Biochemical and Nutritional Effects of Lysine-Reinforced Diets

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Animal experiments by Mitchell[1] have indicated that the lysine needs of weanling rats may be more critical than those of adult rats. The amino acid requirement data of Mitchell[2] and Rose[3] for young adults and those of Albanese[4] for young infants indicate that a similar circumstance may prevail in the human. Calculations from these data disclose that the ratio of lysine to tryptophane needs of young adults is 2.0–3.2, whereas that of the young infant is 6.0. These values suggest that within the limitations of these data the lysine growth needs of the infant are twice as great relative to the tryptophane requirements as the maintenance needs of the young healthy normal adult.

Since tryptophane is probably the limiting essential amino acid in most infant foods; and since the lysine-tryptophane (L/T) ratios of most foods employed for infant feeding, with the possible exception of meat products, are lower than the growth L/T, it was felt that the nutrition of infants, especially those with poor appetites, could be improved by lysine supplementation of the diet. A report of our observations in an extended study of these effects is presented here.

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Experimental

Diets and Methods

The infants studied were fed evaporated or fresh milk formulae with supplementary foods, in accord with prevailing pediatric practice in this area. The caloric intake was maintained at 100–120 calories per kilogram, or 45–55 calories per pound per day, with an approximate percentile caloric distribution of proteins, 15; fats, 35; and carbohydrate, 50. The caloric density of the formulae employed was roughly one calorie per cc.

The data of Williamson[5] were employed for estimating the lysine and protein intake from fresh or evaporated milk. The protein and lysine content of all supplementary foods fed in this study was known from chemical and microbiological analyses performed directly on representative samples of the products employed. Analyses of detailed daily diet records in terms of these data disclosed the protein intake, from all sources, to average 3.5 Gm. per Kg. per day.

The vitamin and mineral intake was maintained at, or better than, recommended dietary allowance levels[6] by the use of good commercially available concentrates.* In addition to the vitamins of known dietary need, these preparations also provided pyridoxine, pantothenic acid, folic acid, and vitamin B_{12} in adequate amounts.

The reported observations were made on 15 infants (age 1–27 months) for periods varying from 9 to 21 weeks. The lysine-supplemented diet periods were from 3 to 4 weeks' duration and were preceded and followed by control

* Kindly supplied to us by Dr. Edward R. Neary of the White Laboratories, Incorporated.

periods of equal time. In several instances, because of obvious clinical needs of the child, the supplemental periods were repeated or prolonged. The supplement was given as L-lysine, HCl* at the rate of about 100 mg. of lysine per Kg. body weight per day. DL-lysine was not employed because the D-form is not utilized by the human.[4] To insure complete consumption and maximum utilization, the calculated amount of the amino acid was added during preparation of the milk formulae.

It was further noted by these investigators that the plasma levels of lysine, isoleucine, and histidine (in that decreasing order) underwent the severest reduction in malnourished individuals. As a prelude to undertaking the detailed metabolic studies outlined above, chromatographic measurements of free blood lysine and total plasma protein levels of 15 infants (age 1–13 months) were performed biweekly for 2 to 3 months. These determinations disclosed that, as in adults, the blood

TABLE I

Amino Acid Requirements of Young Adults and Infants*

	Young adults				Infants, Albanese[4]	
	Mitchell[2]		Rose[3]			
Amino acid	Amount mg./Kg.	Maintenance pattern	Amount mg./Kg.	Maintenance pattern	Amount mg./Kg.	Growth pattern
Tryptophane	6	1.0	7	1.0	30	1.0
Lysine	12	2.0	23	3.2	180	6.0
Threonine	14	2.3	14	1.9	87	2.9
Methionine	7	1.1	31	4.3	85	2.8
Isoleucine	17	2.3	20	2.8	90	3.0

* Growth and maintenance pattern figures were obtained by assigning the value of unity to tryptophane.

Anthropometric and body weight measurements were made at the beginning and end of each diet period. Blood specimens were also collected at these intervals for the microdetermination of total plasma proteins, hemoglobin, and amino acid levels. Multiple 24-hour urine collections were made intermittently during the course of the individual studies for the estimation of nitrogen balance. The amino acid content of the blood and urine were determined by chromatography.[7]

Comparable and parallel measurements were done on 9 infants (age 2–18 months) who received no lysine supplement during the period of observation, which varied from 3 to 20 weeks.

