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Clinical significance of muscle potassium depletion in protein-calorie malnutrition

The muscle potassium depletion which occurs in children with protein-calorie malnutrition has been demonstrated to be due to a reduction in tissue capacity for the ion. Recovery occurs only when the underlying malnutrition is treated. The reduced capacity is not explained simply by a reduction in cytoplasmic mass; it is a functional reduction in the ability of cells to contain potassium and is related to a reciprocal rise in the tissue sodium capacity. Tissue hyperhydration is proportional to tissue sodium concentration. The nature of the functional capacity of muscle for potassium has not been established in this study; however, it is probably related to the reduced energy metabolism observed in the muscle of children with protein-calorie malnutrition. From this study we conclude that muscle potassium depletion is a secondary phenomenon, a symptom of the underlying nutritional deficiency. We agree with Garrow[31] that potassium therapy alone is not valuable, and that clinical attention should be directed toward therapy of the underlying protein and calorie deficiency.

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THE CONCENTRATION of potassium in muscle plays a key role in the depletion of potassium in the body which occurs in protein-calorie malnutrition.[1-7] Therefore, an explanation of the mechanism by which the concentration of muscle potassium is depleted is of clinical significance to those concerned with the management of protein-calorie malnutrition.[5-7] If the reduced muscle potassium concentration is due to a lowering of the capacity of the cell or of its ability to take up potassium, the depletion would be significant only when there is a superimposed loss of total body potassium; this loss would be tolerated poorly because of the diminished muscle reserves of the ion. If, on the other hand, the reduced muscle potassium concentration is the result of incomplete filling or desaturation of the cellular capacity for the ion, potassium therapy may be lifesaving. Alleyne and associates[7, 8]

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Table I. Clinical description of subjects at time of admission

Subject	*Age (mo.)*	*Weight* (Kg.)*	*Per cent of weight/ height*	*Per cent of height/ age*	*Infection*	*Clinical dehydration*	*History of diarrhea (wk.)*	*History of edema (wk.)*
Institute for Nutrition of Central America and Panama (INCAP) series								
179	45	8.8	80	77	+	0	12	12
180	29	9.4	76	93	+	0	2	3
182	16	7.2	75	93	0	0	0	4
185	55	9.8	79	82	+	0	1	12
186	21	7.9	73	96	0	0	12	12
187	58	6.9	60	75	+	0	8	8
188	65	9.8	74	79	+	0	8	4
189	67	8.1	58	83	+	0	8	8
193	70	11.4	82	80	0	0	7	8
194	15	7.4	72	97	0	0	2	6
196	34	8.6	73	84	0	0	4	4
197	23	6.7	68	86	+	+	6	6
Mean ± S.E.	41.5 ± 6.0	8.5 ± .4	72.5 ± 2.1	85 ± 2	7/12	1/12	6 ± 1	7 ± 1
Guatemala General Hospital (HGC) series								
100	37	7.3	71	78	0	—	3	4
101	40	10.9	92	85	+	0	0	6
102	120	18.1	98	77	0	0	2	9
103	76	9.5	70	76	+	+	3	4
104	124	17.9	90	79	0	+	8	5
105	43	10.3	98	82	0	0	2	1
106	43	10.0	90	80	+	0	2	2
108	24	7.7	79	85	0	0	—	6
109	36	11.3	92	90	0	0	—	4
110	60	15.0	98	87	+	0	4	6
Mean ± S.E.	60.3 ± 11.2	11.8 ± 1.2	87.8 ± 3.3	82 ± 1	4/10	2/9	3 ± 1	5 ± 1

*For INCAP series, given weights are minimums following loss of edema; for HGG series, given weights are at time of study.

have defined clearly these alternative states. They confirmed an earlier report[5] of a close correlation between the concentrations of potassium in the total body and in muscle in children with protein-calorie malnutrition and suggested that this correlation represents an alteration in the capacity of muscle and other body tissues to retain potassium. In patients with a concentration of potassium in the body of less than 30 mEq. per kilogram, there was a difference between the concentrations of potassium in total body and in muscle. This difference represented the combined effects of desaturation and the reduced capacity of the cell to take up potassium. In a second study, Alleyne[8] observed significant retention of potassium in the first five days of therapy, which he attributed to accumulation of potassium in previously desaturated tissues. Although his observations would support this thesis, no evidence was given that this retention occurred in muscle.

In order to differentiate desaturation from reduced tissue capacity as a cause of potassium depletion, we have designed a study that maintains potassium intake at a therapeutic level and varies protein intake during recovery from protein-calorie malnutrition. We have reasoned that potassium deficiency resulting from desaturation of muscle stores of this ion would be corrected by replacement therapy with supplementary potassium. On the other hand, a reduction in muscle capacity to store potassium would not be corrected by therapy with potassium supplements but would be corrected only by elimination of the basic protein-calorie deficiency.

METHODS

Children with edematous protein-calorie malnutrition with the clinical characteristics described previously[9] have been studied at the Biomedical Division of the Institute of Nutrition of Central America and Panama (INCAP); 10 children with similar charac-

teristics were studied within the first four days after admission to the pediatric wards of the Guatemala General Hospital (Table I).

