Protein-calorie malnutrition and the significance of cell mass relative to body length[1-3]

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ABSTRACT Fifty-eight boys 2 to 8 years old who came from the same poverty-stricken area of Guatemala were studied for anthropometric growth (length, weight, arm and calf circumference) and for body composition (deuterium space minus corrected bromide space equals intracellular water, ICW). The boys were divided into four subgroups: 1A, those who had been admitted for reasons other than protein-calorie malnutrition (PCM), representing the nutritional status of the general population; 1B, those who had been fed a hospital diet for 6 months and were considered "normal;" 2A, those clinically malnourished with recent edema; 2B, those who had been classed as clinically malnourished but had had approximately 1 month of rehabilitation. All boys were retarded in length and weight for age by Caucasian standards. Subgroup 1B was considered to be the best nourished group and subgroup 2A the worst. In subgroup 1B the weight age was 5 months ahead of the length age. In subgroup 2A the weight age was 5 months behind length age. Arm and calf circumference were reduced for 2A when compared with 1B. Measurement of ICW (or active tissue mass) was considered against body length. These measurements of ICW fell above the median for normal Caucasian boys for subgroups 1A and 1B and below the Caucasian median for subgroups 2A and 2B. It is postulated that a reduction of ICW relative to body length is indicative of a significant reduction in protein reserves. *Am. J. Clin. Nutr.* 30: 851-860, 1977.

It is established that children suffering from protein-calorie deprivation or protein deficiency frequently exhibit sodium retention, expansion of extracellular volume, and reduced ability to excrete sodium effectively (1) (see Reference 2 for review). At the same time, as body stores of protein are reduced (in muscle for example), there is a concomitant loss of body potassium (3-7). Emphasis has been placed by our group on the significance of the intracellular phase, or the intracellular water (ICW), as a measure of active tissue mass (8-10), because the ratio of the protein to water within the cell usually remains constant. Admittedly, in the last stages of congestive cardiac failure (11), uremia (12), or acute hypoxia (13), or in water intoxication (14), to name some examples, a breakdown in ion transport occurs; in particular the "sodium pump" fails in some of these circumstances, so that the above relationship is not maintained. None of the boys reported in this paper, however, suffered from such circumstances.

Over the last 25 years our group has been engaged in the measurement of extracellular volume (see References 15 and 10 for review). Our work indicates that the corrected bromide space is the most precise measure of the true extracellular phase, and is acceptable both biochemically and anatomically.

Total body water can be measured by following the distribution of small amounts of deuterium oxide. The subtraction of the corrected bromide space from the total body

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water gives a close measure or index of the ICW in the body, which, as stated above, is a direct measure of the active tissue mass. Small doses of D_2O and NaBr given quantitatively by mouth distribute rapidly over the respective phases of the body water. A single blood sample taken subsequently at 3 to 12 hr allows analysis of the plasma for deuterium and bromide, and therefore the calculation of the intracellular water ICW.

Work in other areas has shown us that if rats are fed a protein-sufficient but caloric-deficient diet, the reduction of muscle mass is commensurate with the reduction of skeletal mass. If, on the other hand, the rats are fed a protein-calorie deficient diet, the reduction of soft tissue (such as muscle) is greater than the reduction of skeletal mass (16).

In 1972 some 60 boys from 2 to 8 years old were studied in Guatemala; they are reported in this paper. Guatemala is a country where the general population is suffering from mild to moderate protein-calorie malnutrition (PCM) (17). Recently, aboriginal children have been studied in Central Australia and in the Northwestern area (the Kimberley region), 2,500 miles north of Perth. The latter studies will be published subsequent to this paper.

The present work indicates that children assessed clinically as being malnourished have a reduced ICW relative to body length, but such a reduction is not found in boys receiving a hospital diet for 6 months or for those considered to be representative of the environment.

Methods and clinical material

The 60 boys reported here came from similar socioeconomic backgrounds. Eight boys had received a good diet in the INCAP[4] metabolic ward for 6 months at least. Twenty-one boys studied in an orphanage were considered to represent the nutritional status of the population as a whole. These two groups of boys, those from the metabolic ward and those from the orphanage, were considered clinically not malnourished. Fifteen boys studied in hospital had been hospitalized for PCM for 1 to 4 weeks, but in a few instances this period was extended because nutritional recuperation was not proceeding well and clinically they were regarded as malnourished. Fourteen boys had been recently hospitalized for PCM and were studied shortly after disappearance of pitting edema. These latter two groups of boys in the hospital were considered clinically malnourished.

Arm circumference, calf circumference, and supine body length were measured to the nearest millimeter. Weight was taken to the nearest 100 g.

Measurements were made by a trained anthropometrist according to standardized procedures (18, 19). The usual day to day reliability expressed as a standard deviation was 201 g for weight and 0.63 cm for supine length. The anthropometrist's reliability was 20 g for weight and 0.34 cm for length.

