Arch. Dis. Childh., 1967, **42**, 514.

Treatment of Homocystinuria

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Homocystinuria, a condition associated with decreased hepatic cystathionine synthetase activity (Mudd, Finkelstein, Irreverre, and Laster, 1964), is characterized by increased urinary homocystine and methionine, by increased serum methionine levels, and by low cystathionine levels in brain (Gerritsen and Waisman, 1964b). It is not known how these biochemical findings are related to the multiple clinical manifestations, including ectopia lentis, thromboembolism, bone changes, and mental retardation, but the inference from similar inborn biochemical errors is that symptomatic amelioration might follow the return of the amino acid homeostasis to normal. Since the metabolic role of cystathionine is not yet established, and since it is both expensive and rapidly cleared by the kidney, it seemed most appropriate in this study to evaluate possible methods of lowering serum methionine in these patients as the principal objective of treatment.

Methods

The effects on serum methionine were studied following the separate administration of pyridoxine (50 mg., i.m., twice a day), serine (2 g., orally, twice a day), and penicillamine (100 mg./kg., orally) as well as of a low methionine diet. Each of the first four agents was given sequentially for one week to three patients. 24-hour urines and fasting bloods were obtained on several occasions before therapy and on the fifth and sixth day of each regimen; on the seventh day, an oral L-methionine tolerance test (100 mg./kg.) was performed. Similar methionine loads were given to 12 family members, including all 4 parents, and to 8 normal subjects as well.

Serum specimens were deproteinized with 70 mg./ml. sulphosalicylic acid and urine aliquots were brought to *p*H 2·0 with concentrated HCl. Samples were analysed for methionine and homocystine using a high sensitivity modification of the Beckman/Spinco amino acid analyser (O'Brien and Simmonds, 1966). Since the early results showed no significant changes in other amino acids in plasma or urine, elution was accelerated by using only the 0·2M *p*H 4·26 acetate buffer.

Platelet adhesiveness was measured in duplicate by a slight modification on the Hellem technique (Hellem, 1960). Aggregation of platelets was produced by adding ADP or collagen suspension to platelet rich plasma (Born and Cross, 1963).

Received January 30, 1967.

Cases Studied

Five homocystinuric patients from two apparently unrelated Spanish-American families have been studied. The clinical findings are outlined in Table I.

R.M. was found to have homocystinuria during screening by paper chromatography (O'Brien, 1965) and urine nitroprusside (Brand, Harris, and Biloon, 1930) testing of the mentally retarded patients in an institution in Colorado. She was one of two patients with homocystinuria detected among 1700 subjects examined in this manner. A.M. and O.M. were then discovered during family studies. O.M. was moderately retarded and has been in an institution, though she was now at home. A.M. at age 18 months was not yet crawling, walking, or speaking single words, and he was described by his mother as developing in the same manner as his two affected sisters. Three other sibs had negative urinary nitroprusside tests and were of normal intelligence.

TABLE I

Clinical Findings of Homocystinuric Subjects

	Patients				
	R.M.	O.M.	A.M.	P.P.	C.P.
Sex	F	F	M	F	F
Seizure history	−	−	−	+	−
Age at diagnosis (yr.)	8	12	1½	7	3
IQ at diagnosis	<50	<50	78	56	63
Ectopia lentis	+	+	−	−	−
Malar flush	+	+	+	+	+
Fine hair	−	−	−	−	−
Pes cavus	+	+	+	+	+
Genu valgum	+	+	+	+	+
Pectus carinatum	+	+	−	+	−

P.P. was discovered after referral by her school teacher because of a persistent unusual odour on her breath and poor school performance. Family studies revealed consanguinity (Fig. 1) and a sister, C.P., with the same poor language and social development shown by P.P. at a similar age. Two other sibs had negative urinary nitroprusside tests and were of normal intelligence.

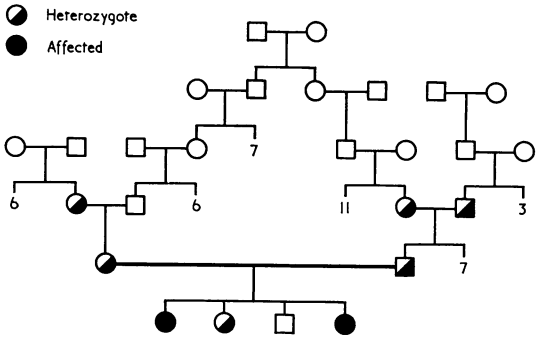

FIG. 1.—*Family tree of patients P.P. and C.P.*

TABLE II

Fasting Serum Methionine Levels (μmole/ml.)