The clinical management of the INCAP group was divided into two general periods. During the admission period (Period A) each child received a maintenance diet that was sufficient to approximate nitrogen balance; he was also treated for infections and specific vitamin deficiencies. The admission diet contained a casein-based preparation to provide 0.7 Gm. of protein per kilogram per day and 70 calories per kilogram per day. The length of the admission period was determined by general clinical considerations; however, the patient was kept on the maintenance diet for two weeks if possible. At the beginning of the therapeutic period (Period T), the dietary intake was adjusted over a 4 day period so that protein intake was 3 Gm. per kilogram per day and caloric intake was 120 calories per kilogram per day. The caloric adjustments were made by varying the quantity of sucrose, corn starch, casein, and corn oil in the diet. Throughout the study each patient received a dietary supplement of 4 mEq. per kilogram per day of potassium given as a KCl solution separate from the diet, and an additional daily mineral supplement of sodium, 10 mEq.; potassium, 10 mEq.; calcium, 1.5 mEq.; magnesium, 1.5 mEq.; and sulfate, 1.5 mEq. A vitamin mixture was administered daily which included vitamin A, 5,000 I.U.; ascorbic acid, 50 mg.; vitamin D, 1,000 I.U.; thiamine HCl, 1 mg.; pyridoxin, 1 mg.; riboflavin, 1.2 mg.; niacin, 10 mg.; and pantothenic acid, 5.0 mg. Iron, B_{12}, and folic acid administration varied according to a separate research protocol but were not found to have an effect on muscle potassium repletion. Casein was used for the test diet because of its high biological quality and our previous extensive experience with this protein. The casein was supplemented with 0.2 per cent methionine. Sodium carbonate was used to solubilize the protein. All patients received penicillin parenterally for the first 10 days of hospitalization.

A percutaneous needle biopsy technique was used to obtain 10 mg. samples of quadriceps muscle for chemical analyses at each subperiod (Table II). The technique of biopsy and validation of the chemical analyses have been described in previous publications.[10, 11] The biopsy data used in this study are based upon the mean values of duplicate samples. Serum samples were obtained for analyses at the same intervals. The muscle concentrations were calculated with the following denominators: fat-free whole weight (FFWW), fat-free dry weight (FFDW), and myofibrillar nitrogen (MFN).

In order to estimate the role of muscle mass in body composition, 24 hour urinary excretion of creatinine was measured according to the method of Clark and Thompson.[12] Total muscle mass was calculated using Cheek's factor of 20. The creatinine excretion per 24 hours was multiplied by this factor to determine total muscle mass (in kilograms).[13] The creatinine height index was calculated as follows:

$$\text{Creatinine height index} = \frac{\text{Creatinine excretion/24 hours}}{\text{Creatinine excretion/24 hours of normal child of same height}} \times 100.$$

The basis for use of this index has been published previously.[14, 15] Total serum proteins were estimated by refractometry and serum protein fractions by cellulose-acetate strip electrophoresis. Anthropometric measurements for height and weight were referred to the Boston standards.

RESULTS

Clinical. The clinical course of a typical child in this study is illustrated in Fig. 1. This child demonstrated improvement in some of the skin and psychological changes of protein-calorie malnutrition but showed no increase in weight, creatinine excretion, or serum protein concentration while receiving the equilibration diet. When the therapeutic diet was begun, muscle mass increased remarkably over a 2 week interval. Further increase in body mass appeared to

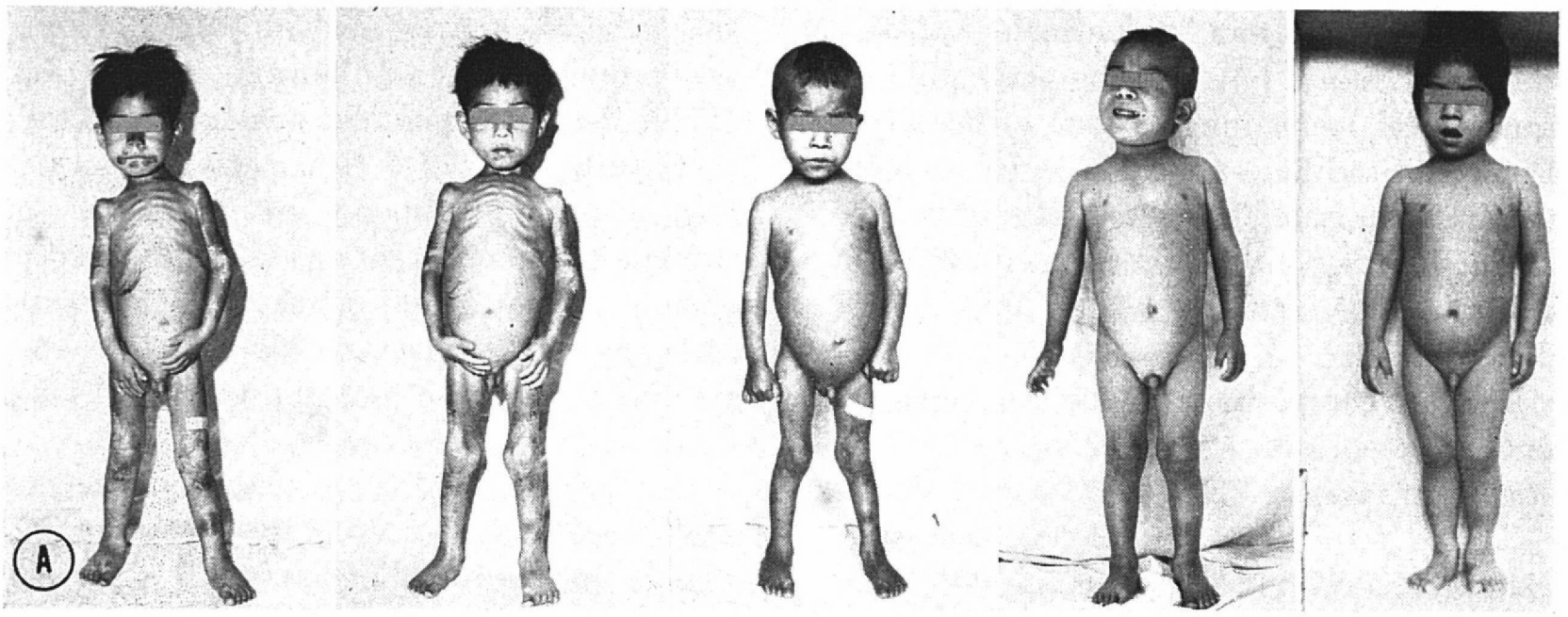
Table II. Clinical and biochemical summary during study*