Results

Everson and Fritschel[8] have shown that in adults decreased levels of the total and individual essential free amino acids of the plasma may serve as an earlier index of malnutrition than the measurement of blood albumin levels.

lysine level is generally a better index of the nutritional state of infants than is the plasma protein level. In addition, it was found from these serial tests that the lysine level served as a good indicator of daily protein intake. This was especially true in infants with poor appetites arising from a variety of causes.

Subsequently, additions of lysine (50–100 mg./Kg./day) to the diet of some of the infants in this group (who were malnourished in terms of body weight and the lysine or total amino acid index) were found to improve appreciably the rate of weight gain with no increase in total protein intake. These preliminary observations seemed to give experimental support to the theoretical deductions derived from the lysine/tryptophane (L/T) ratio concept.

The factual bases of this concept are presented in Tables I and II. It will be noted from Table I that the tryptophane needs of infants on a body weight basis, like the total protein needs, are four to five times greater than those of young adults. However, with the exception of lysine, the pattern of needs of the different amino acids is quite the same

* A synthetic product containing 95% L-lysine, HCl and 5% D-lysine. HCl generously supplied to us by Dr. N. W. Flodin of the Du Pont Company.

TABLE II

Comparison of Lysine—Tryptophane Ratios of Various Foods*

Infant food	Lysine/Tryptophane ratios
Human milk	3.4
Cow's milk	4.3
Soy products	1.0–3.4
Wheat products	2.5–2.7
Meat products	3.2–5.0
Cereal products	1.2–2.3
Protein digest preparations	3.0–3.9
Infant needs*	6.0

* Based on male infants 2–9 months of age, maintained on formula providing 3.5 Gm. protein and 100 calories per Kg. The formulae had a percentile caloric distribution: protein, 15; fat, 35; and carbohydrate, 50. The formulae provided all the known vitamins and minerals in adequate amounts.

for both infants and young adults. Examination of the lysine/tryptophane ratio content of foods commonly employed for infant feeding (Table II) discloses that only meat products approximate the infant L/T ratio.

In the light of these considerations, the results of the preliminary studies encouraged us to undertake a systematic evaluation of the nutritional effects of lysine supplements. Our study showed that of the 15 infants studied the body weight and nitrogen balance of 5 were markedly improved by the addition of lysine to the diet. The infants in this group ranged in age from 6 to 26 months and generally maintained poor appetites. In every instance, prior to determining the effect of lysine supplements, improved nutrition was attempted by increasing the protein content

