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9. ABSTRACT

Milks based on isolated soy protein enriched with DL-methionine rapidly are coming into use in pediatric practice. The biological value of its protein has been measured at critical levels in the initial therapy of malnourished infants and children and during convalescence. Absorption and retention of nitrogen, as well as growth rates, were equivalent to those from modified cow's milk. Normal serum albumin levels were achieved and maintained, as were levels of fasting plasma amino acids, both indicative of dietary protein adequacy. These results confirm the enormous potential of isolated soy protein in human nutrition, particularly in the diet of those intolerant of milk proteins or lactose.

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Dietary Protein Quality in Infants and Children

PN-AAC-588

VI. Isolated Soy Protein Milk

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Milks based on isolated soy protein enriched with DL-methionine are rapidly coming into common use in pediatric practice. The biological value of its protein has been measured at critical levels in the initial therapy of malnourished infants and children and during convalescence. Absorption and retention of nitrogen, as well as growth rates, were equivalent to those from modified cow's milk. Normal serum albumin levels were achieved and maintained, as were levels of fasting plasma amino acids, both indicative of dietary protein adequacy. These results confirm the enormous potential of isolated soy protein in human nutrition, particularly in the diet of those intolerant of milk proteins or lactose.

The successful production of isolated soy protein (ISP) of high biological value[1] has opened up numerous possibilities in human nutrition. Although soy "milks" have been used for many years in the management of infants allergic to cow's milk proteins, their application has been restricted by their obvious soy taste and odor, unpleasant bastrointestinal side effects, inferior digestibility, and often questionable biological value.[2]

Within a few years of their introduction, milks based on ISP enriched with DL-methionine have found wide acceptability, not only in the prolonged management of allergy, but also in that of the transient lactase deficiency which follows many severe diarrheal episodes in general pediatric practice. Isolated soy protein should find wide application in the nutrition of those children, particularly the nonwhite, who are genetically predisposed to lose most of their intestinal lactase activity in childhood[3] and will not tolerate more than small amounts of cow's milk.

As the use of ISP is broadened and its unit cost decreases, it is likely to play an important part in efforts to prevent the widespread malnutrition which plagues the world. Cow's milk and its derivatives are not only expensive and perishable but also inappropriate for mass application in populations where the majority of children lose their lactase activity as a matter of course.[4] In the treatment of severe malnutrition, lactose intolerance is a serious problem, making necessary the use of lactose-free formulas put together from simple ingredients and often defective in their micronutrient content.[5] In those who can tolerate lactose, modified cow's milk has proven far superior to other products in the initial management of the severely malnourished,[6-9] suggesting that in this state differences in protein quality are brought out which are not apparent in healthy infants.

Although animal studies[1,10] have documented precisely the relative biological value of complete milks based on ISP, there have been few critical studies in the human infant. It has been shown that prolonged feeding at generous protein-to-calorie ratios in a mixed diet supported "normal" growth.[11] At much more

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critical ratios just below the minimum level we have found to be consistently satisfactory with modified cow's milk, a moderate fall in serum albumin levels was reported.[12]

The present report details our evaluation of an ISP milk in the diet of convalescent malnourished infants and its use in their initial dietary management. Comparisons were made with milk protein at critical protein-to-calorie ratios.

Materials and Methods

The methods used have been described in previous publications.[13] Although the ISP milk has a full complement of accepted micronutrients, these were diluted when sugar and oil were added to reduce the protein-to-calorie ratio. Consequently, appropriate amounts of vitamins and minerals were added to satisfy the recommended daily intakes. The same was done when milk was the source of protein.

The nitrogen balance studies usually correspond to the entire dietary period reported. When not, they were carried out during the last six to nine days of the diet period.

Changes in body weight of the convalescent children usually parallel the nitrogen retentions. The comparative studies were carried out when "weight age" had at least equaled "height age" and the initially abnormal body water content and distribution had been corrected.[14] In the acutely malnourished, particularly those with hypoalbuminemia and visible or inapparent edema, or those with dehydration, changes in body weight must of course be interpreted differently. Weight loss may be accompanied by excellent nitrogen retentions and a rising serum albumin, while weight gain may be associated with sodium and water retention, poor or no nitrogen retention, and a falling serum albumin.