Clinical and biochemical studies	*HGG series admission period*	*INCAP series admission period*			*Therapeutic period*				*Recovery†*
		A_1	A_{2-3}	A_4	T_1	T_2	T_{3-4}	T_5	
Average duration of diet (days)	3	0	5 ± 1 (6)	14 ± 2 (6)	5 ± 3 (7)	12 ± 1 (9)	22 ± 2 (7)	45 ± 5 (5)	117
Per cent of normal weight for height	88 ± 3 (10)	79 ± 2 (11)	80 ± 4 (6)	77 ± 4 (6)	78 ± 4 (7)	79 ± 3 (9)	84 ± 3 (7)	88 ± 4 (5)	101 ± 2 (26)
Average weight	11.8 ± 1.2 (10)	9.5 ± 2 (11)	10.1 ± 0.8 (6)	9.0 ± 0.7 (6)	9.5 ± 0.9 (7)	9.2 ± 0.7 (9)	9.8 ± 0.9 (7)	10.9 ± 0.5 (5)	13 ± 0.2 (26)
Edema	10/10	11/11	6/6	4/6	4/7	3/9	0/7	0/5	0/29
Infection during preceding 3 days	4/10	5/11	4/6	1/6	0/7	3/9	2/7	2/5	0/29
Volume of 24 hour stool (ml.)	—	253 ± 75 (10)	142 ± 54 (6)	81 ± 17 (6)	92 ± 38 (3)	69 ± 12 (8)	124 ± 46 (6)	173 ± 19 (4)	126 ± 18 (17)
Vomiting	—	3/10	3/9	0/6	0/7	0/9	0/7	0/5	2/29
Dehydration	3/9	1/11	2/9	0/6	0/7	0/9	0/7	0/5	0/29
Total serum proteins (Gm./100 ml.)	4.4 ± 0.2 (10)	3.9 ± 0.1 (11)	4.1 ± 0.1 (5)	4.4 ± 0.3 (6)	5.7 ± 0.3 (5)	6.8 ± 0.3 (7)	7.4 ± 0.2 (7)	7.8 ± 0.2 (5)	7.3 ± 0.1 (21)
Serum albumin (Gm./100 ml.)	2.0 ± 0.1	1.6 ± 0.1	1.5 ± 0.2	1.6 ± 0.2	1.4 ± 0.6	3.0 ± 0.4	3.8 ± 0.3	3.4 ± 0.3	4.0 ± 0.1
Creatinine height index		44 ± 3 (11)	46 ± 9 (6)	50 ± 8 (6)	53 ± 4 (7)	61 ± 4 (9)	78 ± 6 (7)	84 ± 8 (5)	89 ± 3 (26)
Caloric intake (cal./Kg./day)	—	36 ± 7 (11)	73 ± 2 (6)	72 ± 2 (6)	110 ± 7 (7)	113 ± 3 (9)	117 ± 3 (7)	120 ± 0 (5)	110 ± 3 (26)
Protein intake (Gm./Kg./day)	—	0	0.7	0.7	3.0	3.0	3.0	3.0	3.0

A_1 = admission, A_{2-3} = average 5 days after admission, A_4 = last day of admission period. T_1, T_2, and T_{3-4} = observations at 1 week intervals.

*Mean ± standard error; number of patients in parentheses.

†Complete recovery. This group includes INCAP patients who were on other protocols during recovery from protein-calorie malnutrition.