	Pre-treatment	Day of Treatment	Pyridoxine	Serine	Cysteine	Penicillamine	Low Methionine Diet*
Normal Values	0·02-04						
P.P.	0·754	Day 5	0·884	1·216	0·960	1·234	0·165
	0·902	Day 6	1·292	1·064	0·836	1·040	0·326
	1·094	Day 7	1·076	1·032	0·926	1·180	0·358
Average	0·916		1·084	1·104	0·907	1·151	0·283
C.P.	1·152	Day 5	1·133	1·216	1·150	—	0·110
	1·502	Day 6	1·282	1·004	1·041	—	0·060
	0·869	Day 7	1·140	1·241	1·003	—	0·077
Average	1·174		1·185	1·154	1·065	—	0·082
R.M.	0·296	Day 5	0·462	0·528	0·688	0·386	—
	1·000	Day 6	0·504	0·712	0·712	0·867	—
	0·319	Day 7	0·496	0·720	0·656	0·788	—
Average	0·538		0·487	0·653	0·679	0·680	
A.M.	1·128	Day 5	—	—	—	—	0·147
	1·116	Day 6	—	—	—	—	0·090
	1·140	Day 7	—	—	—	—	0·113
Average	1·128						0·117

* Values taken after 1, 2, and 3 weeks of therapy.

Results

The effects of the various regimens on the fasting serum methionine levels and on the methionine tolerance tests are shown in Tables II and III. Methionine levels are not shown for C.P. on penicillamine because of a skin reaction to the drug, necessitating its withdrawal. Only the methionine-restricted diet lowered serum methionine.

Methionine tolerance tests were performed on 12 unaffected members of the 2 families and also on 8 normal subjects. It can be seen from Fig. 2 that the two-hour serum methionine concentrations were higher in all four parents, than in the control patients. With such small numbers, only a very tentative discrimination of the heterozygote can be achieved. It is of interest, nevertheless, to examine the distribution of the two-hour serum methionine levels of the other family members around the critical point at which the relative deviation of parents and normals is equal. In both family M and family P, one unaffected sib appears to be normal, and one a carrier. In family P, however, both paternal grandparents appeared to be heterozygotes (Fig. 1), as did the maternal grandmother. The maternal grandfather was apparently not a carrier, an unexpected finding in view of the distant consanguinity of the parents.

Patient P.P. had increased platelet adhesiveness and aggregation on one occasion, but on retesting on three occasions, had normal results. The other 4 patients with homocystinuria, and the 9 close family members had normal values.

Discussion

Homocystinuria was initially described in 1962 (Carson and Neill, 1962) and in the following four

TABLE III

Serum Methionine Levels After Methionine Loading Tests (μmole/ml.)

Patient	Treatment	Fasting	1 Hr.	2 Hr.	3 Hr.	4 Hr.	6 Hr.
P.P.	Pre-treatment	1·094	2·718	3·000	2·647	1·850	1·510
	Pyridoxine	1·076	2·607	2·848	2·268	1·572	1·560
	Serine	1·032	2·070	2·270	2·355	2·268	1·568
	Cysteine	0·926	1·742	2·112	2·411	1·800	1·641
	Penicillamine	1·180	2·078	2·412	2·850	2·196	2·076
C.P.	Pre-treatment	0·869	1·565	1·965	1·805	1·719	1·670
	Pyridoxine	1·140	1·941	2·212	2·286	1·829	—
	Serine	1·241	1·802	2·333	2·578	2·474	2·648
	Cysteine	1·003	1·819	1·573			1·268
	Penicillamine	—	—	—	—	—	—
R.M.	Pre-treatment	0·319	1·299	1·522	1·525	1·084	0·852
	Pyridoxine	0·496	0·966	1·294	1·563	1·072	1·060
	Serine	0·720	1·493	1·485	2·138	1·448	1·412
	Cysteine	0·656	1·577	1·853	1·470	1·302	1·184
	Penicillamine	0·788	2·115	1·987	1·517	2·115	1·550