Although discordant changes are seen occasionally, we attach considerable significance to serum albumin levels, measured by paper electrophoresis.[15] When these rise or are maintained at normal levels (more than 4.0 gm/100 ml) in association with steady gain in weight, we consider that dietary protein is adequate for the level of calorie intake. If during periods of steady weight gain there is a fall in serum albumin levels, or these are maintained at subnormal values, we assume that body composition is deteriorating or not being corrected and that dietary protein is inadequate.

Interpretation of long-term growth must be made with caution in convalescent malnourished children. Some resume linear growth immediately, others after a lag of some weeks, regardless of the diet. The period of accelerated linear growth is variable in duration and efficiency. Consequently, the timing of such studies may influence the extent of the growth observed. If gains in height age equal or exceed those in chronologic age, satisfactory catch-up growth is occurring. Rapid gains in weight age occur more promptly and may continue to the point of visible obesity.[14] If during these gains serum albumin remains normal, we feel confident that the weight gain is not water retention.[15]

The methods for plasma amino acid determination, as well as our rationale in reporting the results, have been reported.[16,17]

Results

Table 1 summarizes comparisons made in four convalescent children between ISP milk and a modified cow's milk as the sole source of protein at isonitrogenous and isocaloric levels, with 6.4% to 9.4% of calories as protein. In all four the apparent retention of nitrogen as a percentage of intake was moderately, though not significantly, superior on the ISP milk. The same was true for the rates of weight gain. These differences were not due to differences in rates of nitrogen absorption, nor were they large enough to be attributed to differences in biological value. Stool weights were consistently higher on the modified milk, suggesting a greater loss of calories, probably as stool fat. Although limited measurements suggest this to be true, they were not complete enough to be included in this report. In all four cases serum albumin remained at normal levels.

In the fifth child in whom the comparison was made with calcium caseinate as the source of protein, an error of calculation caused the diets to be different in calorie content. The more efficient absorption of nitrogen from casein and the higher calorie intakes probably account for most of the differences in apparent nitrogen retention. Serum albumin also remained normal.

In one child (Table 2) the ISP milk was the sole source of protein for 6.2 months. During the first 2.5 months, 8% of calories were provided as protein. Gain in height age matched the advance in chronologic age; gains in weight age far exceeded chronologic age, but serum albumin remained normal. During the next 1.7 months, protein was reduced to 6% of the same calorie intake; progress in height age actually accelerated as did that in weight age, but serum albumin remained normal. A further reduction in protein to 5% of calories did not slow the accelerated growth and did not reduce serum albumin. Calorie intake was at all times high for this child, and he became markedly obese. There was never any indication of protein inadequacy. Liver biopsy revealed normal architecture at the end of the 6.2 months.

Table 3 summarizes the results in the initial management of five severely malnourished infants. The first, admitted with severe marasmus and a serum albumin level of 4.59 gm/100 ml, initially experienced significant weight loss and a marked fall in serum albumin, at least partly dilutional. Subsequently, both trends were reversed and very satisfactory catch-up growth was established. In the second infant, with a not quite so severe case of marasmus, satisfactory response was more prompt.

The third child, admitted with severe marasmic kwashiorkor and acute dehydration, responded promptly and dramatically after initial rehydration. The fourth, another case of moderately severe marasmus, also responded promptly. The fifth, a case of marasmic kwashiorkor in a 9-month-old infant, also responded well, though not as promptly.

Table 4 summarizes our experience in the initial management of severe-

Table 1.—Nitrogen Balances, Rates of Weight Gain, and Serum Albumin Levels of Convalescent Malnourished Infants*