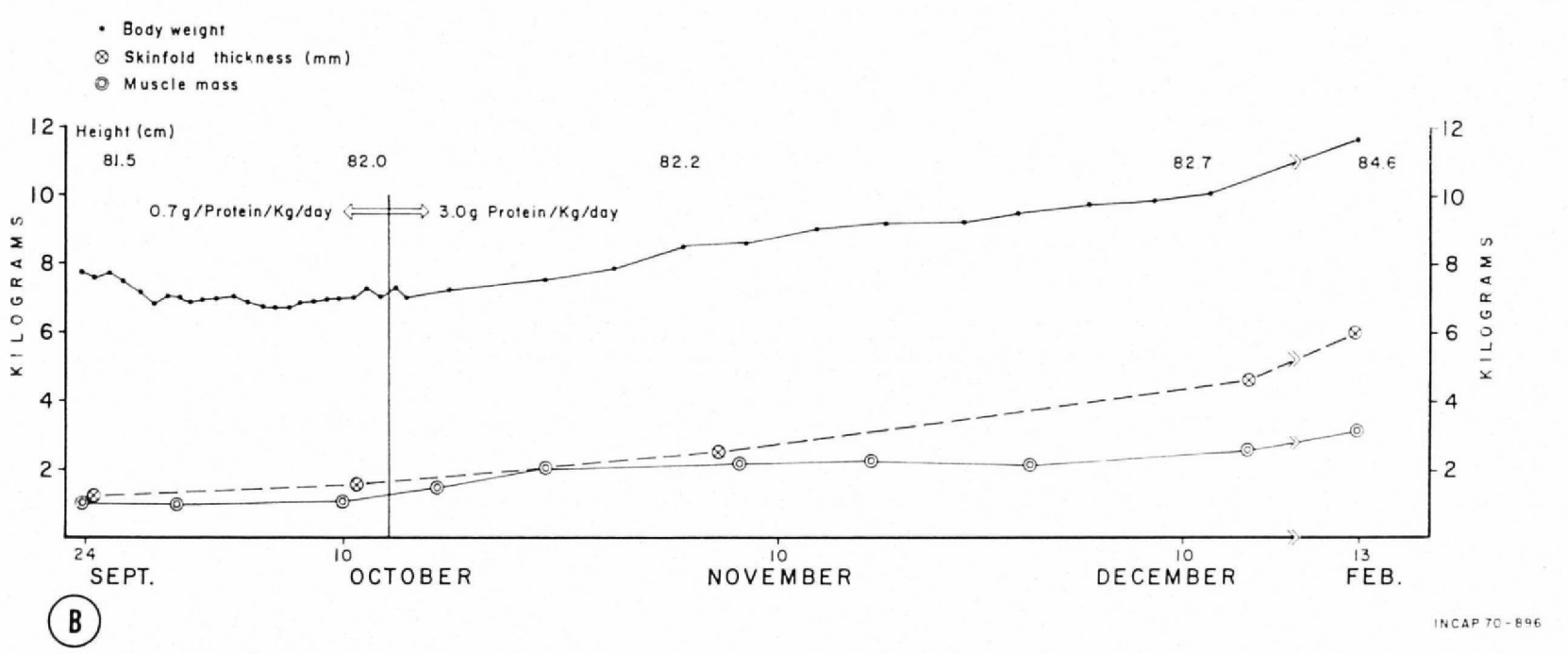


Fig. 1. *A* and *B*, Clinical progress of a typical patient, PC 187. Daily weights are indicated in kilograms, skin fold thickness at the triceps is recorded in millimeters, and the calculated muscle mass based upon creatinine excretion is included. Dietary periods are indicated by the vertical line.

be due to adipose tissue. Skin fold thickness increased proportionally to gain in body weight. Creatinine excretion had a slower rate of recovery.

The clinical descriptions of children included in the longitudinal study are listed in Table I. A summary of the clinical observations of these children at the time of each biopsy is given in Table II. The subjects studied at Guatemala General Hospital had a greater percentage of normal weight for height and higher values for serum protein concentration than did the children admitted to the INCAP metabolic ward. While the INCAP group was on the 0.7 Gm. per kilogram casein diet (Periods A_1 through A_4), there was no significant improvement of percentage of weight for height, creatinine height index, or serum protein concentration. Within five days after the casein intake was increased, there were striking increases in serum protein concentration (T_2). Albumin concentrations were normal after 22 days of therapy. Creatinine height index continued to rise progressively throughout recovery. Weight increase was not significant until 22 days after therapy began but had reached normal for height at the end of the study. At the end of Period A, muscle mass contributed 14 per cent of edematous total body weight. After 22 days of therapy, muscle made up 25 per cent of nonedematous body weight.

Serum concentration. Serum electrolyte values are given in Table III. In the INCAP subjects, serum potassium concentrations

rose significantly from low-normal (A_1, A_{2-3}) to normal values (A_4) during the equilibration period, remaining constant thereafter. The mean sodium and chloride values were constantly normal throughout the study. No significant depletion in serum magnesium concentrations was observed in the INCAP children.

Muscle composition. Muscle potassium content was low at admission when expressed in ratio to FFWW or FFDW (Table III). No significant recovery in potassium content was observed until 10 days after the high protein-calorie regimen was begun. Sodium per kilogram of FFWW rose significantly after admission then fell slowly during recovery. Chloride per kilogram of FFWW increased throughout the equilibration period and returned slowly to control values during the therapeutic period. The ratio of potassium to myofibrillar nitrogen MEN was not significantly reduced at the time of admission but fell at the end of Period A. This reduced ratio persisted throughout the first 12 days of therapy. Sodium and chloride in ratio to myofibrillar nitrogen were significantly elevated at the time of admission and unchanged during the equilibration period, returning slowly to control values during therapy.

