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9. ABSTRACT

It is rapidly becoming evident that a large sector of populations in developing countries can handle only limited amounts of lactose, and must have other sources of dietary protein for optimum growth. Thus we must concentrate on enriching cereals and developing new sources of protein to provide essential amino acids, particularly methionine, lysine, threonine, and tryptophan. This report summarizes our studies with infants and children in the enrichment with methionine or lysine of a variety and number of protein sources, particularly soy and wheat. The addition of small amounts of DL-methionine very significantly enhances the biological value of soy proteins. The striking lysine deficiency of wheat flour, which limits the use of this versatile and acceptable cereal, can also be corrected in a vareity of ways. The addition of FPC at the 10 percent level corrects the lysine deficiency and doubles the protein content. With wheat flour alone, or with a mixture of flour and wheat concentrate, the supplementary effect of lysine is dramatic. In the many areas of the world where lactose intolerance is the rule rather than the exception, and in which the introduction of milk, even if economically feasible, results in many adverse reactions and frequent rejection, such a measure should yield immediate benefits to children and many adults.

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Methionine or Lysine Fortification of Dietary Protein for Infants and Small Children

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If the developed nations of the world were suddenly confronted with the disappearance or unavailability of the domestic cow, synthetic essential amino acids, particularly methionine and lysine, would immediately need to become a part of the daily fare of nearly all weaned infants and small children. Within a very short time methods would be developed to produce threonine and tryptophan economically and these as well as other essential amino acids would find wide applicability, probably compulsory.

Our very heavy dependence on cow's milk and its modifications for the feeding of normal infants and children makes any concern for the quantity and quality of protein in the remaining components of the diet almost fatuous. It is only in the management of patients intolerant of milk, or having inborn errors of amino acid metabolism, or in chronic renal failure, and in a few other limited situations where this has been of interest and concern to physicians and dieticians. Kwashiorkor has been reported in infants with cystic fibrosis of the pancreas if they have been fed an unenriched soy milk;[1] in patients after the curtailment of essential amino acid intake in the management of errors of amino acid metabolism;[2] and in controlling milk allergy with a rice diet.[3] It is rapidly becoming evident that a large sector of the nonwhite population can handle only limited amounts of lactose,[4] and must have other sources of dietary protein for optimum growth.

If we could safely and economically make cow's milk available to all growing human beings, we almost certainly would not need to hold a conference on amino acid fortification of foods. It is because we cannot, and must perforce depend on cereal proteins and possibly on new sources of protein, that we must worry about their quality, this the result of their content of essential amino acids, particularly methionine, lysine, threonine, and tryptophan. Historically, a deficiency of this last amino acid in many individual diets also low in niacin resulted in the development of endemic pellagra in various regions. If we had looked at

the amino acid composition of the protein available to entire communities, we most probably would have decided that no single amino acid was first limiting. Despite this, it is evident that many individuals or groups within the larger community may and actually do consume diets deficient in protein or in particular amino acids.

In the specific case of lysine, the food balance table for a particular country may not suggest a shortage, mostly because of abundant legumes and fish. In actual practice, however, we find small children consuming a cereal as the nearly exclusive source of protein, while an available source of lysine is withheld for a variety of reasons, some quite valid. When the cereal in question has lysine as its first limiting amino acid, and when a significant incidence of protein deficiency exists, the addition of lysine to the cereal can very appreciably increase the protein value of the diet as commonly consumed. The cereal, if readily available and generally acceptable, can then assume most of the role of milk and its consumption can be stimulated rather than discouraged by the prevalent injudicious practice of calling it a "starch."

In addition, one of the most valuable sources of protein available to man is the soybean. Modern technology has made possible its consumption in an incredible variety of forms, now added to many already well established soy foods used in many parts of the world. The correction of its well-known methionine deficiency offers the possibility of multiplying its nutritional value.