Total body water was measured by giving each boy an oral dose of 2 g of D_2O (99.8%) simultaneously with 80 mg of NaBr/kg of body weight. A sample of blood was drawn after approximately 3 hr, and 3 ml of plasma were taken for analysis. Plasma bromide was determined by the microdiffusion method (20) and the corrected bromide space was calculated as:

$$\text{correct bromide space} = \text{mEq of Br given} - \frac{10\%}{\text{plasma Br (mEq/L} \times 0.88)}[5]$$

Deuterium oxide in plasma was subjected to vacuum distillation and the distillate was analyzed by infrared spectrophotometry using the Wilks Miran instrument according to previous description (21). ICW equaled the D_2O space minus the corrected bromide space.

Calculations and statistics

The weight age and length age for the boys in each of the four subgroups were calculated by taking the age they would be if their length or weight fell on the 50th percentile of the Harvard growth chart together with mean values and standard deviations. In addition, the differences between weight age and length age for each individual boy in the subgroups were found and mean values and standard deviations were calculated for each subgroup. Comparisons were made among the four sets of data by application of a paired t test and by comparing the derived value against zero. If a difference exists one can determine the statistical significance.

The assessment of cell mass (or ICW in liters) against length was carried out by constructing the line for the quadratic equation $ICW = 3.0705 - 0.0674\,x + 0.00098\,x^2$ where x equals the length in centimeters for normal Caucasian male infants and boys. The ICW data for malnourished boys were then plotted (as one group), and also the data points for boys considered clinically not to be malnourished or representative of the environment (as a second group). As points for these two groups in general fell on either side of the normal line, a regression equation was calculated for each set of data points and statistical analyses were carried out by comparing the two resulting linear regressions by analysis of covariance to see whether the slopes of the two linear regressions, or the intercepts on

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[4] INCAP = Institute of Nutrition of Central America and Panama. The authors are indebted to Fernando Viteri, M.D., Ph.D., head of the metabolic ward, for the opportunity to examine these boys and for his interest in these studies.

[5] The 10% value represents (by experiment) nonextracellular bromide; 0.88 represents the correction for serum water and Donnan equilibrium: $0.93 \times 0.95 = 0.88$.

the ordinate, were statistically different. Full descriptions of these methods are given by Mellits (22).

Results

Table 1 contains data concerning boys considered clinically not to be malnourished. Their age, (months) and arm and calf circumference (cm) are recorded. Their length and weight are recorded together with their length age and weight age. In addition, data are given in liters for the extracellular and intracellular volume. The ICW represents total water minus extracellular volume (ECV).

The top part of Table 1 records data from the boys in the orphanage and the lower part records data for boys who had received an adequate diet for 6 months on the INCAP metabolic ward. Table 2 records similar data from the boys who had recently shown edema and considered clinically malnourished (top part) and data from boys who had been hospitalized for malnutrition but who had recently not shown edema and who were considered to be poorly nourished (lower part).

Table 3 documents the mean values for weight age and length age for the four subgroups studied. By taking the length age from the weight age for each individual boy and using a paired *t* test and by comparing the value against zero it is possible to determine significant departures. The group of eight boys given an adequate diet for 6 months had a weight age 5 months ahead of height age. The group of 14 boys in the worst state of nutrition (recent edema) had a weight age that was 5 months behind height age. The 21 boys from the orphanage who were admitted for nonnutritional reasons showed reductions in length age and weight age similar to those of boys admitted with malnutrition. All subgroups were behind by Caucasian standards.