The constituents of the dry solids of muscle are also listed in Table III. The water-soluble or sarcoplasmic nitrogen fractions were little affected by the equilibration period and therapeutic diet. The alkali-soluble myofibrillar nitrogen was reduced but relatively constant from admission through the equilibration phase and during the first three weeks of the therapeutic period. Alkali-insoluble collagen nitrogen was increased in concentration in those samples with reduced myofibrillar nitrogen.

DISCUSSION

Although the patients admitted to this study had some clinical improvement during the period of maintenance diet, there was no significant increase in values for total serum proteins, serum albumin, or creatinine height index on the protein intake of 0.7 Gm. per kilogram. This level of protein intake, therefore, was negligible in its effect on protein nutrition during this period. When the protein intake was increased to a therapeutic level of 3 Gm. per kilogram per day, a prompt response in the indices of protein metabolism occurred. Total serum protein values were increased significantly after five days, the serum albumin level rose significantly after 12 days, and muscle mass was increased significantly after 22 days of therapy. Clinical edema persisted in a few of the patients for as long as 12 days. Increases in per cent of normal weight per height were evident at 22 days as muscle mass replaced the edema present at the time of admission.

In the present study we have attempted to measure the degree of functional potassium saturation of muscle in the state of protein depletion and during recovery. We have reasoned that potassium desaturation can be identified by the uptake of potassium by the depleted tissue, and that the functional capacity of the tissue can be defined by the concentration of potassium if no uptake is occurring. This concept is widely accepted by those studying the saturation of other biological and inanimate systems.[17-19]

Potassium supplements of 4 mEq. per kilogram per day were administered throughout the study. A significant rise in serum potassium concentrations occurred during Period A, which indicates that some depletion of extracellular potassium was present at the time of admission, but within five days the average range was attained. Linder and coworkers[20] demonstrated that children on a similar protocol were retaining 2.3 mEq. of potassium per kilogram per day. In an associated study (in preparation), we have confirmed a retention of 1.3 mEq. per kilogram per day in the INCAP patients reported here. This positive balance negates the possible cumulative role of gastrointestinal or renal losses of potassium during the study. During the maintenance diet (Period A), no significant repletion of muscle potassium concentrations occurred, despite the recovery of the extracellular concentrations of potassium, the cessation of diarrhea, and the positive potassium balance. The obvious

conclusion is that no desaturation of the muscle for potassium was present at the time of admission or at the end of the admission dietary period.

Muscle potassium concentrations, which had stayed relatively constant on the maintenance diet, fell significantly during the first five days of therapy. Thereafter, the potassium concentration rose significantly in an exponential trajectory. Recovery, however, was not complete for several weeks, which is in contrast to the recovery within a few days of the acute depletion of potassium.[21] Muscle sodium and chloride concentrations fell as a function of days of therapy along an exponential trajectory, chloride falling as a function of time more smoothly than sodium. The response of muscle electrolyte concentration to the therapeutic diet confirms the conclusion made in the discussion of Period A that no desaturation was present at the time of admission. As muscle mass recovered, as evidenced by the creatinine height index, muscle electrolyte concentration also became normal. From this we conclude that the changes in the capacity of muscle for potassium form the basis for the low muscle potassium concentrations seen in protein-calorie malnutrition.

In general, our conclusion agrees with that of Alleyne and associates[7] that altered muscle potassium concentrations in protein-calorie malnutrition represent a reduction in capacity for the ion. In their most severely malnourished children (those with total body potassium below 30 mEq. per kilogram), Alleyne and associates postulated that a superimposed potassium desaturation of muscle had occurred. They reported values of 100 ± 20 mEq. per kilogram fat-free dry weight. Their values for severely malnourished children are much lower than ours and much lower than those reported by any other investigator in this field (see Nichols and associates, Table V[5]). For this reason it can be assumed that Alleyne and associates did in fact observe acute desaturation superimposed on chronic reduction of muscle potassium capacity.

One mechanism by which the capacity of muscle for potassium is restricted in protein-calorie malnutrition and recovers during therapy could be the loss of cytoplasmic mass. Such changes are evident histologically in children dying with protein-calorie malnutrition at this Center and elsewhere. In Guatemalan children[22] the modal fiber diameter of skeletal muscle in this disorder is approximately 10μ and that in normal muscle, 20μ. Montgomery[23] found by planimetric analysis of similar muscle samples in malnourished Jamaican children that the intracellular space could be halved and the extracellular space doubled. Such changes should be evident in the chemical composition of muscle. Increased concentration of collagen, the chief extracellular component of the dry solids of muscle, was observed in the patients admitted to Guatemala General Hospital and INCAP. This observation is consistent with the results of previous investigations.[1, 6, 24] The elevation of collagen present at admission was present throughout Period A. It fell significantly at 12 days of therapy but did not fall further until 45 days. In the INCAP series, the myofibrillar nitrogen values were remarkably uniform throughout the admission period and for the first 22 days of therapy; the values rose very late in therapy. The ratio of myofibrillar to collagen nitrogen was relatively constant from admission through the first three weeks of therapy despite the early increase in muscle mass as evidenced in the creatinine excretion on the therapeutic diet. This observation suggests that initially, muscle mass was increasing through an increase in number of fibers, and that changes in fiber size occurred late. The reported reduction in muscle fiber number in protein-calorie malnutrition supports this thesis.[25] Our data suggest that collagen is being synthesized at very nearly the same rate as cellular protein during early recovery. Such a concept is supported by the observations of Picou and coinvestigators[26] and Graham and associates,[27] who observed increased hydroxyproline excretion which paralleled creatinine during recovery from protein-calorie malnutrition.