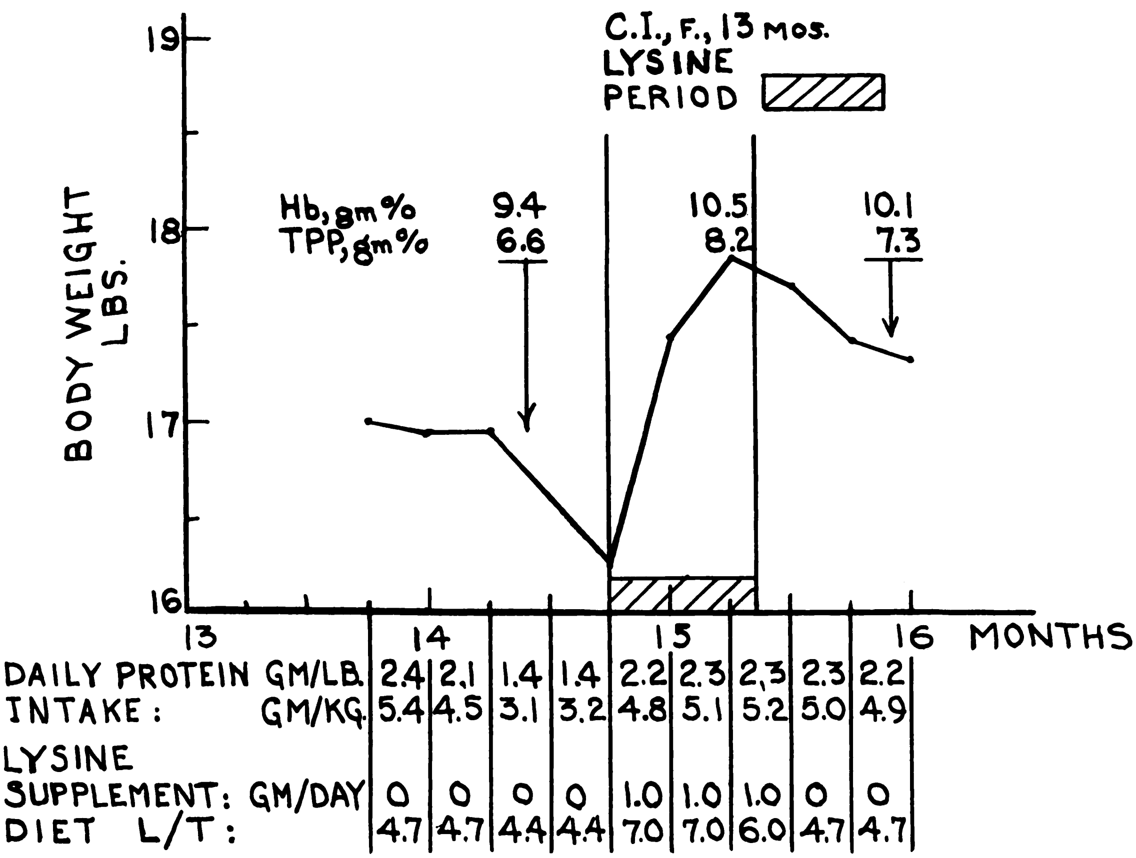

Fig. 1. Effect of lysine supplement on body weight and blood proteins of underweight child, who because of her aversion to solid foods was fed milk formula reinforced with milk protein preparations. High protein and high caloric diets were without effect except for reducing appetite of the child. Addition of lysine improved appetite and utilization of dietary protein.

of the diet (4 to 6 Gm./Kg.). In most infants the increased protein intake caused a transient increase in weight gain and nitrogen balance, which was soon followed by greater decreases in appetite and body weight. A good example of this phenomenon is shown in the data given in Figure 1. This infant was about 5 pounds underweight for her age. Attempts to improve her nutrition by high protein or high caloric diets prior to the period shown in the figure had met with consistent failure. However, when the lysine content of the diet was increased by supplementation, appetite was improved, high protein diets were better tolerated, and body weight increased. Concomitantly, the blood protein levels rose during the lysine-supplement period and fell in the post-control period. As might be expected from our previous experience, the free lysine levels of the blood were two to three times greater during the lysine period than in the pre- or post-control periods.

The data graphically collected in Figure 2 illustrate the application of lysine supplementation to a casein digest product (Nutramigen®). The use of this product was indicated by an allergic reaction in the infant to cow's milk in any form. Although the allergy symptoms (eczema) disappeared with the feeding of Nutramigen as 60–80% of the total protein intake, growth continued to be poor. The effect of the addition of lysine in changing the L/T ratio from 4.0 to 6.4 can be clearly seen in Figure 2. As before, the improvement with supplementation, and the decline in body weight after removal of lysine, were accompanied by parallel changes in blood protein levels. Attention is called to the lag effect which is sometimes observed both with the onset and termination of improved nutri-