The present report summarizes our experience with infants and children in the enrichment with methionine or lysine of a variety and number of protein sources, particularly soy and wheat.

Methods

Severely malnourished infants and small children, most of them with complicating diarrhea, are admitted to the British American Hospital in Lima, Peru for treatment and study. Once their acute problems are under control they are rehabilitated on a variety of diets. Their predictably rapid rates of growth and prolonged strict dietary management make possible the comparative evaluation of different sources of protein at levels that are critical enough to bring out differences in protein quality. Diets are recalculated daily on the basis of body weight to provide a predetermined protein and calorie intake. A "complete" vitamin and mineral mixture is given daily.[5]

Criteria for adequacy of dietary protein in short-term studies are the rate of weight gain, the apparent nitrogen retention, and changes in

levels of plasma amino acids and serum albumin. Of these, nitrogen retention and plasma amino acids are most sensitive.[6] In long-term studies the criteria of adequacy are the rates of linear growth, weight gain, changes in serum albumin levels, and the microscopic appearance of liver biopsy tissue. The maintenance of normal serum albumin levels during satisfactory weight gain is the most useful indicator of adequacy. Other measurements, such as creatinine and hydroxyproline excretions, estimations of body water compartments, and measurements of cellular growth have proved to be of interest but are not susceptible to routine application.[7]

Results

Table 1 summarizes our experience with DL-methionine supplementation of a number of products in which its effect was minimal or inapparent. For the first child, quinoa, an Andean "cereal" of high biological value, was the source of protein at a level critical enough for the demonstration of a supplementary effect of methionine if this, as it would seem from its amino acid composition, is its first limiting amino acid. No such effect was apparent, suggesting that another factor was at least as limiting as methionine.

In the second child, receiving wheat flour with 10 percent Viobin fish protein concentrate (FPC), a questionably positive effect on nitrogen retention and serum albumin was apparent as a result of the supplement. The relative duration of the study suggests that the favorable effect on serum albumin was real. In other experiences we have been impressed with the possibility that a methionine deficiency would first become apparent as a fall in serum albumin level and an increase in liver fat, without adversely affecting weight gain or nitrogen retention.

The first of the two studies with corn-soybean milk (CSM: 68 percent corn; 25 percent soybean; 5 percent dried skim milk) in which the amino acid composition suggests that methionine is first limiting, revealed no enhancement of its biological value from supplementation, possibly because of the child's more advanced age and the short duration of each study period. In a second experiment, at a slightly more critical level in a younger child, there was a positive effect on nitrogen retention, weight gain, and serum albumin level.

Table 2 summarizes our experience with DL-methionine supplementation of a soy milk based on toasted flour. In each case there was a striking improvement in nitrogen retention, and in the last case an additional favorable effect on serum albumin. In this instance, the

Table 1 Supplementation of quinoa, wheat flour enriched with 10 percent fish protein concentrate (FPC), and a corn-soybean-milk mixture (CSM) with DL-methionine. Minimal effects on nitrogen retention, weight gain, and serum albumin levels. Casein used as a control for the CSM studies.

Age (month)	Protein	% (kcal)	DL-methionine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Wt change (g/kg/d)	Serum Albumin change	Serum Albumin final
14	Quinoa	6.0	–	12	239	45	1.6	0.12	3.89
	Quinoa	6.0	20	29	240	54	0.5	0.37	4.26
13	Wheat flour	6.7	–	27	400	112	5.7	−0.44	3.29
	+ 10% FPC	6.7	20	48	400	133	3.8	0.34	3.63
27	Casein	6.6	–	10	264	98	2.7	−0.25	4.30
	CSM*	6.6	–	15	257	59	1.8	−0.19	4.11
	Casein	6.6	–	9	264	113	2.9	−0.14	3.97
	CSM*	6.6	10	15	262	64	1.9	−0.35	3.62
	Casein	6.6	–	9	264	89	–	0.32	3.94
15	Casein	6.4	–	9	320	102	3.2	0.19	3.87
	CSM*	6.4	–	15	320	82	2.6	−0.18	3.69
	Casein	6.4	–	9	320	112	3.9	0.01	3.70
	CSM*	6.4	12	15	320	114	5.0	0.21	3.91
	Casein	6.4	–	9	320	124	3.2	0.73	4.64

* Corn 68 percent; soya 25 percent; and milk 5 percent.