From the data presented in this paper and

Table III. Electrolyte values of serum and muscle in children with protein-calorie malnutrition*

Electrolyte studies	*HGG series*	*INCAP series admission period*			*Therapeutic period*				*Recovery*
		A_1	A_{2-3}	A_4	T_1	T_2	T_{3-4}	T_5	
Average duration of diet (days)		0	5 ± 1	14 ± 2	5 ± 3	12 ± 1	22 ± 2	45 ± 5	117
Serum electrolytes (mEq./L.)									
Potassium	4.1 ± 0.03 (10)	3.9 ± 0.2 (11)	4.0 ± 0.3 (7)	4.7 ± 0.2 (7)	4.5 ± 0.3 (6)	4.5 ± 0.2 (10)	4.5 ± 0.2 (7)	4.6 ± 0.1 (5)	4.4 ± 0.1 (25)
Sodium	132 ± 1 (10)	136 ± 2 (11)	138 ± 3 (7)	138 ± 3 (7)	135 ± 2 (6)	136 ± 2 (10)	136 ± 3 (7)	137 ± 0.4 (5)	136 ± 1 (25)
Chloride	103 ± 2 (10)	99 ± 2 (11)	102 ± 3 (6)	102 ± 2 (7)	99 ± 1 (6)	99 ± 1 (10)	100 ± 1 (7)	98 ± 1 (5)	100 ± 1 (25)
Magnesium	1.01 ± 0.09 (8)	1.33 ± 0.10 (10)	1.40 ± 0.06 (8)	1.16 ± 0.12 (5)	1.13 ± 0.11 (6)	1.26 ± 0.09 (10)	1.32 ± 0.11 (5)	1.44 ± 0.11 (5)	1.28 ± 0.09 (20)
Muscle electrolytes and water									
Water % FFWW	85 ± 1 (10)	84 ± 1 (11)	80 ± 1 (7)	83 ± 2 (7)	82 ± 3 (7)	80 ± 1 (10)	81 ± 0.4 (6)	81 ± 1 (5)	80 ± 0.2 (27)
Water L./Kg. FFDW	5.9 ± 0.5 (10)	5.6 ± 0.4 (6)	4.0 ± 0.2 (7)	5.5 ± 0.8 (7)	4.9 ± 0.6 (6)	4.1 ± 0.2 (10)	4.2 ± 0.1 (6)	4.3 ± 0.2 (4)	3.9 ± 0.1 (22)
Potassium FFWW (mEq./Kg.)	42 ± 5 (10)	49 ± 5 (11)	47 ± 3 (7)	44 ± 2 (7)	40 ± 3 (7)	50 ± 4 (10)	59 ± 4 (6)	67 ± 5 (5)	70 ± 2 (26)
Sodium FFWW (mEq./Kg.)	70 ± 7 (10)	70 ± 5 (11)	86 ± 6 (7)	77 ± 10 (7)	80 ± 17 (7)	75 ± 5 (10)	66 ± 7 (6)	64 ± 5 (5)	62 ± 3 (27)
Chloride FFWW (mEq./Kg.)	24 ± 3 (10)	37 ± 4 (11)	41 ± 5 (7)	38 ± 5 (7)	36 ± 5 (7)	40 ± 2 (10)	31 ± 2 (6)	29 ± 5 (5)	28 ± 2 (27)

Potassium FFDW (mEq./Kg.)	300 ± 47 (10)	296 ± 21 (11)	244 ± 21 (7)	278 ± 29 (7)	231 ± 34 (7)	258 ± 19 (10)	303 ± 16 (7)	354 ± 14 (5)	345 ± 8 (27)
Sodium FFDW (mEq./Kg.)	478 ± 52 (10)	449 ± 31 (11)	437 ± 26 (7)	497 ± 84 (7)	389 ± 38 (7)	389 ± 39 (10)	342 ± 33 (7)	342 ± 25 (5)	300 ± 14 (28)
Chloride FFDW (mEq./Kg.)	162 ± 15 (10)	237 ± 26 (11)	211 ± 29 (7)	233 ± 30 (7)	211 ± 31 (7)	206 ± 16 (10)	160 ± 10 (7)	155 ± 24 (5)	138 ± 10 (28)
Potassium MFN (mEq./Gm.)	2.8 ± 0.4 (9)	4.0 ± 0.5 (11)	3.6 ± 0.6 (7)	3.1 ± 0.4 (5)	2.8 ± 0.4 (6)	3.1 ± 0.3 (8)	3.9 ± 0.3 (7)	4.4 ± 0.8 (5)	3.8 ± 0.2 (25)
Sodium MFN (mEq./Gm.)	4.4 ± 0.5 (9)	6.2 ± 1 (11)	6.6 ± 1.1 (7)	5.6 ± 0.6 (5)	6.0 ± 1.5 (5)	4.8 ± 0.5 (8)	4.4 ± 0.6 (7)	4.0 ± 0.6 (5)	3.4 ± 0.3 (26)
Chloride MFN (mEq./Gm.)	1.4 ± 0.1 (9)	3.4 ± 1 (11)	3.2 ± 0.6 (7)	2.9 ± 0.4 (5)	3.3 ± 0.8 (5)	2.5 ± 0.4 (8)	2.1 ± 0.2 (7)	1.9 ± 0.4 (5)	1.5 ± 0.1 (26)
Muscle nitrogen fractions									
Sarcoplasmic FFDW (N/Kg.)	29 ± 5 (7)	16 ± 3 (9)	12 ± 3 (4)	17 ± 8 (4)	14 ± 3 (4)	12 ± 2 (3)	12 ± 5 (2)	27 ± 14 (4)	15 ± 3 (18)
Myofibrillar FFDW (N/Kg.)	118 ± 6 (9)	84 ± 8 (11)	76 ± 9 (7)	85 ± 16 (6)	86 ± 14 (6)	86 ± 10 (8)	81 ± 7 (7)	95 ± 9 (5)	96 ± 4 (26)
Collagen FFDW (N/Kg.)	35 ± 7 (9)	28 ± 6 (11)	27 ± 6 (7)	34 ± 2 (6)	30 ± 11 (6)	29 ± 3 (8)	27 ± 5 (7)	12 ± 4 (5)	21 ± 3 (27)