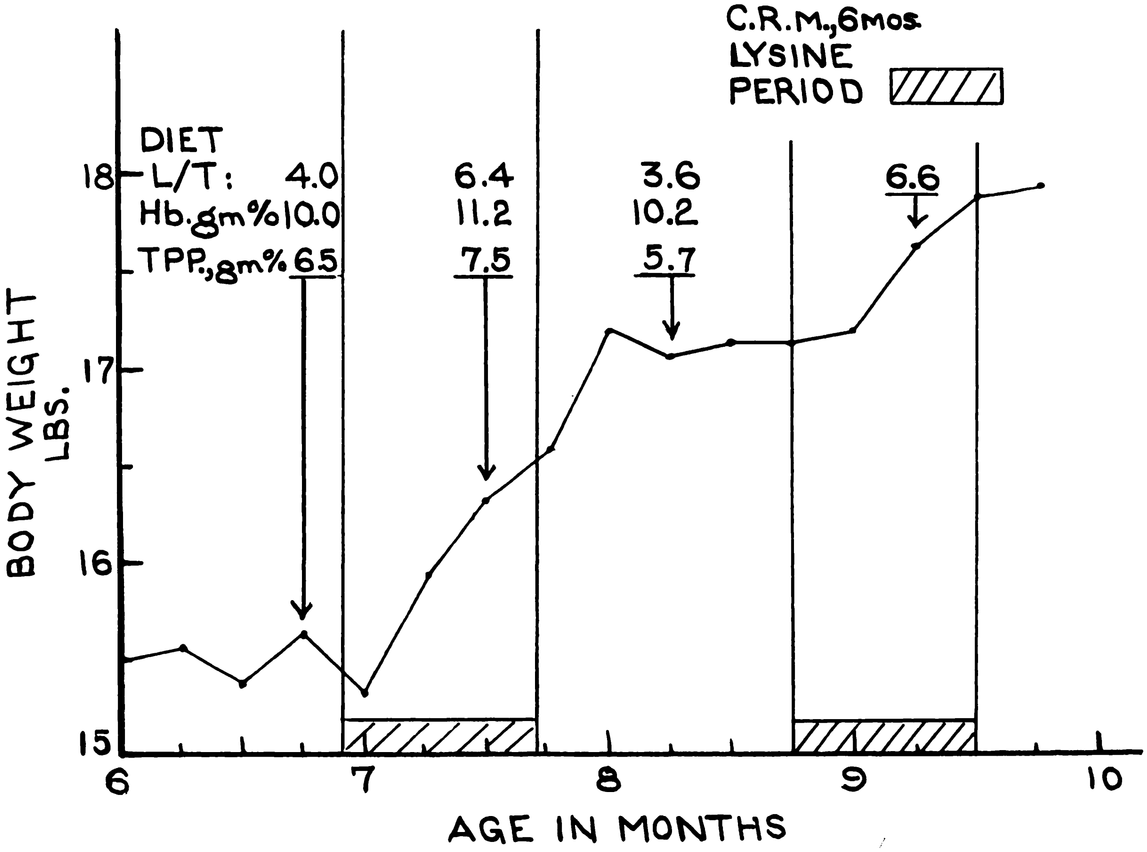

Fig. 2. Effect of lysine on nutrition of infant who because of allergic symptoms to cow's milk was maintained on a protein digest preparation (Nutramigen®) as a primary source of dietary nitrogen.

tion in relation to the periods of high lysine intake.

The prolonged effects of lysine supplementation are shown in an underweight child in Figure 3. Measurements based on multiple 24-hour urine collections at various intervals changes in the biochemical criteria, rather than by the marked body weight changes. A typical illustration of these findings is shown in Figure 4. It will be noted that a high nitrogen retention prevails, in spite of the limited body weight change. This seemingly

