts of cholesterol in liver have also been reported from India (41, 47).

The French West African workers (46) report the methionine content of both liver and muscle to be normal. The low protein values cited in table 2 agree with reports from Jamaica (34) and French West Africa (46). In evaluating enzyme activity Waterlow has also determined that the ribonucleic acid in liver is low in relation to desoxyribonucleic acid and rises with treatment (28). This is evidence of an increase in cytoplasmic protein with treatment.

PHYSIOLOGICAL CHANGES

Nitrogen Balance. A recent study of 44 two-day nitrogen balance experiments on children suffering from severe Kwashiorkor in the Belgian Congo (48) found positive balances. About half of the nitrogen fed was retained when levels up to 3.6 gm of milk protein per kilogram were fed. Our own preliminary figures on cases after initial recovery are lower. Dean mentioned a child with Kwashiorkor who absorbed 72 and 79% respectively of nitrogen fed at the beginning and end of 25 days of treatment (49). Children who were malnourished but who did not necessarily have Kwashiorkor were studied in India (50, 51) and found to have a positive balance on a poor vegetarian diet containing rice despite a protein intake of only 1.2 gm/kg of body weight Positive balances in Kwashiorkor have also been found in West Africa (52) and Mexico (53). Bray (52) cites evidence to show that African children on a poor diet retain a higher portion of the total nitrogen it contains than do United States or European children.

Amino Acid Metabolism. We are indebted to the laboratory of Holt (54) for most of the limited information on amino acid metabolism in Kwashiorkor. These preliminary findings show the excretion of threonine in urine to be reduced and the ratios of isoleucine to leucine and of phenylalanine to tyrosine to be higher than normal. Since it has now been shown that a mixture of 18 amino acids will suffice to bring about initial recovery (55), it now appears established that a deficiency of amino acids or their imbalance is primarily responsible for the basic clinical syndrome.

Fat Balance. Fat balances were obtained in 45 children with Kwashiorkor studied in the Belgian Congo (48) on intakes ranging from 0.5 to 5.6 gm/kg. A 'lower-than-normal-value' of 82% retention was obtained. Dean in Uganda (49) reports a child treated for 25 days on a soya-banana diet who increased his absorption of fat from 86 to 96%. Holt (53) reports one case studied in Mexico City with an absorption of 50% on admission and 80% following six weeks therapy. In a case treated for six weeks we found a fat retention of 71%. Another treated case which developed mild diarrhea during part of the five-day balance study retained only 60%.

Authors in South Africa (56), Uganda (38), Dakar(57), the Belgian Congo (24), Ceylon (58), India (28) and Curaçao (43) have mentioned the steatorrhea which is common in Kwashiorkor.

Blood Volume. Gómez and co-workers have studied 51 children with signs of Kwashiorkor in Mexico (59) by Evan's blue dye dilution method and conclude that the extracellular fluid (thiocyanate space) and plasma volume calculated in grams per kilogram of body weight are increased in malnutrition. However, when edema is present, the selection of the correct body weight to use in the formula for calculating blood volume and the correct weight to which blood volume should be related is always uncertain.

We encounter cases which despite their edema appear clinically to be dehydrated as determined by the condition of the mucous membranes, eyeballs and skin. This is supported by the initial drop in hematological values which is frequently observed and is illustrated in figure 1.

Electrolytes. From work in South Africa (60) and Uganda (61) it appears definite that Kwashiorkor is associated with a state of potassium depletion and usually low blood serum levels of potassium. Although this is probably due initially to the diarrhea, protein therapy in acute Kwashiorkor without supplementary potassium has been stated to result in potassium deficiency (61). Relatively low values for plasma chlorides have been reported from India (62) and the Belgian Congo (24).

Kidney Function. Gopalan (28) reports that only 5 out of 26 children with untreated nutritional edema in India had normal 24-hour urine outputs while the majority of the remainder had pronounced oliguria. This has also been our own clinical experience in cases of acute Kwashiorkor.

Cardiac Function. Abnormal electrocardiograph findings have been reported from Mexico (63), South Africa (64) and the Belgian Congo (24) to consist principally of low voltage and minor abnormalities.

Gopalan (28) reports from India not only a profound diminution in the amplitude of all deflexions but also occasional prolongation of the QT interval. Rarely, abnormalities of rhythm occur.