TABLE 1
Data for boys not considered clinically malnourished

Patient no.	Chronological age (mos)	Wt (kg)	Wt age (mos)	Length (cm)	Length Age (mos)	ECV (L)	ICW (L)	Upper arm circumference (cm)	Calf circumference (cm)
A, patients representative of the environment (orphange)									
1	56	15.78	42	101.0	45	4.03	6.89	15.5	19.5
4	51	11.58	18	86.9	24	3.07	4.63	14.3	18.3
5	52	16.50	48	99.5	45	5.07	6.89	17.3	21.9
8	67	14.70	37	96.0	36	3.27	7.42	16.0	20.0
9	46	12.30	23	94.5	33	3.89	4.45	14.6	18.6
10	67	15.00	41	100.5	42	3.63	5.90	15.5	19.8
23	86	19.00	60	105.4	54	5.49	7.54	17.0	22.5
25	38	12.00	20	86.0	24	3.79	4.90	14.9	18.8
27	46	15.34	42	95.6	36	4.51	6.60	15.1	18.7
45	36	13.40	30	88.3	26	3.85	5.87	15.3	19.7
46	66	16.45	50	100.1	42	5.06	6.66	16.2	20.3
48	72	18.00	56	105.9	54	5.48	5.47	16.4	22.2
49	62	18.63	59	101.6	45	5.43	7.71	16.8	21.5
50	54	18.30	58	100.1	42	5.17	6.87	17.5	21.7
51	68	16.25	48	97.0	36	4.73	6.90	15.8	20.4
54	47	15.90	46	94.0	33	4.84	6.37	15.7	20.2
68	31	10.04	12	81.4	18	3.19	3.78		
75	42	11.40	18	86.0	24	2.98	5.17	14.4	17.8
103	25	10.53	13	79.9	17	2.81	3.53	13.9	17.3
105	42	12.72	24	88.2	24	3.54	4.93	13.9	18.8
106	30	13.50	29	89.8	27	3.33	5.17	14.3	19.8
B, patients rehabilitated (6 months of adequate diet)									
58	30	11.43	17	82.1	18	2.95	4.89	15.2	18.5
59	26	10.90	15	75.0	12	2.47	4.68	14.2	17.8
61	22	9.82	12	77.5	10	2.16	3.96	14.4	17.0
62	66	14.11	34	89.5	27	3.08	6.02	15.3	17.5
63	52	13.89	32	87.6	24	3.37	5.64	16.6	20.2
64	32	13.79	32	87.4	24	3.52	5.89	16.4	18.6
66	30	13.68	31	81.7	18	3.45	4.95	16.7	19.0
67	25	10.95	15	72.4	10	2.24	4.07	15.3	17.3

TABLE 2
Data from boys considered clinically malnourished

Patient no.	Chronologic age (mos)	Wt (kg)	Wt age (mos)	Length (cm)	Length age (mos)	ECV (L)	ICW (L)	Upper arm circumference (cm)	Calf circumference (cm)
A, clinically malnourished (previous edema)									
15	85	16.36	48	105.7	54	6.37	4.82	13.2	18.8
22	66	12.98	26	92.8	30	4.99	4.42	12.6	17.3
33	100	19.00	60	110.2	60	5.94	5.59	15.1	20.2
35	66	13.60	30	92.7	30	4.27	4.89	13.1	17.5
36	70	14.54	36	102.5	48	5.85	4.51	12.2	16.9
37	55	11.27	17	84.2	19	3.71	3.76	12.9	18.0
39	30	8.27	7	68.5	6	2.13	2.72	12.4	14.5
40	70	13.18	27	89.9	27	4.36	3.77	11.8	16.8
41	77	12.71	24	94.3	33	4.27	4.71	12.3	17.9
86	46	12.10	21	89.8	27	3.54	4.68		
92	63	13.18	27	95.7	36	3.75	5.58		
95	84	13.53	29	105.8	54	4.24	5.34	12.0	16.6
98	27	9.97	12	76.4	12	2.82	2.57	12.0	15.9
100	37	9.53	10	76.8	14	3.34	3.29	10.8	14.5
B, clinically malnourished (under initial rehabilitation)									
11	42	15.14	41	91.8	30	4.04	4.54		
14	63	13.63	30	89.0	27	4.69	5.20	14.4	19.0
16	75	14.40	36	97.6	38	5.64	4.32	13.5	18.4
18	60	13.00	26	92.9	30	4.71	4.27	13.7	17.8
20	60	11.45	17	86.6	24	4.12	3.74	13.3	16.5
21	35	12.50	24	89.6	27	3.58	4.98	12.8	18.1
24	80	19.00	60	110.0	60	6.74	5.08	16.4	22.1
29	97	20.57	68	110.0	60	5.82	6.51	17.3	22.0
30	53	12.48	24	91.2	30	4.40	4.31	14.2	19.0
31	81	14.60	37	95.7	36	5.28	4.44	14.4	19.7
32	54	12.50	24	85.1	21	3.75	3.74	14.4	17.3
42	64	14.54	36	95.8	36	4.90	5.24	13.7	18.2
91	97	17.09	53	102.5	48	4.27	7.91	16.1	19.3
94	68	14.11	34	94.4	33	3.57	4.48	13.3	18.0
96	36	12.53	24	86.4	24	3.64	4.10	13.8	16.8

TABLE 3
Mean values for weight age and length age for the four subgroups studied[a]

Group	N.	Chronological age	Wt age	Length age	Wt age − length age
		mos			
1A, Normal patients (orphanage, no history of clinical malnutrition)	21	51.6 (15.8)	36.9 (15.9)	34.6 (11.0)	+2.3 (7.3)
1B, boys considered normal (after 6 months of adequate diet on INCAP metabolic unit)	8	35.4 (15.4)	23.5 (9.5)	17.9 (6.7)	+5.6* (4.3)
2A, clinically malnourished (previous edema)	14	62.6 (21.5)	26.7 (14.4)	32.1 (16.8)	−5.4* (6.9)
2B, clinically malnourished (under initial rehabilitation)	15	64.3 (19.3)	35.6 (14.6)	34.9 (12.2)	+0.7 (4.9)

By taking the length age from the weight age for each individual boy and using a paired *t* test and by comparing the value against zero it is possible to determine significant departures. The group of eight boys given an adequate diet for 6 months had a weight age 5 months ahead of length age. The group of 14 boys in the worst state of malnutrition had a weight age that was 5 months behind length age. The 21 boys from the orphanage representing environmental standards showed reductions in length age and weight age similar to those of boys with malnutrition but under initial rehabilitation. Note that all subgroups were behind by Caucasian standards. SD is in parentheses; asterisk indicates statistical significance ($P < 0.01$).