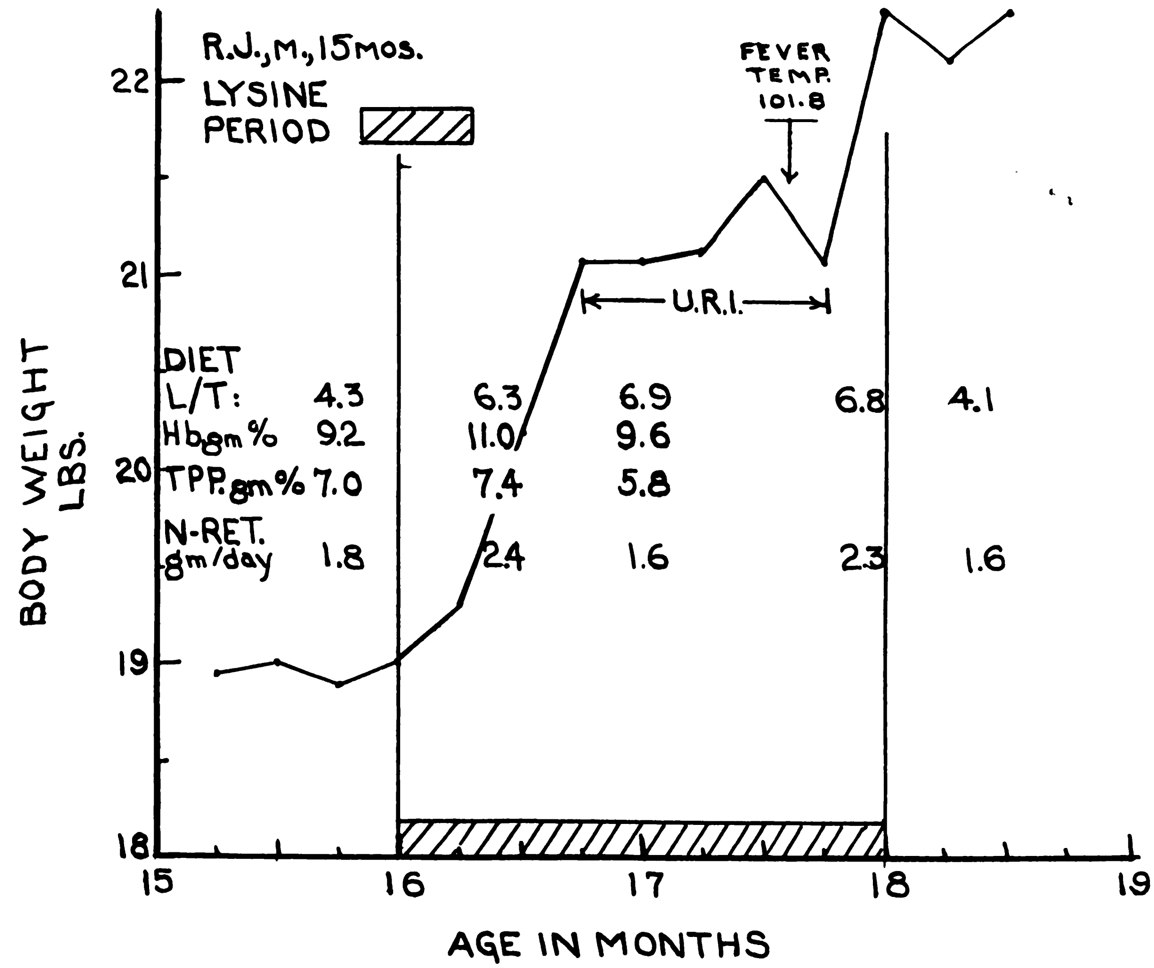

Fig. 3. Nutritional and biochemical effects of prolonged lysine supplementation on anorexic and underweight infant.

throughout the course of the study showed that improved body weight gain was paralleled by increased nitrogen retention. However, improvement was decreased by an intercurrent infection.

The other two infants of this first group showed similar marked responses to the addition of lysine to their diets.

The effects of lysine supplementation in the second group (6 infants, age 3–21 months) were characterized by significant and definite anomalous observation is a rather common finding in infants.[9] It arises primarily from the possibility that tissue water and fat can be mobilized independently of body proteins.

The significant biochemical changes associated in this group with increased dietary L/T ratios are shown in Table III. It will be seen therefrom that a rise in both hemoglobin and total plasma protein levels occurred with additions of lysine to the diet. Reductions in these values often occurred with cessation of the supplement. The conclusions derived from the blood protein measurements were well supported by the findings on total amino acid and lysine levels of the blood.

The four remaining infants (age 2–6 months) of the 15 studied showed no improvement in any of the criteria employed as the result of lysine additions to their diet. This finding may be explained in part by the unusually high growth rate of these infants in terms of the Wetzel grid[10] or the University of Iowa standards.[11] They were also superior in this respect to our own control group of 9 infants.