Age in Months†			Diet Protein gm/kg/Day and kilocalorie/kg/Day			No. of Days	Nitrogen Balances‡ mg/kg/Day		% of Intake		Δ Weight gm/kg/Day	Serum Albumin gm/100 ml	
CA	HA	WA					Int	Ret	Abs	Ret		Δ	Final
31	9	9	M	2.0	100	20	320	64	84	20	2.9	−0.07	4.57
			S	2.0	100	14	320	78	82	24	3.3	0.02	4.59
32	11	11	S	2.0	100	9	320	96	83	30	5.5	−0.06	4.24
			M	2.0	100	11	320	66	84	21	3.0	0.25	4.49
26	12	13	M	2.0	125	10	304	58	78	19	3.7	0.46	4.43
			S	2.0	100	8	320	66	80	21	2.1	−0.15	4.28
			S	2.0	125	7	291	77	80	26	6.4	−0.11	4.17
28	16	18	S	2.0	85	8	320	45	86	14	1.4	0.08	4.36
			M	2.0	85	6	320	36	81	11	−2.6	0.05	4.41
11	4	4	S	2.5	138	8	400	79	74	20	9.6	−0.10	4.20
			C	3.0	150	9	480	140	91	29	10.7	0.36	4.56
			C	2.5	150	6	400	119	85	30	6.5	−0.41	4.15

* Children received modified milk (M), casein (C), or ISP milk (S) as the sole source of dietary protein.
† Chronologic (CA), height (HA), and weight (WA) ages at time of study.
‡ Intake (Int), retention (ret), and absorption (abs).

Table 2.—Prolonged Feeding of ISP Milk as the Only Source of Dietary Protein

Initial Age (mo)*			Protein gm/kg/Day	Kilocalories Per kg Per Day	Kilocalories % Protein	Progress (mo)*			Serum Albumin gm/100 ml	
CA	HA	WA				CA	HA	WA	Δ	Final
31.5	10.0	10.5	2.0	100	8.0	2.5	2.5	6.5	−0.24	4.33
34.0	12.5	17.0	1.5	100	6.0	1.7	2.5	6.0	0.04	4.37
35.7	15.0	23.0	1.25	100	5.0	2.0	3.5	7.0	−0.13	4.24

* Chronologic (CA), height (HA), and weight (WA) ages.

Table 3.—ISP Milk in the Initial Dietary Management of Severely Malnourished Infants

Age, Height, Weight	Protein gm/kg/Day	Kilocalories Per kg Per Day	Kilocalories % Proteins	No. of Days	Δ Weight gm/kg Per Day	Serum Albumin gm/100 ml Δ	Serum Albumin gm/100 ml Final
13 mo,	2.0	100	8.0	7	−10.0	−0.41	4.18
66 cm (26 in),	2.5	125	8.0	4	−7.2	−0.80	3.38
4.9 kg (11 lb)	3.0	150	8.0	12	6.2	−0.95	2.43
	4.0	150	10.3	23	6.5	1.42	3.85
	3.0	150	8.0	17	3.9	0.59	4.44
7 mo,	1.7	71	9.6	9	8.0	−0.23	3.54
64 cm (25½ in),	2.4	93	10.3	14	−1.8	0.28	3.82
4.9 kg (11 lb)	2.5	125	8.0	11	3.8	0.23	4.05
	2.5	150	6.7	28	6.5	0.17	4.22
22 mo,	Intravenously administered fluids			2	10.0	−1.13	2.28
71 cm (28 in),	1.7	46	12.6	4	0.4	0.44	2.72
5.9 kg (13 lb)	2.4	73	13.1	9	−2.2	0.71	3.43
	2.5	100	10.0	5	6.7	0.15	3.58
	3.0	125	9.6	26	6.3	0.79	4.37
15 mo,	2.1	83	10.1	9	1.8	0.15	3.73
70 cm (27½ in),	2.5	125	8.0	20	0.7	0.44	4.17
5.9 kg (13 lb)	2.5	150	6.7	22	5.7	0.42	4.59
9 mo,	1.75	47	14.9	5	−10.0	0.34	3.02
64 cm (24 in),	2.5	75	13.3	4	3.9	0.18	3.20
4.6 kg (10 lb)	2.5	112	9.0	6	5.0	−0.15	3.05
	3.0	140	8.6	10	7.9	0.24	3.29
	4.0	150	10.7	35	6.7	0.95	4.24

ly malnourished twin boys, 9 months of age, with marasmic kwashiorkor and acute dehydration. Intravenous rehydration resulted in marked weight gain and a further dilutional fall in serum albumin. After this, one was given modified cow's milk and the other the ISP milk. Because of individual differences, adjustments in protein and calorie intakes, though similar, were not exactly parallel. Both had a satisfactory diuresis, a gradual but satisfactory correction of the hypoalbuminemia, complete disappearance of hepatic steatosis on biopsy, and establishment of steady weight gain. The fact that both were extremely sick initially, as well as their young age, probably accounts for responses that were not as rapid and steady as those usually seen in older children with uncomplicated kwashiorkor.