Abbreviations: FFDW = fat-free dry weight, FFWW = fat-free wet weight, MFN = myofibrillar nitrogen.

*Mean ± standard error; number of patients in parentheses.

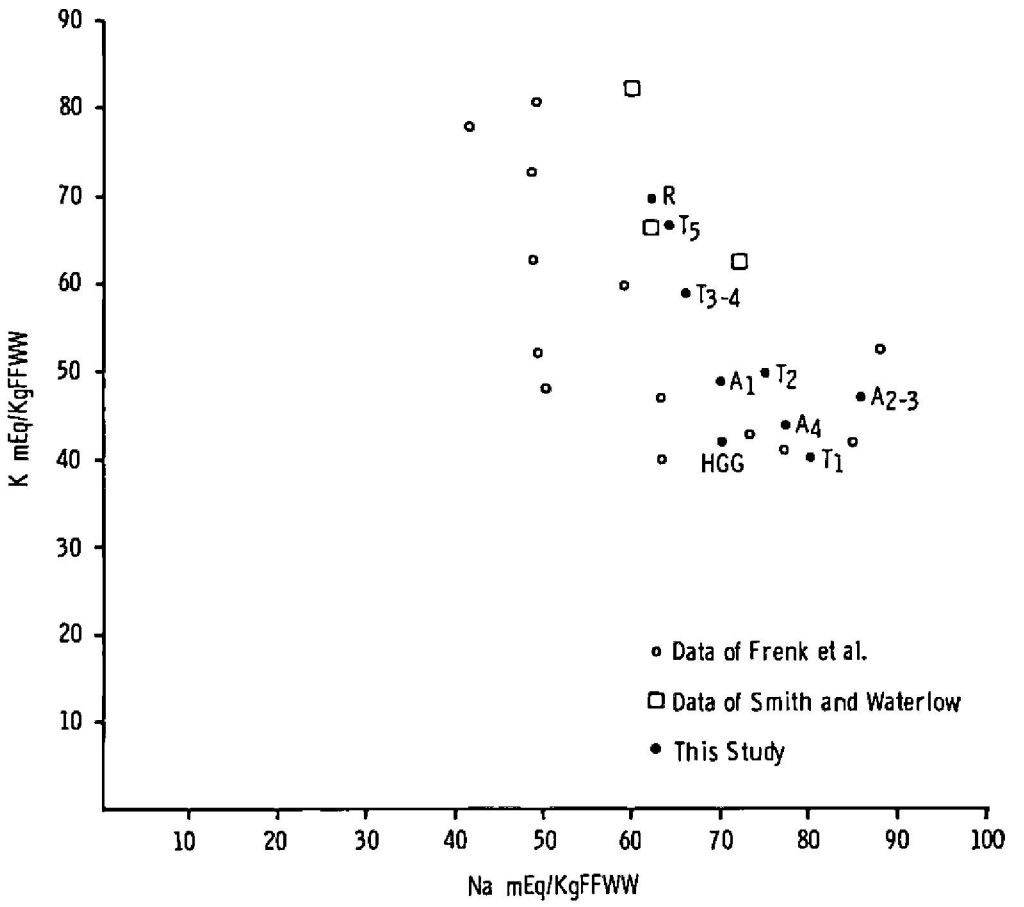


Fig. 2. The relationship between muscle potassium and sodium in milliequivalents per kilogram FFWW. The values are taken from Table II. The data in this paper are fit by the equation $K = 166 - 1.6 \times Na$; the R value is -0.960. The data from previous studies of muscle composition in protein-calorie malnutrition[2, 4] are indicated as open figures.

the premises discussed above, we can develop a hypothesis that describes the muscle electrolyte alterations in the malnourished state. As discussed previously, the potassium supplementation was ineffective in altering the chemical composition of muscle in Period A. For this reason we can state that the tissue was saturated at this period and that altered capacity for potassium accounted for reduced concentration of the ion. The role of the underlying nutritional status is clearly documented by the orderly recovery during the therapeutic period. The mechanism that controls the altered capacity in Period A can be studied by an analysis of the progressive changes during recovery. A close correlation ($R = 0.960$) exists between the concentrations of sodium and potassium of muscle observed in our study (Fig. 2). The relatively constant ratio of myofibrillar to collagen protein during the rapid changes in sodium and potassium concentration indicates that this is a change of functional capacity and not simply of anatomic cytoplasmic capacity. The computed slope of the relationship demonstrates that approximately two sodium ions are gained for each three potassium ions lost. This is not significantly different from the slope computed from the data on total tissue concentration in Cooke and Segar's[32] review of the changes in muscle composition in acidosis and alkalosis.