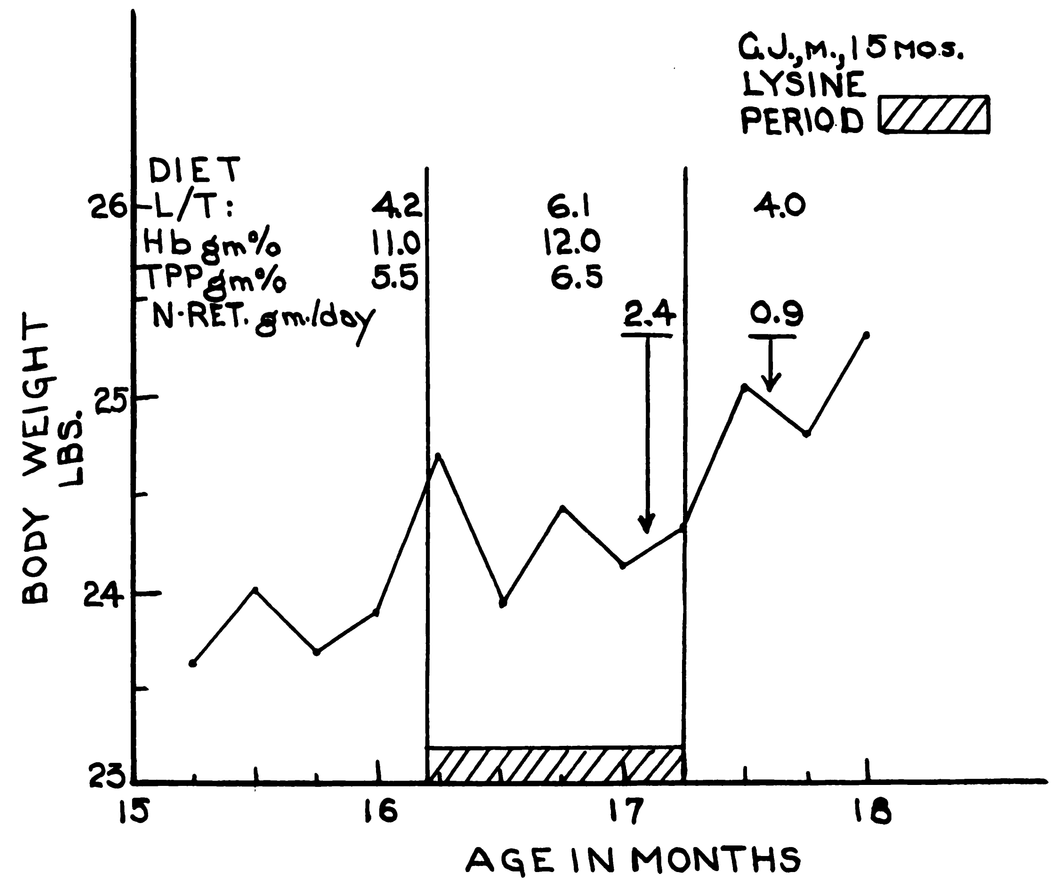

Fig. 4. Effect of lysine supplement on nitrogen retention of infant of average body weight and appetite. Dietary protein was derived in equal amounts from evaporated milk formulae and supplementary baby foods, e.g. meats, vegetables, etc.

Comments

The possibility that lysine supplementation of cereal foods, especially wheat products, would enhance their food value has long been recognized and amply demonstrated by animal and human experiments.[2] The reported findings now suggest that the nutritional value of many infant foods, including cow's milk, can be improved by small additions of lysine. This seemingly revolutionary idea arises from our newer knowledge of the specific amino acid needs of infants.

The nutritional limitations of feeding only milk and sugar beyond the sixth month of life (or earlier) have long been recognized by pediatricians in their recommendation for supplementary foods. Curiously enough, these recommendations include for the most part meat preparations which have high L/T ratios (Table II). These measures have been shown to succeed with infants of good appetite and to fail with infants of poor appetite. Recent evidence points to the fact that these failures