years, some 70 additional cases were reported (Kennedy, Shih, and Rowland, 1965; Carson, Dent, Field, and Gaull, 1965; Laster, Spaeth, Mudd, and Finkelstein, 1965; Schimke, McKusick, Huang, and Pollack, 1965; Dunn, Perry and Dolman, 1966). The frequency of the disease remains uncertain, but it is becoming more accurately known as the understanding of the phenotype evolves. Initial case reports included only patients with mental retardation, but a recent study of patients with dislocated lenses (Schimke *et al.*, 1965) indicated that normal intelligence might be present. Three of the present group of patients, P.P., C.P., and A.M., are the first untreated patients described without dislocated lenses, confirmed on slit-lamp examination. The 5 patients included in this report are also the first cases of Spanish-American heritage.

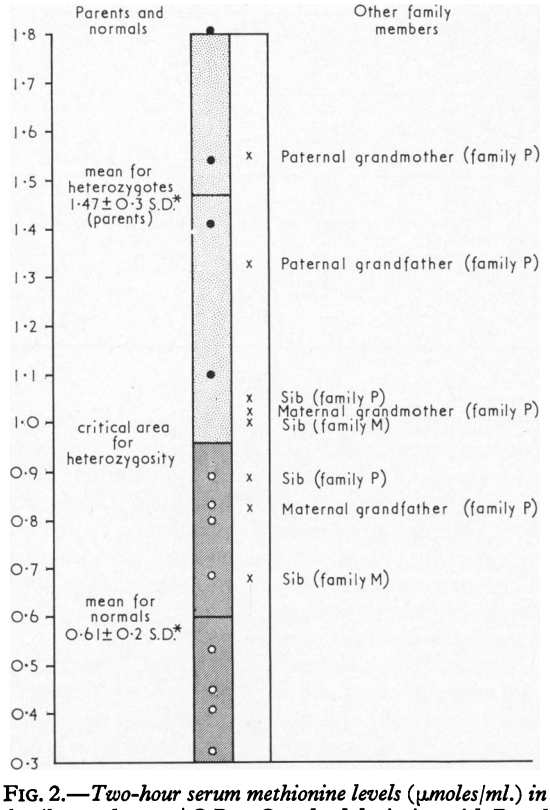

FIG. 2.—*Two-hour serum methionine levels (μmoles/ml.) in family members.* **S.D.* = *Standard deviation with Bessel correction for small sample bias* $\sqrt{(\Sigma\chi^2/_n - \overline{\chi}^2)}$. n/n−1. *The two means are significantly different* ($p = 0{\cdot}002$ *by the Mann-Whitney U non-parametric test.*

Fine hair was not a reliable characteristic in these patients. Nevertheless, they all demonstrated genu valgum and pes cavus, and 3 of them had prominent pectus carinatum. The odour on the breath and body of patient P.P. was similar to that of methionine. All the patients in this report were developing slowly intellectually. In this respect, A.M., aged 18 months, was following a similar pattern to his two older retarded sibs. C.P., aged 3 years, also showed delayed development, similar to her older sister, P.P.

Fig. 3 demonstrates the metabolic defect in homocystinuria. It can be seen that pyridoxine is required by the defective enzyme, cystathionine synthetase, in order to form cystathionine from serine and homocysteine. Three approaches toward lowering blood methionine levels were considered. The first involved an attempt to increase cystathionine synthetase activity, initially through maximal supplementation of pyridoxine co-factor, and then by supplying increased quantities of the co-substrate serine. Pyridoxal phosphate has been shown to decrease cystathionine excretion in cystathioninuria (Frimpter, Haymovitz, and Hor-