Table 2 Supplementation of a soy milk based on toasted soy flour (Sobee) with DL-methionine. Comparison with a soy milk based on an isolated soy protein already enriched with DL-methionine (ProSobee). Effect on nitrogen retention, weight gain, and serum albumin levels.

Age (month)	Protein	% (kcal)	DL-methionine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Wt change (g/kg/d)	Serum Albumin change	Serum Albumin final
21	Sobee	6.0	–	6	240	42	1.5	0.15	4.42
	Sobee	6.0	11	12	232	70	–	0.57	4.99
23	Sobee	5.0	–	12	194	23	0.2	0.35	4.65
	Sobee	5.0	14	19	198	54	1.8	–0.34	4.31
13	ProSobee	6.4	–*	9	320	95	5.8	0.09	4.11
	Sobee	6.4	–	15	320	79	7.0	–0.55	3.56
	ProSobee	6.4	–*	16	317	105	4.0	0.39	3.95
	Sobee	6.4	22	18	320	106	3.6	0.24	4.19

* ProSobee comes enriched with DL-methionine.

methionine supplementation brought the value of the soy milk up to the level of a newer product based on an isolate already enriched with methionine during its manufacture.

In four studies using a different soy protein isolate (Table 3), the supplementary effect of methionine was quite clear in the nitrogen retention results and in two of them by an increase in serum albumin level. An equally favorable effect from a full-fat soy flour was also demonstrated.

At three different protein-calorie levels the supplementary effect of lysine on a milk-solids–wheat-flour product was only minimal (Table 4). At the most critical level, in the youngest child, there was a very modest improvement in nitrogen retention, a seemingly favorable effect on weight gain, and a more impressive effect on serum albumin level. At such a low protein-calorie intake the continued fall in serum albumin is not surprising. In the remaining two cases, in which nitrogen balance was not determined, no effect was apparent, possibly because the second child was older and because the third child was consuming more protein. It is more likely, however, that in a mixture in which milk provided over 50 percent of the protein, lysine was no longer the first limiting factor.

Table 5 summarizes our failure to demonstrate a supplementary effect of lysine in three different cottonseed flours in which levels of available lysine were probably adequately conserved in processing. In a single case, lysine also failed to enhance the protein value of a wheat-soy flour mixture.

In the case of a wheat flour-wheat concentrate mixture (Table 6), the supplementary effect of lysine was unmistakable.

Table 7 summarizes our already reported experience[6] with the lysine enrichment of white wheat flour at three different levels in six infants and children. The first level was calculated to make lysine equally limiting with threonine, the second to make its fraction of essential amino acids equal to that in human milk, and the third to make its fraction of total protein equal to that of breast milk. Theoretically, there should have been no enhancement beyond that achieved at the first level, but there was a further effect at the second level, and possibly an even further one from the third, apparent only in the nitrogen retention.

In Table 8 the prolonged feeding of wheat enriched at the same levels of lysine confirms the apparent superiority of the second over the first level, and of the third over the second, at least in the one case in which it was used.

Table 3 Supplementation of a soy protein isolate (SPI) and of a full fat soy flour (FFS) with DL-methionine. Effect on nitrogen retention weight gain, and serum albumin levels.