Endocrinological Findings. Very few studies of endocrinological alterations have been done. Gopalan attributes the oliguria of Kwashiorkor to a failure of the liver to destroy antidiuretic hormone (28) Certain features of the recovery syndrome described in Mexico by Gómez and co-workers (65) especially changing eosinophile count and hypertrichosis have been attributed to a rapid return to normal of pituitary function.

There have been several excellent studies of the endocrinological consequences of severe chronic malnutrition in adults which are pertinent to the subject but which cannot be reviewed here (66–68).

ETIOLOGY AND RELATION TO MARASMUS

The syndrome of Kwashiorkor in its classical form occurs in children whose caloric intake is not necessarily deficient, but whose protein intake is grossly inadequate in quality and quantity. However, many children in underdeveloped areas suffer from a very severe deficiency of both calories and protein, as well as all other nutrients, and develop the syndrome known as marasmus. Jelliffe (69) points out that the clinical picture of marasmus has been somewhat neglected because it lacks some of the dramatic attributes of Kwashiorkor. It should be clearly understood that many of the characteristics of Kwashiorkor, including a considerable proportion of the biochemical and physiological findings may also apply to marasmus. In both Mexico (observation by senior author in February 1956) and Jamaica (35) considerable attention has been given to this problem and it is now under intensive investigation by us. Not until thorough studies of marasmus comparable to those which have been described for Kwashiorkor have been completed, will it be possible to state what proportion of the findings are limited to one or the other of these conditions.

Even is this can be done, the problem is somewhat academic since any degree of combination or shading between marasmus and classical Kwashiorkor can and does occur. In fact the great majority of cases of Kwashiorkor in Latin America, India, the Belgian Congo and many other areas of the world represent just such a combination and are spoken of as the marasmic type of Kwashiorkor. Our knowledge of these conditions does not justify any attempt to discuss separately biochemical and physiological characteristics of the classical and marasmic types of Kwashiorkor in the present report. The most crucial clinical differences seem to lie in the marked degree of muscular wasting in the latter together with the loss of subcutaneous fat revealed when the edema has disappeared. The differences in dietary and social background of the two conditions have been well reviewed by Autret and Behar (4) and Trowell *et al.* (45).

It is not the function of this paper to discuss the etiology of Kwashiorkor, but it is clear that as our knowledge of the syndrome increases, more and more features of the condition which are local variants or inconstant findings are being related to specific factors apart from protein deficiency. Thus the primary characteristics of the relative deficiency of protein common to all cases and forms of Kwashiorkor are gradually becoming clearer. The recent work of Brock *et al.* in South Africa (55) showing that satisfactory initial recovery and clearing of the major clinical signs and symptoms can occur promptly with the administration of a mixture of pure amino acids, is a major contribution in this regard.

THE TASK AHEAD

The future work with Kwashiorkor would seem to lie in two mutually complementary directions: *1*) the development of practical prophylactic measures whereby young children can be given increased amounts of biologically adequate protein; *2*) the identification of specific etiological factors associated with the basic syndrome and with the various local or variable concomitant signs and symptoms.

The former will necessarily include the use of plant as well as animal protein resources and the latter will lead the investigator into the complex realm of the deficiency of specific amino acids and their inter-relationships with other amino acids, with vitamins and with the relative availability of calories.

SUMMARY

The clinical and pathological characteristics of the condition known as Síndrome Pluricarencial de la Infancia in Latin America and Kwashiorkor in most other parts of the world are briefly summarized and the presently available biochemical and physiological information regarding this syndrome is reviewed in detail.

Data obtained from studies in Central America pertaining to aspects of the condition which have not previously been described are given as follows: neither blood levels for thiamine nor serum levels for total and 'free' riboflavin are decreased. A very poor absorption of oral vitamin A was found in patients with Kwashiorkor on admission compared with normal absorption following five days of treatment. The results of assays for vitamin A, carotene, niacin, thiamine and riboflavin in the livers of seven fatal cases of Kwashiorkor are given. The excellent hematological response to protein therapy of the

normocytic or mildly macrocytic anemia most frequently encountered is also illustrated

The continuous variation from classical Kwashiorkor to marasmus is stressed with the warning that many of the so-called characteristics of Kwashiorkor are also to be found in the latter.

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