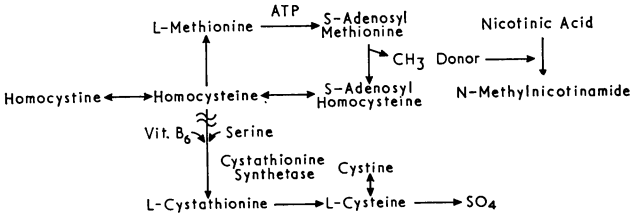

FIG. 3.—*The metabolism of homocystine.*

with, 1963), even though it did not restore cystathionine synthetase activity when added to liver biopsy samples from patients with homocystinuria (Mudd *et al.*, 1964). A previous report (Gerritsen and Waisman, 1964a) described a decreased urinary excretion of homocysteine in one patient when given a load of methionine with 1 g. L-serine, compared to when methionine was given alone. In these patients, however, fasting serum methionine concentrations (Table II) and methionine tolerance (Table III) were not altered by pyridoxine or serine administration. The mean urinary excretion coefficients of 0·29 μmole/min. 1·73 m.^{2} for methionine (normal $\leqslant$ 0·04 μmole/min. 1·73 m.^{2}) and 0·21 μmole/min. 1·73 m.^{2} for homocysteine were not significantly altered by this treatment, although oral doses of up to 500 mg./24 hr. pyridoxine (Hooft, Carton, and Samyn, 1967) may be remarkably effective in some cases.

The second approach to therapy was directed at lowering the serum methionine concentration through removal of homocysteine as the disulfide complexes of cysteine and penicillamine. Cystine has been given as a supplemental amino acid to a 5-year-old homocystinuric girl with no apparent clinical benefit, though serum methionine levels were not reported (Carson *et al.*, 1965). Penicillamine forms a stable disulphide complex with homocysteine, as well as with cysteine (Milne, 1964) and has been used in the treatment of cystinosis (Clayton and Patrick, 1961) and to decrease urinary cystine excretion as such in patients with cystinuria (Crawhall, Scowen, and Watts, 1963). In the present group, treatment with cysteine or penicillamine resulted in a decrease in urinary homocysteine, which was accompanied by a corresponding increase in the urinary disulfide. No changes in urine or serum methionine concentrations were observed (Tables II and III).

The final approach to therapy, and the only successful method of decreasing serum methionine concentrations, was by means of a low methionine intake. This methionine exchange diet, outlined as exchange tables in Appendix I, includes foods for which methionine content could be found in the literature (*Recommended Dietary Allowances*, 1964; Bowes and Church, 1963), or in which it was derived empirically from the protein content. It can be seen that serum methionine concentrations were maintained at substantially reduced levels in patients A.M. and C.P. while on 15-20 mg. methionine/kg. day. A.M. has now been treated uneventfully for seven months, during which time he has maintained fasting serum methionine levels of between 0·07 and 0·21 μmole/ml. while accelerating his rate of motor-social development. As an index of over-all adequate nutrition, his height and weight have continued at the 50th centile for his age during treatment. Serum methionine concentrations were reduced in patient P.P. while in the hospital, but, due to social factors, could not be maintained at home. The number of servings from each exchange list and the quantity of Sobee* milk can be adjusted for the individual patient, as shown for A.M. in detail in Appendix II. Although Sobee is the formula lowest in methionine content, a milk substrate with an even lower methionine concentration is needed, especially in the first months of life, and would allow increased variability in diet with increasing age. Patients P.P. and C.P. were initially treated with a very low protein diet and serum methionine concentration decreased to normal levels ($<$ 0·04 μmole/ml.). Large rises in serum methionine concentrations were then seen, as well as an increase in liver alkaline phosphatase, SGOT, and LHD in patient P.P. These changes were probably related to nutritional deprivation, and have been described as a complication of low protein intake in phenylketonuria (Umbarger, 1960). The present diets provide an adequate intake of essential amino acids, and gains in height and weight have continued in all three patients. The dietary intake of iron, calcium, and B-complex vitamins does not meet recommended levels, and these must be added as supplements. Patients are also given added cysteine, 1 g., orally, twice a day, as it cannot be synthesized from homocysteine in these patients and presumably becomes an essential amino acid.

* Registered trade name.

It is of special interest to compare this experience with those of Komrower, Lambert, Cusworth, and Westall (1966) and Perry, Dunn, Hansen, MacDougall, and Warrington (1966). Together, these three studies show that serum methionine levels can be sustained in infancy and early childhood at normal or near normal levels by a low methionine diet. Both the gelatine base supplemented with amino acids and the soya base regimen seem to be acceptable and nutritionally satisfactory. The former is more costly, more difficult to dispense, and thus less practical if larger numbers are to be treated; at the same time, it appears to afford somewhat better control in terms of serum methionine levels. In a syndrome which, like hyperphenylalaninaemia, may reflect a spectrum of enzymatic changes, it is still important to remember, however, that the relation between a high serum methionine and the development of clinical manifestations is not yet affirmed. Whether all cases will require dietary control and whether treatment is required in early infancy, as well as the duration of treatment and the critical levels of serum methionine, are questions still to be solved.