Age (month)	Protein	% (kcal)	DL-methionine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Wt change (g/kg/d)	Serum Albumin change	Serum Albumin final
6	SPI	4.0	–	10	238	12	6.1	–0.91	3.34
	SPI	4.0	20	9	240	44	0.6	0.93	4.27
8	SPI	4.0	–	6	240	63	2.8	0.33	4.27
	SPI	4.0	20	6	240	88	4.0	-0.13	4.14
15	SPI	4.0	-	9	239	27	4.2	–0.18	3.76
	SPI	4.0	20	9	242	57	4.5	0.28	4.04
21	Casein	6.4	–	11	320	107	6.9	0.04	4.25
	SPI	6.4		15	320	77	6.3	-0.37	3.88
	Casein	6.4	–	9	320	137	5.2	0.10	3.98
	SPI	6.4	16	6	320	107	6.3	0.13	4.11
19	FFS	7.0	–	32	280	69	2.3	0.17	3.93
	FFS	7.0	20	20	282	109	1.8	0.40	4.33
	FFS	7.0		41			2.3	0.62	3.71

Table 4 Supplementation with L lysine of wheat flour enriched with milk solids (MW). Questionable effect on nitrogen retention, weight gain, and serum albumin levels.

Age (month)	Protein	% (kcal)	Lysine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained	Wt change (g/kg/d)	Serum change	Albumin final
8	MW	5.3	–	24	320	73	4.1	–0.70	3.40
	MW	5.3	30	15	320	87	7.5	–0.16	3.24
	MW	5.3	–	13	320	73	5.6	–0.60	2.64
34	MW	6.0	–	18			–0.8	–0.38	3.82
	MW	6.0	12.5	12			0.6	–0.33	3.49
13	MW	8.0	–	139			2.6	–0.24	3.93
	MW	8.0	15	11			2.2	0.28	4.21
	MW	8.0	30	31			3.3	–0.41	3.80

Table 5 Supplementation with L-lysine of three different cottonseed flours (CF 27, 21, and 22) and of a wheat-soy mixture. Lack of demonstrable effect on nitrogen retention, weight gain, and serum albumin levels.

Age (month)	Protein	% (kcal)	Lysine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Wt change (g/kg/d)	Serum Albumin change	Serum Albumin final
18	CF27	8.0	–	15	480	98	3.9	0.15	4.00
	CF27	8.0	30	25	480	74	2.4	–0.07	3.93
21	CF27	8.0	–	43	400	82	5.2	0.26	4.43
	CF27	8.0	15	16	393	102	0.5	0.57	5.00
10	CF21	6.7	–	21	400	121	5.7	0.34	4.42
	CF21	6.7	16	7	400	130	5.8	0.02	4.44
11	CF22	6.7	–	6	400	100	5.1	–0.06	4.38
	CF22	6.7	16	6	400	113	3.6	0.02	4.40
10	CF27	6.4	–	36			3.3	0.82	4.68
	CF27	6.4	30	28			1.9	–1.05	3.63
	CF27	6.4	–	17			5.9	0.15	3.78
	CF27	6.4	30	30			2.1	0.74	4.52
	CF27	6.4	–	17			2.1	0.34	4.86
12	Wheat/soy	8.0	–	30	320	91	1.6	0.26	4.49
	Wheat/soy	8.0	22	14	320	79	1.0	–0.23	4.26

Table 6 Supplementation with L-lysine of a wheat flour-wheat concentrate mixture (MS-15). Casein used as a control. Effect on nitrogen retention, weight gain, and serum albumin levels.

Age (month)	Protein	% (kcal)	Lysine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Wt change (g/kg/d)	Serum change	Albumin final
9	Casein	6.7	–	9	400	130	7.7	–0.07	4.20
	MS-15*	6.7	–	15	385	80	6.0	–0.35	3.85
	Casein	6.7	–	9	372	191	6.5	0.48	4.33
	MS-15*	6.7	48	15	400	157	8.0	–0.24	4.09
	Casein	6.7	–	12	400	208	5.7	0.17	4.26
5	Casein	6.7	–	9	400	178	5.8	0.27	4.28
	MS-15*	6.7	–	15	400	89	4.2	–0.98	3.30
	Casein	6.7	–	9	400	164	5.7	0.11	3.41
	MS-15*	6.7	48	15	400	125	6.5	–0.34	3.07
	Casein	6.7	–	12	400	172	4.4	0.44	3.51

* Wheat flour-wheat concentrate with 25 percent protein

Table 7 Weight gains and nitrogen retentions as a percentage of those preceding, during, and following casein periods in six infants receiving various experimental diets and associated plasma amino acid levels and ratios.