Inspection of the individual data from the 21 boys from the orphanage in (Table 1) who were considered to be normal (by environmental standards) showed that many of them were behind in both length age and weight age when compared with the Caucasian standards. Doubtless this reflects the poor nutritional status of the children in general.

Inspection of the data for ECV in the

malnourished boys (Table 2) revealed values that are excessive if comparison is made against values obtained for normal children with the same length and weight (10, 23).

Attention is directed to Figure 1, however, where the data for ICW are plotted against the values for body length.

It can be noted that the points for most of the malnourished children fall below the expected median level for Caucasian children (23), whereas those boys considered to be nutritionally normal have points which in general fall on or above this line. Analysis of covariance for the two groups (Fig. 2) reveals that the slopes of the lines for the points in the two groups were not dissimilar, but the intercepts on the ordinate were distinctly different.

Of further interest was the fact that the measurements for arm circumference and calf circumference (Fig. 3) were reduced in the patients with severe malnutrition when the values were compared with the eight boys on an adequate diet for 6 months. Length age is defined on the abscissa. Thus, large departures in intracellular mass were reflected by these simple anthropometric measurements, whereby arm circumference differentiates better than calf circumference between those with malnutrition and the better nourished boys (Fig. 3).

The above observations are reinforced when the ICW is plotted for the eight boys considered to be nutritionally normal against values for those boys who were clinically malnourished with previous edema (Fig. 4). Length age is again given on the abscissa. The two sets of points are distinct.

Discussion

Traditionally, the assessment of growth in the clinic is accomplished by measurement of height and weight, whereas bone age may reflect maturation in one tissue, namely skeleton. Length itself is a measure of maturation (24). Our earlier studies on human growth (8, 9) have indicated that the simultaneous investigation of body composition is valuable, especially in PCM. Measurement of the intracellular phase (which excludes edema) accounts for the active tissue mass. Indeed, the basal metabolic rate has a defined mathematical relationship with the ICW (10) as it is defined here. With the progress of growth from infancy to child-