In the meantime, it seems reasonable to start treatment with a low methionine diet in infancy if older sibs with the disease are retarded or at any time in infancy or early childhood if development is impaired at the first visit, or becomes impaired during supervision.

Summary

This study shows that a substantial reduction in serum methionine levels in homocystinuria may be achieved by a low methionine diet, but not by the administration of pyridoxine, serine, cysteine, or penicillamine.

Details of a simple, workable low methionine exchange diet have been evolved and are presented for the first time.

The authors wish to thank Mrs. Barbara Miles and Miss Nancy Welch for their help in biochemical assays, Miss Julie King and Miss Joanne Carter for the diet tables, and Dr. Ed Genton for carrying out the platelet adhesiveness tests. The work was supported by USPHS grants No. MOI-FR-69, TI-HD-108, 5K3-HD-22, and HD-00-329.

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APPENDICES

Dietary Information for Care of Patients with Homocystinuria

1. *General.*
   a. In early infancy, Sobee* should be used instead of a conventional milk formula, but should be supplemented with 100 mg. cystine/kg. 24 hr. and with iron, calcium, and B-complex vitamins. It is important to monitor serum methionine levels, physical growth, and intellectual development.
   b. In later infancy, Sobee should continue to be used as the basic formula, but mixed feeding with *purée* of vegetables and fruit may be introduced as directed in the food tables.
   c. In later childhood, a menu can be devised that is based on the exchange lists given below.
2. *Food exchange lists for low methionine diet*—Appendix I.
3. *Suggested menus for an 18-month infant*—Appendix II.
4. *Nutrient content of sample menu*—Appendix III.

Appendix I: Methionine Exchange List

Soybee Milk: 1 : 1 dilution provides 0·95 g. protein and 10·45 mg. methionine per oz.

BREAD—CEREAL LIST
(25 mg. methionine)

Bread (4% milk sol)	1 slice	23 g.
Cornflakes	3/4 cup	20 g.
Grapenuts	1/8 cup	14 g.
Rice flakes	1 cup	32 g.
Shredded wheat	1 bisc.	22 g.
Wheat flakes	1/2 cup	18 g.
Barley, cooked	1/3 cup	70 g.
Farina, cooked	1/2 cup	100 g.
Oatmeal, cooked	1/4 cup	60 g.
Rice, cooked	1/2 cup	100 g.
Crackers, soda	4	22 g.
Crackers, graham	2	20 g.
Macaroni, cooked	1/4 cup	35 g.
Noodles, cooked	1/3 cup	50 g.
Rice, cooked	1/3 cup	50 g.
Spaghetti, cooked	1/4 cup	35 g.

FRUIT LIST
(3 mg. methionine)

Applesauce	2/3 cup	90 g.
Avocado	1/8	25 g.
Banana	1/4	25 g.
Grapefruit	1 cup	200 g.
Orange	1 small	100 g.
Papayas	1/3	100 g.
Pineapple	1/2 cup	140 g.

1/2 cup of each: apples, apricots, berries, cherries, fruit cocktail, grapes, melons, peaches, pears, rhubarb, fruit juices.

JUNIOR FOODS

7 tbsp. each: applesauce, applesauce and apricots, applesauce and pineapple, apricots and tapioca, bananas, bananas and pineapple, fruit dessert, peaches, pears, pears and pineapple = 100 g. methionine per serving.

VEGETABLES—LIST A
(15 mg. methionine)

Asparagus	1/3 cup	50 g.
Beans, green or wax	1/2 cup	100 g.
Broccoli	1/4	40 g.
Brussel sprouts	1/4 cup	35 g.
Cauliflower	1/3 cup	35 g.
Corn	1/4 cup	50 g.
Greens (spinach)	1/4 cup	50 g.
Okra	1/2 cup	50 g.
Onions	1/2 cup	100 g.
Peas, green	1/4 cup	40 g.
Potatoes	1/2 cup	100 g.
Rutabagas	1/2 cup	100 g.
Squash, winter	1/2 cup	100 g.
Sweet potatoes	1/4 cup	50 g.

STRAINED AND JUNIOR FOODS

Green beans	7 tbsp	100 g.
Peas	3 tbsp	40 g.
Squash	7 tbsp	100 g.
Sweet potatoes	5 tbsp	80 g.