Measurements of fasting plasma amino acids were made in four infants receiving ISP milk at 6.4% to 6.7% of calories as protein, a generally very critical level. In one, a single determination was made; in the others, three separate determinations, at least 15 days apart, were made. The individual results are reported in Table 5; a comparison with the results obtained in similar children receiving other sources of protein at similar, though not quite so critical levels, is reported in Table 6. Total free amino acids were not significantly different from those of infants receiving cow's milk protein[17] or wheat flour enriched with lysine.[18] They were moderately higher than those of infants on a corn-soy-milk (CSM) blend, a significantly less well absorbed protein mixture.[19] Essential plus semiessential amino acids, both

Table 4.—ISP Milk or Modified Cow's Milk as the Sole Source of Protein*

	Protein gm/kg/Day	Kilocalories Per kg Per Day	Kilocalories % Protein	No. of Days	Δ Weight gm/kg/Day	Serum Albumin gm/100 ml Δ	Serum Albumin gm/100 ml Final
Twin A, 9 mo, 58.5 cm (23 in), 3.91 kg (8 lb 9 oz)	Intravenously administered fluids only			2	40.0	−0.64	2.15
Modified milk	0.45	18	10.0	2	−22.9	0.15	2.30
	1.6	62	10.0	2	18.3	−0.18	2.12
	3.0	78	15.4	6	−6.6	0.92	3.04
	3.0	100	12.0	4	12.2	0.44	3.48
	3.0	125	9.6	10	3.0	0.26	3.74
	3.0	150	8.0	30	7.0	0.52	4.26
Twin B 9 mo, 57.5 cm (22½ in), 3.61 kg (7 lb 15 oz)	Intravenously administered fluids only			2	50.0	−0.35	2.55
ISP	1.2	47	10.0	4	−6.2	−0.42	2.13
	3.0	81	14.8	6	−2.9	0.97	3.10
	3.0	100	12.0	4	10.8	0.37	3.47
	3.0	125	9.6	10	2.5	−0.19	3.28
	3.0	150	8.0	5	−3.5	−0.18	3.10
	3.0	175	6.8	27	9.2	0.91	4.01
	2.5	138	7.3	32	6.1	0.19	4.20

* Initial dietary management of severely malnourished twin boys.

in micromols per milliliter and as a fraction of the total, were moderately but not significantly lower than when children were on the milk diets. There were significantly ($P<0.05$) higher than when children were given the other two sources of protein. We interpret these values, particularly the molar fraction, as indicative of dietary protein adequacy, and to a lesser extent, of the amino acid composition of the dietary protein. Methionine concentration, as a fraction of the essentials, was not different from that found on milk or CSM diets.

Table 5.—Fasting Plasma Free Amino Acids of Infants Receiving the ISP Milk as the Sole Source of Dietary Protein, Minimum 15 days*

Case No.	CA (mo)	HA (mo)	Dietary Protein gm/kg/Day	Dietary Protein % of Kilocalories	Plasma Amino Acids AA (μmol/ml)	EAA (μmol/ml)	EAA/AA	met/EAA
171	9	6	2.5	6.7	2.556	0.537	0.210	0.050
215	14	3	2.0	6.4	2.771	0.617	0.223	0.042
	15	4	2.0	6.4	3.211	0.634	0.197	0.036
	16	6	2.0	6.4	3.274	1.001	0.306	0.012
208	19	8	2.0	6.4	1.996	0.593	0.297	0.035
	20	8	1.65	6.6	2.016	0.611	0.303	0.029
	21	9	1.65	6.6	2.195	0.655	0.298	0.026
229	14	10	1.5	6.7	2.205	0.627	0.284	0.038
	15	10	1.5	6.7	2.273	0.559	0.264	0.042
	16	12	1.5	6.7	2.279	0.692	0.304	0.045
Mean	...		...	...	2.478	0.657	0.269	0.036
SD	...		...	...	0.456	0.128	0.043	0.011

* AA indicates total amino acids; EAA, total essential amino acids; EAA/AA, ratio of essentials total; met/EAA, methionine as molar fraction of essentials; CA, chronologic age; HA, height age at time of sampling.

