Hyperdibasicaminoaciduria, hyperammonemia, and growth retardation: Treatment with arginine, lysine, and citrulline

A 9-year-old girl with hereditary dibasicaminoaciduria has been studied for three years. Initially, clinical features were: growth failure, anorexia and aversion to protein, spontaneous daily protein intake averaging only 10 gm; fasting and postprandial venous hyperammonemia; subnormal plasma concentrations of lysine, arginine, ornithine, and citrulline, with generalized hypermonobasic-aminoacidemia; abnormally high renal clearances of lysine, arginine, and ornithine; and intestinal malabsorption of lysine and arginine. Intestinal absorption of citrulline, a precursor of arginine and ornithine, was normal. The patient was observed during four sequential 6-month periods as follows: no treatment (Period I); dietary supplement of arginine and lysine (Period II); dietary supplement of citrulline and lysine (Period III); no treatment (Period IV). During Periods II and III growth rate increased 3- to 4-fold, spontaneous protein intake increased 2- to 3-fold, and abnormalities in blood NH₃ and the plasma aminogram were partially corrected. In most respects the citrulline plus lysine supplement was more beneficial than that of arginine plus lysine.

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Since 1965, investigators in Finland, Canada, Japan, and the United States have described 32 patients with hereditary hyperdibasicaminoaciduria ("lysin-uric protein intolerance"). All patients had abnormally large renal clearances of arginine, lysine, and ornithine. Plasma levels of lysine, arginine, and ornithine tended to be reduced, while those of alanine, serine, and methionine were sometimes elevated. The Finnish, Japanese, and American patients had in common growth failure and infantile aversion to protein, vomiting, and diarrhea. About half the affected individuals were mentally retarded. Some subjects had hyperammonemia. Heredity in the more severely affected Finnish and Japanese patients was described as autosomal recessive and in the milder Canadian ones, as autosomal dominant. These two forms of the syndrome may represent different alleles at the genetic locus that controls epithelial transport of dibasic amino acids.

In hyperdibasicaminoaciduric patients, Simell and Perheentupa found the specific high-affinity transport system in renal tubular epithelium for lysine, arginine, and ornithine to be defective; a lower affinity transport system appeared to be intact. Observations in three studies of transport across intestinal epithelium based on oral tolerance curves and on fecal amino acid analyses indicated that there was a similar transport defect in intestinal epithelium; in contrast the data of one study of in vitro mucosal uptake and jejunal perfusion indicated that this function was normal. Hyperammonemia and resulting neurologic disturbances were thought to reflect inadequate function of the Krebs-Henseleit cycle for urea synthesis caused by deficiency of arginine and ornithine.

Long-term treatment has received little attention in previous reports. A low-protein diet has usually been advised. Arginine or lysine supplementation of a low-protein diet has also been suggested. The chemical and...
clinical effects of such regimens, however, have not been documented.

In 1970, a child was referred to this clinic because of growth retardation, anorexia, and seizures. She was found to have hyperdibasicaminoaciduria. During the ensuing four years, we have documented the effectiveness of long-term treatment by supplementing her diet with appropriate amino acids.

CASE REPORT

Patient M. W., a 9 1/2-year-old Negro girl, was hospitalized for evaluation of growth restriction. She had been adopted at 8 months of age; neither familial nor perinatal history was available. From 8 months until 2 1/2 years of age she vomited frequently after meals and refused milk, meat, and egg products. Food intake and weight gain were poor. At 2 1/2 years she experienced her first seizure, characterized by lethargy, ataxia, and progression to confusion and stupor. Electroencephalogram two days later revealed abnormally slow background activity, with frequent bursts of synchronous high-amplitude discharges. She had four such seizures from 2 1/2 to 10 years of age despite treatment with phenobarbital and diphenylhydantoin. Height and weight remained consistently below the third percentile (Fig. 1).

Physical examination revealed a 14 kg, 112 cm, undernourished black girl with distended abdomen, moderate kyphoscoliosis, mild genu recurvatum, and slight valgus deformity of proximal femurs. The skin was hyperelastic. Interphalangeal and metacarpophalangeal joints and elbows were hyperextensible. A smooth, nontender liver edge was palpable 2 cm below the right costal margin.

Hematocrit and urinalysis were within normal limits. Red blood cells showed microcytosis, anisocytosis, poikilocytosis, and polychromatophilia. Hemoglobin electrophoresis revealed 64% Hb-A, 4% Hb-A2, 30% Hb-S, and 2% Hb-fetal. White cell count averaged 2,700/mm³ with normal differential. Following fasting, blood (serum, plasma) concentrations were within normal range: Na, K, CO₂, Cl, Ca, P, iron, glucose, creatinine, uric acid, total protein, albumin, α, β, and γ globulins, and glutamic-oxaloacetic acid transaminase. Blood urea nitrogen averaged only 7 mg/dl. Lactic dehydrogenase (405 mU/ml) and alkaline phosphatase (510 mU/ml) were elevated. Fecal nitrogen and fat contents, while the patient ate 10 gm of protein and 30 gm of fat daily, were 0.5 and 0.8 gm daily, respectively. Insulin-arginine provocative test for human growth hormone was within normal limits, as were plasma thyroxine and cortisol concentrations. Roentgenographic skeletal survey revealed severe, generalized osteoporosis. Partial collapse of several vertebrae had caused a dorsal kyphosis and exaggerated lordosis. Bone age was 7 years, 10 months. Electroencephalogram showed generalized slowing and occasional paroxysms of bilateral temporal, parietal, and occipital high-voltage polyspike activity.