VEGETABLES—LIST B
(6 mg. methionine)

Beets	1/2 cup	100 g.
Cabbage, raw	1/2 cup	50 g.
Cabbage, cooked	1/4 cup	100 g.
Carrots, raw	1/2 cup	50 g.
Carrots, cooked	1/2 cup	100 g.
Celery, raw	1/2 cup	50 g.
Chard	1/2 cup	75 g.
Cucumbers	1 medium	100 g.
Eggplant	1/2 cup	100 g.
Green pepper	1/2 cup	50 g.
Lettuce	1 cup	100 g.
Pumpkin	1/3 cup	65 g.
Squash, summer	1/2 cup	100 g.
Tomatoes	1/2 cup	100 g.
Turnips	1/2 cup	75 g.

STRAINED AND JUNIOR FOODS

Beets	7 tbsp	100 g.
Carrots	7 tbsp	100 g.

Free list: (negligible amount of methionine) Butter, Coffee Rich†, fat, hard candy (life-savers, suckers, etc.), honey, jam, jelly, Kool-aid†, margarine, oil, Rich's Topping†, soft drinks, sugar.

Foods to avoid: (high methionine content) Dry beans (pinto, navy, etc.), cheese, eggs, fish, meat, milk, and milk products, mushrooms, poultry.

* Prosobee is a more palatable product, but should not be used as a substitute for Sobee as it has a significantly higher methionine content.
† Registered trade names.

Appendix II: Patient A.M.

(A) DAILY DIETARY ALLOWANCE:	
Sobee (normal dilution)	8 oz.
Bread-cereal list	3 servings
Vegetable list A	2 servings
Vegetable list B	1 serving
Fruit list	4 servings
Free list	As desired
(B) SAMPLE MENU FOR ONE DAY (A.M.)	
Breakfast	
1 serving bread-cereal list	1/2 cup rice krispies
	1/2 slice toast
1 serving fruit list	1/2 cup orange juice
As desired, free list	Coffee Rich*, sugar, butter, jelly
3 oz. Sobee*	3 oz. Sobee
Lunch	
1 1/2 servings bread-cereal list	1/4 cup cooked spaghetti
	2 soda crackers
1 serving vegetable list B	1/2 cup stewed tomatoes
2 servings fruit list	1/2 cup pineapple juice
	1/4 banana
As desired, free list	Butter
	Jelly
2 oz. Sobee	2 oz. Sobee*
Supper	
2 servings vegetable list A	1/2 cup potatoes
	1/3 cup asparagus
1/2 serving bread-cereal list	2 soda crackers
1 serving fruit list	1/2 cup applesauce
As desired, free list	Butter
	Jelly
3 oz. Sobee	3 oz. Sobee

* Registered trade name.

Appendix III: Nutrient Content of Sample Menu (A.M.) for 12 kg. Child

	8 oz. Sobee	3 Svgs. Bread-Cereal List	2 Svgs. Veg. List A	1 Svg. Veg. List B	4 Svgs. Fruit List	Free List*	Total	R.D.A.
Calories	160	240	225	50	15	622	1,312	1,300
Calcium (g.)	0·25	0·06	0·08	0·02	0·06	—	0·47	0·8
Iron (mg.)	2·0	1·8	1·4	0·2	1·8	—	7·2	—
Vitamin A (I.V.)	375	—	1320	105	1215	—	3015	2000
B_1 (mg.)	0·13	0·21	0·07	0·02	0·15	—	0·58	0·5
B_2 (mg.)	0·25	0·12	0·10	0·03	0·11	—	0·61	0·8
C (mg.)	13	—	14	4	59	—	80	50
Protein (g.)	7·6	6·0	2·4	0·6	2·0	—	18·6	24
Methionine (mg.)	84	75	30	6	12	—	207	—
Isoleucine (mg.)	304	247	76	29	—	—	656	—
Leucine (mg.)	488	363	100	37	—	—	988	—
Lysine (mg.)	448	159	110	42	60	—	819	—
Phenylalanine (mg.)	352	263	76	22	60	—	773	—
Threonine (mg.)	272	195	70	26	—	—	563	—
Tryptophane (mg.)	80	52	34	8	12	—	186	—
Valine (mg.)	312	286	100	30	—	—	728	—

* 'Rich's Topping', butter, margarine, sugar, jelly.