	Casein	Wheat	Wheat + 0.12% lysine	Wheat + 0.20% lysine	Wheat + 0.40% lysine
Weight gains (%)	100	67 ± 12	83 ± 14	97 ± 23	91 ± 15
N retention (%)	100	63 ± 12	87 ± 10	98 ± 11	106 ± 10
Serum albumin (g/100 ml)	4.23 ± 0.11	4.02 ± 0.15	4.12 ± 0.25	4.32 ± 0.14	4.14 ± 0.28
Plasma amino acids (μM/ml)	2.36 ± 0.24	2.22 ± 0.39	2.21 ± 0.24	2.14 ± 0.20	2.34 ± 0.32
Essential amino acids (μM/ml)	0.71 ± 0.11	0.58 ± 0.19	0.54 ± 0.11	0.52 ± 0.07	0.58 ± 0.16
Essential amino acids/ free amino acids	0.30 ± 0.02	0.26 ± 0.05	0.24 ± 0.03	0.24 ± 0.03	0.24 ± 0.02
Lysine/essential amino acids	0.15 ± 0.04	0.10 ± 0.05	0.17 ± 0.06	0.18 ± 0.03	0.19 ± 0.04
Threonine/essential amino acids	0.17 ± 0.04	0.20 ± 0.04	0.17 ± 0.04	0.14 ± 0.03	0.13 ± 0.03

Table 8 Prolonged feeding of wheat flour enriched with L-lysine at three different levels. Progress in height and weight ages, nitrogen balances (compared with preceding and following casein periods), and serum albumin levels. Liver fat is that found (basis 0 to 4+) on biopsy at end of diet.

Age (mo)	Ht/age (mo)	Wt/age (mo)	Protein Protein	% (kcal)	Lysine (mg/kg/d)	Days	Intake (mg N/kg/d)	Retained (mg N/kg/d)	Serum Albumin change	Serum Albumin final	Liver fat
10	5½	6½	Casein	6.6	–	6	264	66	–0.03	4.28	
10	5½	6½	Wheat	6.6	17.7	92	260	58	–0.43	3.85	3+
13	7½	8½	Casein	6.6	–	9	264	114	0.04	3.89	
43½	17	18	Casein	8.0	–	9	320	83	0.19	4.43	
43½	17	18	Wheat	8.0	21.5	42	320	91	–0.31	4.12	
			Wheat	7.9	21.5	40			0.09	4.21	
			Wheat	7.3	21.5	51	320	95	0.15	4.36	0
48	22½	29½	Casein	7.3	–	6	313	120	–0.05	4.31	
15	7½	7	Casein	8.0	–	10	320	113	0.34	4.43	
15	7½	7½	Wheat	8.0	35.9	38	306	61	0.06	4.49	
			Wheat	7.3	35.9	81			–0.20	4.29	
			Wheat	8.0	35.9	18	188	26	0.01	4.30	0
19½	12	12	Casein	8.0	–	9	269	84	0.24	4.54	
15	5½	3½	Casein	6.7	–	9	400	138	0.14	3.44	
15	5½	4½	Wheat	6.7	44.8	46	388	48	–0.38	3.06	
			Wheat	6.4	35.9	29			0.17	3.23	
			Wheat	8.0	35.9	62	320	98	0.62	3.85	0
19½	9	17	Casein	8.0	–	7	320	149	–0.24	3.61	
12½	6½	5½	Casein	8.0	–	8	400	143	0.21	3.58	
12½	[illegible]½	6	Wheat	8.0	90.8	126	400	144			
							381	149	0.73	4.31	0
16½	13	16	Casein	8.0	–	9	349	115	0.40	4.71	