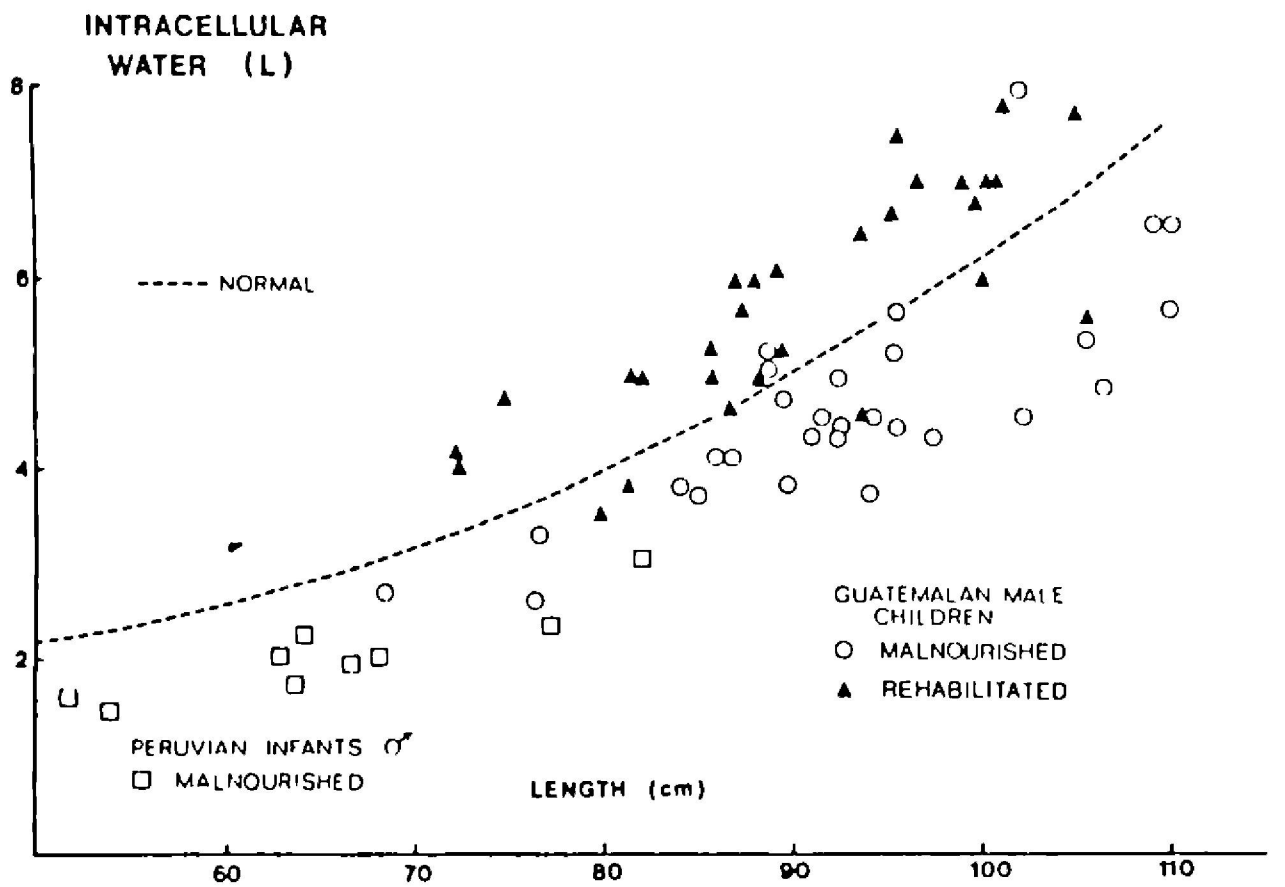

FIG. 1. ICW in liters is plotted against length in centimeters for individual Guatemalan children who were malnourished (*open circles*—data from Table 2) or rehabilitated (*solid triangles*—data from Table 1). The *individual points* for malnourished Peruvian infants (*open squares*) are also illustrated. The *hatched line* indicates the predicted median for the ICW on length for normal Caucasian children calculated from the relationship. ICW = $3.0705 - 0.0674\,\chi + 0.00098\,\chi^2$ where χ equals length in centimeters. Note the clear separation between malnourished and rehabilitated in the Guatemalan population.

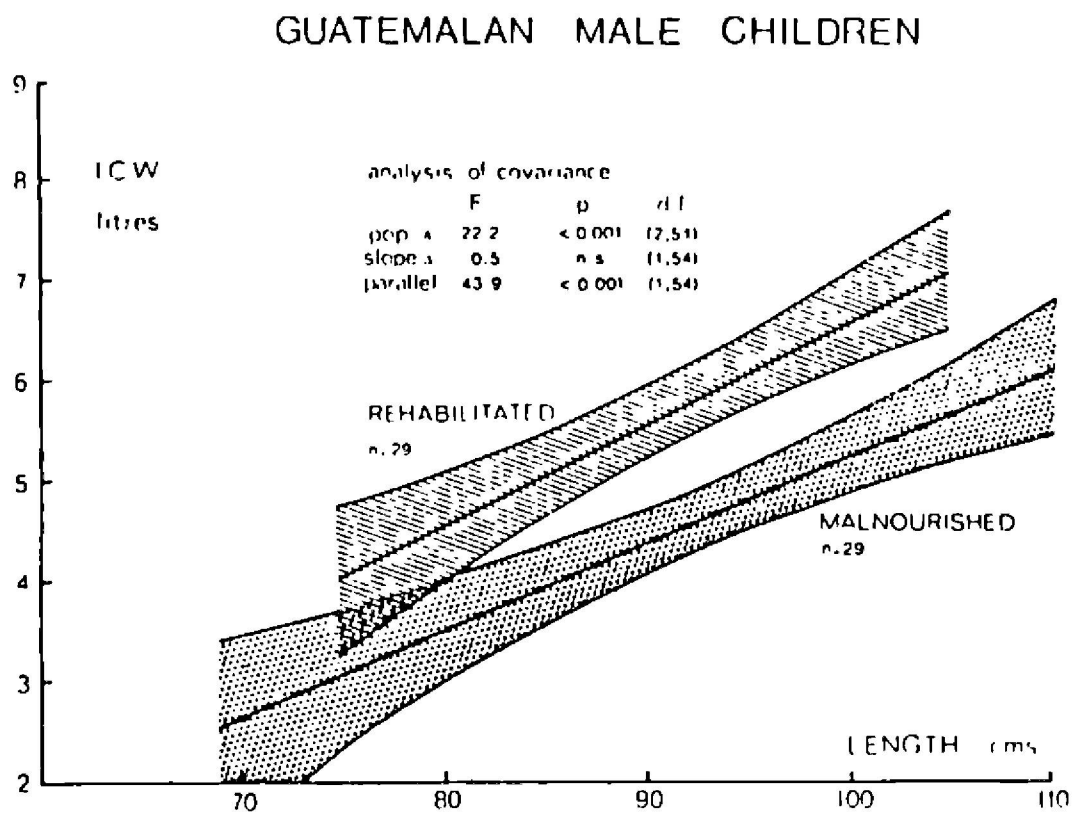

FIG. 2. ICW in liters plotted against length in centimeters is illustrated as regression lines with 95% confidence limits for malnourished Guatemalan children (*cross-hatched area* – data from Table 2) and rehabilitated Guatemalan children (*single-hatched area* – data from Table 1). The two regressions, when tested by analysis of covariance, are found to be two separate populations ($P < 0.001$) which are essentially parallel ($P < 0.001$). From this figure, it can be demonstrated that a Guatemalan boy of 90 cm in length who has been determined clinically to be nutritionally normal has 1.2 liters more ICW than a malnourished Guatemalan boy of the same length.