The patient was anorectic and avoided protein-containing foods. When she was given access to an unlimited menu, her spontaneous daily food intake averaged only 10 gm of protein, 31 gm of fat, and 135 gm of carbohydrate (Table I). The initial diagnosis was growth failure caused by protein starvation. Accordingly, the patient was persuaded to eat and drink protein-containing supplements, and daily intake increased to 40 gm of protein, 42 gm of fat, and 215 gm of carbohydrate. Stool nitrogen remained less than 1 gm/day during this period. After 7 days of 40 gm protein intake, electroencephalogram deteriorated, she became lethargic, and had three seizures of generalized twitching involuntary movements. Hyperammonemia, generalized hyperaminoacidemia with hypodibasicaminoacidemia, and hyperdibasicaminoaciduria were now recognized (Table II). On return to the 10 gm protein diet, the neurologic symptoms cleared.

METABOLIC STUDIES

A series of short-term metabolic studies was undertaken to determine: (a) whether the patient could absorb supplements of lysine, arginine, or the monobasic arginine-precursor citrulline, and (b) if absorbed, how these amino acid supplements would influence the patient's distorted amino acid pattern, her aminoaciduria, and her hyperammonemia. During the metabolic studies, her
Table I. Ad lib dietary intake of Patient M. W.*

<table>
<thead>
<tr>
<th></th>
<th>Minimal daily requirement normal 10 yr girl†</th>
<th>Un-treated</th>
<th>Period I</th>
<th>Period II</th>
<th>Period III</th>
<th>Period IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>36</td>
<td>10</td>
<td>9</td>
<td>18</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Fat</td>
<td>31</td>
<td>28</td>
<td>30</td>
<td>39</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>135</td>
<td>131</td>
<td>167</td>
<td>200</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Calories</td>
<td>2,400</td>
<td>819</td>
<td>812</td>
<td>1,007</td>
<td>1,267</td>
<td>869</td>
</tr>
<tr>
<td>Essential amino acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>0.12</td>
<td>0.05</td>
<td>0.04</td>
<td>0.09</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Threonine</td>
<td>1.00</td>
<td>0.2</td>
<td>0.2</td>
<td>0.9</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>1.00</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Leucine</td>
<td>1.50</td>
<td>0.5</td>
<td>0.5</td>
<td>0.9</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Lysine</td>
<td>1.60</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.80</td>
<td>0.08</td>
<td>0.09</td>
<td>0.2</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>0.80</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6</td>
<td>0.8</td>
<td>0.4</td>
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<tr>
<td>Valine</td>
<td>0.90</td>
<td>0.4</td>
<td>0.3</td>
<td>0.7</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Histidine</td>
<td>0.75</td>
<td>0.1</td>
<td>0.09</td>
<td>0.3</td>
<td>0.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* All values are in grams.
† Estimations of amino acids in Patient M. W.'s diet were based on ref. 21.

Daily dietary intake was fixed at 10 gm of protein, 30 gm of fat, and 135 gm of carbohydrate. The techniques which were employed in these experiments for measuring plasma amino acids, urinary amino acids, renal clearance of plasma amino acids, and venous blood NH₃ are described in the cited references. To measure the patient's ability to absorb lysine, arginine, citrulline, and (for comparison) phenylalanine, two types of procedures were used.

**Oral tolerance test.** After five to eight days on a 10 gm protein diet, and after a 14-hour fast, 0.67 mmole/kg of a specified amino acid was administered by mouth; at 1 to 2 hour intervals from 0 to 6 hours, the plasma level of the specified amino acid was measured. 15

**Absorption of ¹⁴C-labeled amino acid.** One gram of a specified amino acid, of which 5 μCi was uniformly labeled with ¹⁴C, was ingested at 8 A.M. with breakfast. Stools were collected for the next 48 hours and analyzed for radioactivity. 15, 18 Percentage of absorption of each amino acid so tested was calculated as:

$$\text{absorption} = \frac{\text{dpm} \ ¹⁴\text{C} \ \text{recovered}}{\text{dpm} \ ¹⁴\text{C} \ \text{administered}} \times 100.$$

In control experiments with ¹⁴C-labeled arginine, lysine, citrulline, or phenylalanine in subjects without gastrointestinal defect, absorption of each amino acid was 90 to 100%.