TABLE III

Effect of Lysine Supplements on Blood Protein Levels of Infants

Diet periods	Pre-control				Lysine Supplement				Post-control			
Subject, sex, age & initial body weight	Wks.	Diet, L/T*	Hb.† Gm., %	TPP‡ Gm., %	Wks.	Diet L/T	Hb. Gm., %	TPP Gm., %	Wks.	Diet L/T	Hb. Gm., %	TPP Gm., %
W. W., m., 3 mos., 10.9 lb.	3	4.8	10.0	4.8	3	8.0	11.0	7.3	4	4.7	10.4	6.8
B. V., f., 4.5 mos., 9.7 lb.	2	4.7	10.4	6.8	3	7.0	11.2	8.3	3	4.6	11.7	6.1
D. W., m. 5.0 mos., 10.5 lb.	4	4.3	9.1	6.6	4	6.5	10.0	7.1	5	4.0	8.3	6.4
C. G., m., 8.0 mos., 13.5 lb.	2	3.8	10.9	5.9	4	6.0	10.2	7.4	4	4.0	10.6	7.1
C. J., m., 15 mos., 23.5 lb.	3	4.1	11.5	5.5	4	6.3	12.1	5.6				
V. M., f., 24 mos., 17.5 lb.	4	4.2	9.2	7.4	8	6.3	11.5	7.2	3	4.1	11.0	6.3

* Lysine-Tryptophane ratio. † Hb.: hemoglobin. ‡ TPP: total plasma proteins.

may be associated with digestive enzyme deficiencies which prevail in young infants.[12] In the face of such circumstances, other methods for enhancing the nutritional value of milk need to be explored. The addition of easily assimilated lysine to infant formulae seems to offer one solution to the problem.

Summary

Studies were initiated to determine whether or not the nutritive value of milk could be improved by lysine supplements. Fifteen infants (1–27 months) were studied for periods ranging from 9 to 21 weeks. These children were fed standard fresh or evaporated milk formulae with supplementary foods in accord with prevailing pediatric practice. The vitamin and mineral content of the diet was as high as, or higher than, the recommended levels. The lysine-supplemented diet periods were from 3–4 weeks' duration and were preceded and followed by control periods of equal duration. The supplement was given as L-lysine, HCl at the rate of 100 mg. of lysine/Kg./day. The biochemical effects of the lysine supplements were determined in terms of anthropometric and body weight changes, nitrogen balance, hemoglobin, total plasma protein, and blood lysine levels. Comparable and parallel measurements were done on 9 infants (2–18 months) who received no lysine supplement during observation periods which ranged from 3–20 weeks.

The results of our studies showed that the body weight and nitrogen balances of 5 of the 15 infants were markedly improved by the lysine supplement. Six of the children showed no spectacular weight gains, but urinalyses showed that more nitrogen was retained than before the lysine was added, indicating that these children gained in strength and sturdiness. Blood protein levels also increased during this period. The remaining 4 infants showed no observable improvement when lysine was added to their diet, indicating that lysine-fortified diets are only effective with children who are not getting adequate nourishment from their food. The growth rate of these 4 infants was already well above average. The results of these studies bear the implication that the nutritional value of many infant foods, including cow's milk, can be substantially improved by small additions of lysine.

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Food Propaganda and Food Consumption

"It is certainly most interesting that where the consumer has been at last given back his choice he has elected to spend his money on the highest quality protein that he can buy. It was not Hitler's bombs or his shadowy parachutists, or what have you, that daunted us during the early years of the war, but the frightful lumps of indigestible material which we were compelled to accept by way of sustenance at the hands of authority. No doubt authority had no option in the matter; rationing was unavoidable, and once rationing began choice naturally disappeared. All the same, it is an interesting commentary on the value—or lack of value—of propaganda. How many so-called experts were enlisted to persuade us that before the war we had eaten 'far too much meat,' that 'fish was better' for us, and that there was no nutritional or other discoverable difference between canned products and fresh? Of course, there has been a considerable easing off of recent years of this sort of nonsense, but even so, one might have expected that the lean years would have left a more prominent mark on our food habits. . . .

"Getting back to propaganda, it is quite clear that, however well intentioned, it is only successful if it is based on truth. The good habits, and they were many, that the Ministry of Food tried to inculcate during the war, have persisted, for again, according to the *Financial Times,* the consumption of milk, despite price increases, is still some 80 per cent higher than it was before the war. On the other hand, the consumption of bread has declined, though of the bread that is eaten the 'white loaf' of 70 per cent extraction flour, or lower, forms only 3 per cent of the total, and the 'national' loaf is supreme. That sterling but dull component of our menus—the potato—is also falling back toward its true level and is now very nearly at its pre-war consumption figure. . . . On the whole, then, the war has taught us to be a good deal wiser in what we eat, which is, one supposes, the only benefit we have derived from it."

—*The Medical Press* 232: 369–370, 1954.