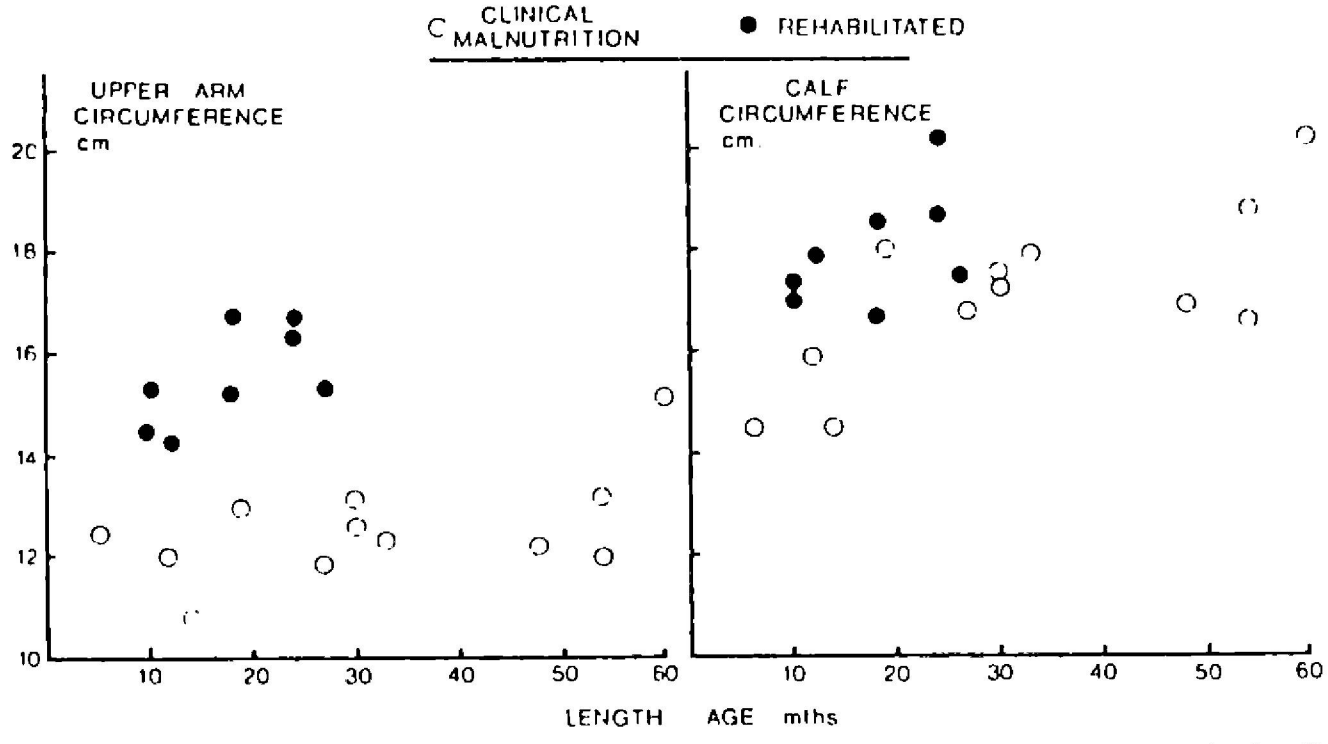

FIG. 3. Upper arm and calf circumferences in centimeters are plotted on length age in months for Guatemalan boys who were clinically malnourished (group 2A) or rehabilitated by Guatemalan standards (group 1B). Note the increase in muscle girth for the rehabilitated group. The measurement of upper arm circumference appears to be most meaningful in assessment of nutritional status.

hood to adolescence, more and more of the ICW is found in muscle, such that from 3 to 17 years muscle ICW content increases from 30 to 70% of the ICW (10). As maturity is reached, muscle represents the major protein reserve of the body.

PCM in our experience has a greater effect on the infant than on the child. In Figure 1, points for ICW of male Peruvian infants suffering from severe PCM fall well below the expected normal for length, as is also shown elsewhere (8). Even after 5 or 6

months of rehabilitation with adequate diet, some of these infants did not increase their cellular mass significantly (8, 9), nor did they return to a positive nitrogen balance (Graham, personal communication).