Comment

Of the many sources of protein which we have evaluated in a similar manner in human infants,[7,11,16] this is the first which we have found to match cow's milk protein in nutritional value in all the situations tested. It is possible that if the comparative studies had been carried out at a slightly more critical level, below 6.4% of calories as protein, a modest inferiority might have been apparent as in the studies of Fomon.[12] In the single instance of prolonged feeding, even at 5% of calories as protein an

Table 6.—Comparison of Plasma Free Amino Acids of Infants Receiving ISP Milk With Those Receiving Milk Protein, Wheat Flour With Added Lysine, or as the Source of Dietary Protein

Source	(n)*	Protein in the Diet gm/kg/Day Mean	gm/kg/Day (Range)	% of Kilocalories Mean	% of Kilocalories (Range)	Plasma Amino Acids AA (μmols/ml)	EAA (μmols/ml)	EAA/AA	met/EAA
ISP	(10)	1.8	(1.5-2.5)	6.6	(6.4-6.7)	2.478 ±0.465	0.657 ±0.128	0.269 ±0.043	0.036 ±0.011
MILK	(17)	1.9	(1.5-2.5)	6.7	(6.4-6.9)	2.310 ±0.291	0.692 ±0.103	0.295 ±0.034	0.040 ±0.008
WL†	(24)	1.9	(1.5-2.0)	6.9	(6.4-8.0)	2.205 ±0.274	0.552 ±0.104	0.244 ±0.025	...
CSM	(11)	2.4	(2.0-3.0)	6.9	(6.4-8.0)	1.931 ±0.450	0.483 ±0.190	0.247 ±0.057	0.042 ±0.013

* Number of samples from which the mean value was determined.
† WL indicates wheat flour with added lysine.

accelerated linear growth rate was maintained. Because of a calorie intake that was excessive for the child's age and stage of recovery, weight gain proceeded to the point of obvious obesity. Serum albumin levels remained normal, and there was no accumulation of liver fat, probably because of the lower protein requirement of the child's age. In the most critical situation, that of the initial rehabilitation of severely malnourished infants, the response was as complete as it might have been with modified cow's milk. The results in equally malnourished twins were as satisfactory with ISP milk as with modified cow's milk. Although in the past we have obtained good results with 8% or less of milk protein calories,[11] we are now more inclined to increase this to 10%, at least for a few days. The risks of sodium and water retention are seemingly less at such levels.

The fact that ISP has only one third of its nitrogen as essential and semiessential amino acids while modified cow's milk has nearly 50% in the same form would suggest that inferior nutritive value should be demonstrated consistently at critical levels. That it is not supports the observation that the first-limiting factor in cow's milk protein is total nitrogen and that considerable dilution with "unessential" nitrogen is possible before a shortage of the next-limiting factor, methionine, can be demonstrated.[19] In this "excess" of essential amino acids lies one of the main reasons for its excellent supplementary value to most diets of poor protein quality. We did not test the ability of either product to supplement such diets.

We have previously demonstrated in the human infant that methionine is first-limiting in soy proteins.[20] Its addition to the ISP milk makes the balance between the essential amino acids nearly ideal. The slight excess of lysine in the final product is of no concern and, if anything, permits significant supplementation of lysine-poor cereals typically given to infants and small children as an important part of the diet.

The critical levels at which most of these studies were carried out and the very satisfactory results in severely malnourished infants both indicate that "milks" based on a high-quality ISP appropriately enriched with methionine are the practical equivalent of the best modified cow's milk products as the main or only source of protein in the diet of rapidly growing infants and small children. On the basis of the respective amino acid composition, it is probable that cow's milk protein would prove superior as a supplement to a diet in which the main source of energy was a cereal or tuber deficient in protein quality and content. This assumption was not tested in these studies.

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