Ling[18] has presented a unified view of muscle function which facilitates the interpretation of our data. His basic tenet is that ions and water within cells are not in a state of free solution. Ions are absorbed to macromolecules whose selectivity is determined by the state of energy production in the tissue. The interaction of adenosine triphosphate (ATP) with the macromolecule results in changes in the fixed charges of the organic molecule causing them to prefer potassium over sodium. When energy metabolism is reduced, the production of ATP can no longer match the rate of its hydrolysis and ATP concentration is reduced. The relative reduction in ATP concentration results in the alteration of fixed charges on the macromolecules such that a fraction of the sites occupied by potassium are instead

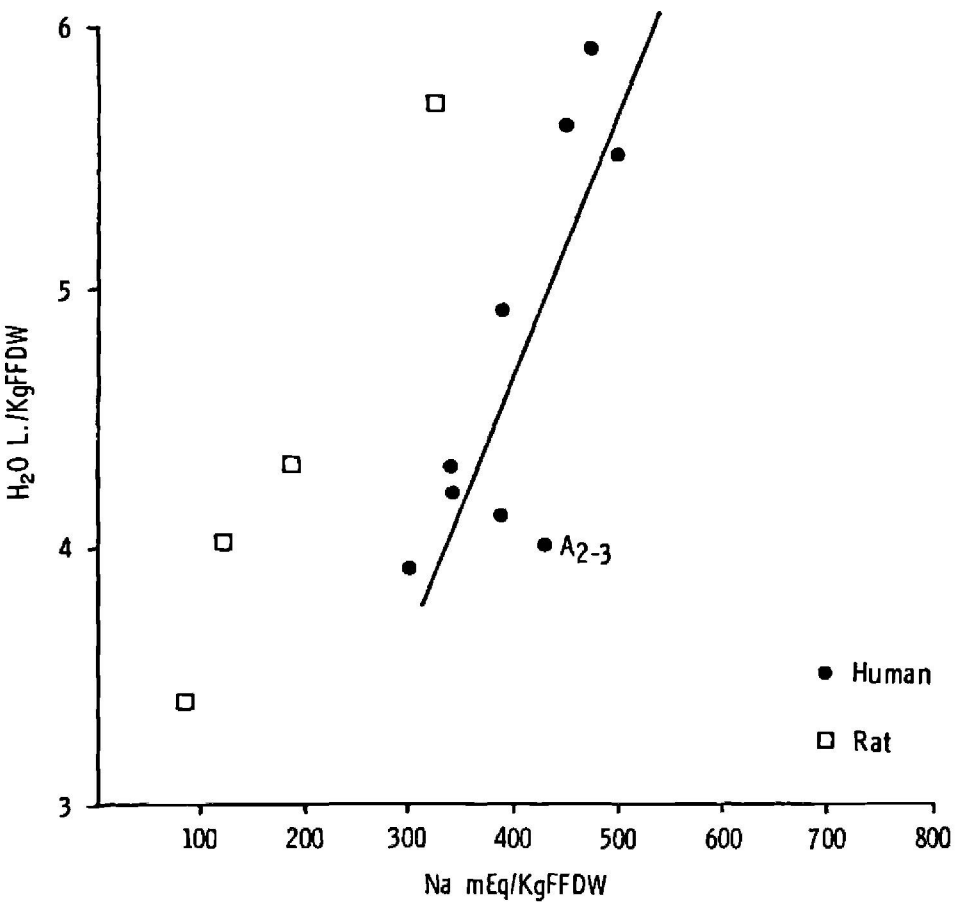


Fig. 3. The relationship between muscle sodium and water per kilogram per FFDW. The values are taken from Table II and from our earlier study in rats.[28] For the patients with protein-calorie malnutrition (solid figures), the data are fit from the equation $H_2O = 0.76 + 0.01 \times Na$; the R value is 0.920. For the rat (open figures) $H_2O = 0.03 + 0.007 \times Na$ with an R value of 0.980.

occupied by sodium. The number of fixed charges preferring potassium determines the capacity of the tissue for potassium and sodium. Our earlier report of reduced mitochondrial metabolism in the muscle of children with protein-calorie malnutrition is consistent with the applicability of this view to our data.[33]

Fig. 3 gives insight into the mechanism that controls muscle hydration. A highly significant correlation (R = 0.920) exists between sodium and water per FFDW. The correlation of water with potassium per FFDW is negligible. Sodium, therefore, is intimately associated with the water content of muscle in protein-calorie malnutrition. This is a generalized biological principle. (The data from a study in immature rats[28] are included in Fig. 3 to illustrate this point.) We have obtained evidence[29] that water is not in free solution in tissue. We have also observed that the increased concentration of sodium in the muscle of immature rats is associated with a less ordered structure of the water molecules[30]; the increased muscle sodium concentrations may represent the increasing solvent properties of water for sodium in the malnourished as well as the immature state.

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