When points for ICW were plotted against creatinine excretion (an index of muscle mass) for Peruvian infants with PCM before and after partial rehabilitation, a linear relationship was defined. This linear relationship did not depart from the normal relation calculated for 20 normal infants of the same age range (9). By analysis of covariance, the relations did not differ. It appears that the ratio of muscle mass to total cell mass remains the same during malnutrition, and even then creatinine excretion still reflects muscle mass, despite suggestions to the contrary from [^{15}N] creatine studies (25), which are difficult to perform precisely. It can be mentioned in passing that ECV did not hold a constant relationship with creatinine excretion, there being an excess of ECV relative to creatinine in PCM.

Widdowson and McCance as early as 1951 (26) demonstrated the expansion of ECV in PCM and loss of potassium. Several workers have monitored whole body potassium in PCM by ^{40}K counting (3, 4, 27, 28). However, as pointed out by Nichols et al. (28), reduction of body potassium with an unknown decrease in intracellular K concentration renders impossible the calculation of the intracellular phase. Their data showed a reduction of N and K in muscle, but there was no satisfactory point of reference. The increase in muscle water made interpretation difficult. Later studies (7) established a quantitative loss of K and N in human muscle. It is also clear that a reduction of magnesium occurs with the shrinkage of cell cytoplasm (5, 9).

Our earlier studies concerning starvation in rats (29) and the balance of whole body K, Na, Cl, N, and water showed a 20% loss of fat-free dry solid (80% protein) and a 27% loss of K with a relative expansion of the extracellular phase and contraction of the ICW over an 8-day period. The concentration of K within the cellular phase remained at 150 mEq/liter. There was no reason to believe that Cl entered cells (nor for that matter would Br, because the two ions distribute similarly in the body—see Reference 30 for review).

Alleyne (31) has reemphasized recently the reduction of the intracellular phase that