Discussion and Summary

It is quite obvious that the addition of small amounts of DL-methionine will very significantly enhance the biological value of soy proteins, an already established practice in animal feeding and a reality in the new generation of soy milks now being used so successfully in this country. Our studies in the human infant confirm the very striking enhancement to be expected, suggesting that in any product designed for the feeding of children in which soy is the exclusive or nearly exclusive source of protein, enrichment with methionine should be obligatory.

If processing has not damaged the protein in other ways, this simple measure makes it possible to duplicate very nearly with soya the protein quality of the best modified cow's milk. In studies not yet reported we have used one of the new soy milks, based on a soy protein isolate enriched with DL-methionine, with repeated success in the initial dietary management of infants with severe marasmus or kwashiorkor, the most stringent test of the nutritional value of a protein. In calculating the amount of methionine which should be added to bring its level at least to that of the next limiting factor, allowance must be made for the approximate 25 percent of D-methionine in the product. It has been shown that the human infant cannot utilize D-methionine and that it is almost quantitatively excreted in the urine.[8]

In the corn-soybean-milk mixture now being widely used throughout the world, most of the methionine deficiency of the soy flour has been corrected by the other sources of protein. It was still possible, however, to document a supplementary effect of methionine, and it might be advisable to supplement the mixture with this amino acid. Further studies are under way to confirm its supplementary effect.

We could not demonstrate a lysine deficiency in a number of well processed cottonseed flours.

The striking lysine deficiency of wheat flour limits the use of this most versatile and acceptable of cereals. It is possible to correct this in a variety of ways. The addition of FPC at the 10 percent level corrects the lysine deficiency and doubles the protein content. In the process, at least with the FPC used in our studies, methionine may become first limiting. If this is confirmed, and it is desirable to increase the protein content to this degree, methionine could be added. Otherwise, the addition of only 5 percent FPC very nearly eliminates the lysine deficiency without creating one in methionine. Further improvements in processing of FPC promise to eliminate the methionine problem.

In a wheat flour–milk solids mixture most of the lysine deficiency

had undoubtedly been corrected. In a wheat-soy blend there was no effect from adding lysine, indicating complete correction of the lysine deficiency of wheat alone. Studies are planned to determine whether or not methionine has become first limiting.

With wheat flour alone, or with a mixture of flour and wheat concentrate, the supplementary effect of lysine is dramatic. Probably because of more rapid absorption and partial deamination of the free lysine, some of it is wasted, requiring supplementation beyond the theoretical maximum or perhaps for the development of a more slowly absorbed product.

In view of the results obtained with the lysine fortification of wheat flour, and because of its large and ready consumption by infants and children in areas of this country and many parts of the world where protein malnutrition is a problem, the addition of either synthetic lysine or some good natural source of this amino acid to the wheat flour consumed in those areas would be a measure of obviously enormous potential. Very particularly, in the many areas of the world where lactose intolerance is the rule rather than the exception and in which the introduction of milk, even if economically feasible, results in many adverse reactions and frequent rejection, such a measure should yield immediate benefits to children and many adults.

It serves no useful immediate purpose to point out that good sources of lysine are available and not used, or that this is not the first limiting amino acid in the overall diet of a particular country. We have already pointed out that, try as we might, we will not get the whole world, a whole country, and most particularly a whole family to sit at the same table and distribute the sources of protein and essential amino acids evenly. To the physician, the nutritionist, and the public health workers, the possibility of promoting, with good reason, the consumption of a cereal already enjoying great prestige is obviously of great attraction. It is not often that we can so reconcile what people want with what is good for them and, especially, for their children.

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