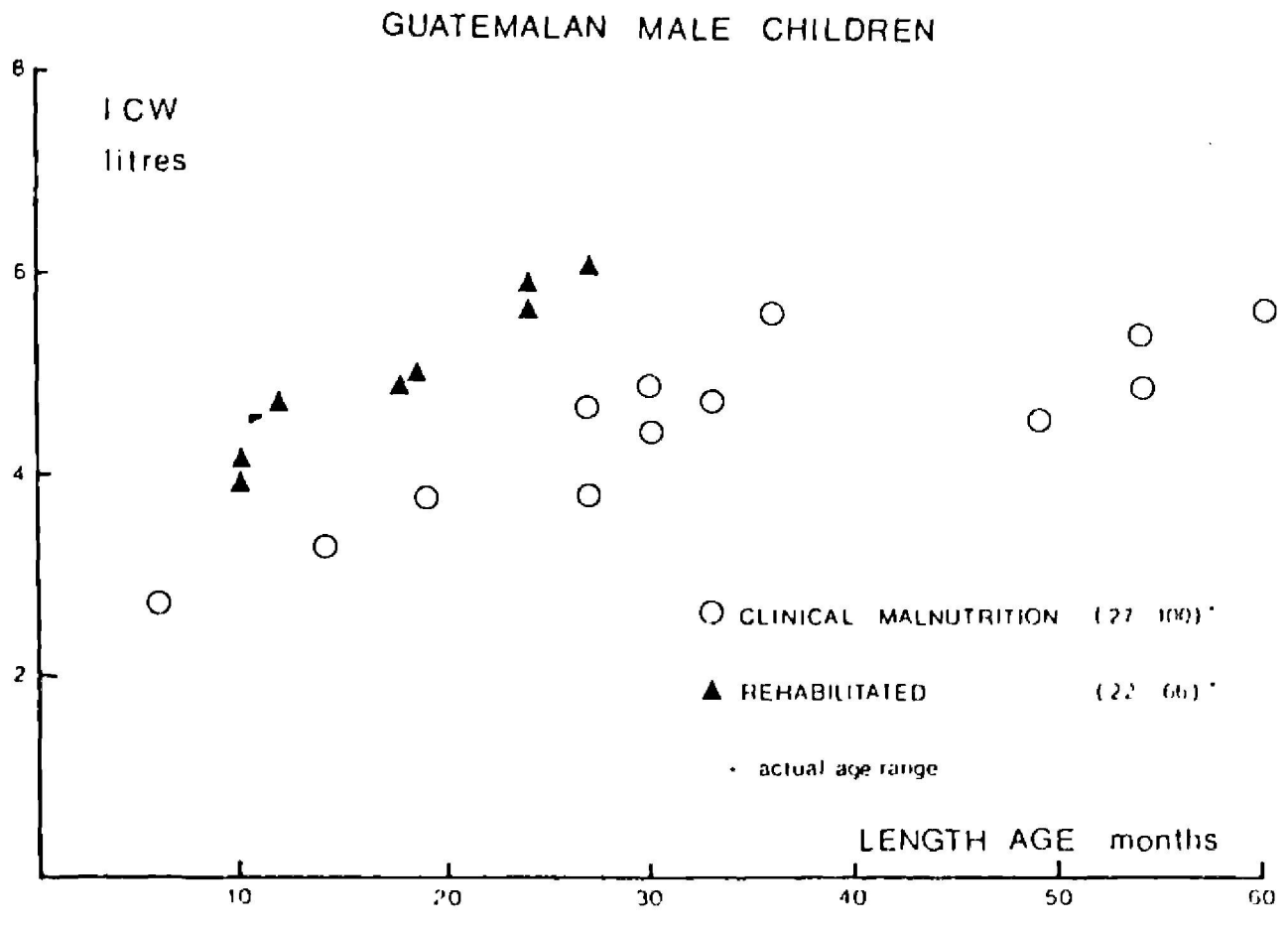

FIG. 4. ICW in liters is plotted against length age in months for the same Guatemalan children defined in the legend of Figure 3. Compare this figure to the relationship of upper arm circumference to length age found in Figure 3. Note the distinct separation between the two groups for ICW and upper arm circumference.

accompanies protein loss through malnutrition. This is accomplished by a potassium loss, partly because the protein binding of the intracellular potassium is lost and partly because the kidney of the malnourished child is unable to clear sodium and retain potassium. The sodium retention also explains in part the increased extracellular volume.

The gross reduction of cell size in human muscle was shown histologically by Montgomery (32) and chemically by our own laboratory (9) and that of Mendes and Waterlow (33) (reduced protein to DNA ratio, or reduced nonchloride space).

Our previous work (see Reference 34 for review) and that of Durand et al. in France (35) has shown that calorie restriction in rodents without protein restriction causes a cessation of cell multiplication (or nuclear increase in the muscle fiber) but no change in cytoplasm or cell size. Howarth (36), using abnormal diets containing high methionine, which can alter insulin secretion (37), has challenged our results (36). However, recent work by Goldberg and Goldspink (38) confirms our earlier work and that of Durand et al. It appears that cell mass, and in particular muscle mass, remains proportional to skeletal mass if protein restriction is minimal (16). If one extrapolates to the human situation, one might find in PCM retarded growth, but provided that protein deficiency is not gross, cell mass will continue to be commensurate with body length. By contrast, rats subjected to protein deficiency voluntarily restrict their calorie intake, and there is gross reduction of muscle cytoplasm and nuclear number in muscle tissue (39) (see Reference 34 for review). Hence muscle mass is reduced relative to skeletal mass (16). Again, extrapolating to the human situation, a reduction of cell mass relative to body length may be taken as evidence that significant protein deficiency exists for body size (irrespective of age). However, the fact that changes in the growth of bone occurs concomitantly is recognized (40).

In the present studies, boys receiving a hospital diet for 6 months showed a return to proportionality. Such a relationship existed for the boys from 2 to 8 years old from the orphanage. However, both of these groups showed a retardation in weight and length for age. Peruvian infants, as mentioned, showed little "catch-up" growth (8, 9). We and others have postulated that such a delay in restoration of cell mass is due to poor insulin secretion (8) (see Reference 41 for review) and possibly due to inhibitory factors in plasma in PCM that counter the cell-multiplying factor, somatomedin B (42). Indeed, with respect to muscle growth we have postulated for some years (see Reference 43 for review) that insulin is concerned with cytoplasmic growth and growth hormone with nuclear replication within the myofibre. Both hormones are compromised in PCM. There is some evidence that the action of insulin in PCM is aberrant because of glucagon deficiency (41).

Of interest are the ongoing findings in free-living Australian aboriginal children, where it appears that a reduction of weight and, to a lesser extent, height for age exists (by Caucasian standards and by standards for white Australian children). The reduction in cell mass is not proportional to the body length for aboriginal girls. Girls may have reduced protein reserves for their body size. Moreover the climate of opinion suggests that they are suffering from PCM.

The finding of a correlation between arm or calf circumference with the fall in ICW in gross examples of PCM adds weight to the value of anthropometric measurements, which are easy to perform in the field. It is our impression from these data that arm circumference is a more sensitive indicator of loss of muscle mass than is calf circumference. In children with different calorie intakes, however, such circumferences may reflect differences in subcutaneous fat more than they do muscle mass.

A major problem regarding research in malnourished children is that there are often no laboratory facilities where the clinical material is located. Exactly 20 years ago Waterlow (44), recognizing that muscle and not liver sustains the major loss of protein in PCM, wrote:

"At the present time there is no way of assessing with any accuracy the degree to which a human being is

depleted of protein. Until this gap in scientific and medical knowledge is filled it will be difficult to plan preventive measures in the most effective way."

In the intervening years the creatinine height ratio has been used by our laboratory (45) and later by Viteri and Alvarado (46). However, the present approach made in this paper is also worthy of consideration.

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