**Absorption of arginine, lysine, citrulline, and phenylalanine.** Following a single oral dose of 0.67 mmole/kg arginine or lysine in the fasted state, concentrations of these amino acids in the patient's plasma increased temporarily. The magnitudes of these increases, however, were less than one-tenth those observed in four normal children under the same conditions (Fig. 2). Contrasting ly, 0.67 mmole/kg of citrulline or phenylalanine produced a similar increase of the plasma level in Patient M. W. as in normal subjects. When the patient ate ¹⁴C-labeled arginine, lysine, citrulline, or phenylalanine, she absorbed 38%, 42%, 96%, or 97%, respectively (normal value, > 90% in each instance).

**Effect of amino acid supplements on plasma and urinary amino acids.** While receiving the 10 gm protein diet without supplements, the patient's fasting plasma amino acid pattern showed abnormally low values for lysine, arginine, ornithine, and citrulline, and abnormally high values (P < 0.05) for nearly all other amino acids, elevations of glutamine and alanine being especially marked (Table II). The rate of urinary excretion of amino acids...
Table II. Fasting concentrations of plasma amino acids (μM/L) and blood NH₃ (μg/dl) in 8 normal children aged 8-14 years; and in Patient M. W. while receiving 10 gm protein diet, or this diet supplemented for 5 to 8 days by 3 gm daily lysine, arginine, or citrulline, respectively.

<table>
<thead>
<tr>
<th>Plasma amino acid</th>
<th>Normal</th>
<th>M.W. untreated (10 gm protein daily)</th>
<th>M.W. after 5-8 days during which 3 gm daily of either lysine, arginine, or citrulline was added to 10 gm protein diet</th>
<th>M.W. during long-term treatment (Fig. 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Period II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Period III</td>
</tr>
<tr>
<td>Serine</td>
<td>98 ± 11</td>
<td>375 ± 64†</td>
<td>363 ± 41</td>
<td>185 ± 26</td>
</tr>
<tr>
<td>Glutamine</td>
<td>595 ± 38</td>
<td>3,400 ± 410†</td>
<td>3,720 ± 500</td>
<td>2,640 ± 285</td>
</tr>
<tr>
<td>Proline</td>
<td>146 ± 11</td>
<td>330 ± 78†</td>
<td>340 ± 41</td>
<td>1,120 ± 168</td>
</tr>
<tr>
<td>Citrulline</td>
<td>12 ± 2</td>
<td>4 ± 1</td>
<td>5 ± 1</td>
<td>20 ± 3†</td>
</tr>
<tr>
<td>Glycine</td>
<td>196 ± 22</td>
<td>595 ± 83†</td>
<td>610 ± 75</td>
<td>285 ± 34†</td>
</tr>
<tr>
<td>Alanine</td>
<td>300 ± 15</td>
<td>1,075 ± 251</td>
<td>1,020 ± 98</td>
<td>534 ± 64</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>53 ± 4</td>
<td>75 ± 12†</td>
<td>82 ± 10</td>
<td>173 ± 20</td>
</tr>
<tr>
<td>Leucine</td>
<td>100 ± 9</td>
<td>160 ± 20†</td>
<td>143 ± 15</td>
<td>135 ± 15</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>48 ± 6</td>
<td>80 ± 12†</td>
<td>100 ± 15</td>
<td>59 ± 7†</td>
</tr>
<tr>
<td>Ornithine</td>
<td>53 ± 4</td>
<td>3 ± 1†</td>
<td>3 ± 1</td>
<td>18 ± 3†</td>
</tr>
<tr>
<td>Arginine</td>
<td>63 ± 4</td>
<td>5 ± 2†</td>
<td>4 ± 1</td>
<td>28 ± 5†</td>
</tr>
<tr>
<td>Lysine</td>
<td>121 ± 10</td>
<td>20 ± 4†</td>
<td>65 ± 9†</td>
<td>6 ± 1†</td>
</tr>
<tr>
<td>NH₃</td>
<td>55 ± 6</td>
<td>120 ± 18†</td>
<td>160 ± 18</td>
<td>55 ± 6†</td>
</tr>
<tr>
<td>Column</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>P value for comparison:</td>
<td>vs col 1</td>
<td>vs col 2</td>
<td>vs col 2</td>
<td>vs col 2</td>
</tr>
</tbody>
</table>

*Values represent mean ± SEM, n = 8 for “normal” data and n = 3 for “M.W.” data. Blood samples taken at 8 AM, 14 hours after last supplement and meal.
†Indicates P < 0.05 for comparison indicated in bottom line of table. Corresponding urine values are given in Tables III and IV. Concentration of these unlisted amino acids were normal in Patient M. W.: threonine, glutamic acid, valine, methionine, phenylalanine, histidine.

after an overnight fast was 10 times elevated compared to age-matched control subjects for lysine, 3- to 4-fold elevated for glutamine, glycine, and alanine, and not significantly (P > 0.05) elevated for any other amino acid (Table III). Renal clearances were abnormally high (P < 0.05) for lysine (70 times normal), arginine (4 times normal), and ornithine (4 times normal) (Table IV).

Patient M. W. now ingested 3 gm daily (1 gm with each meal) of arginine, lysine, or citrulline, alone or in combination. After 5 to 8 days of supplementation, and 14 hours after dinner plus supplement, plasma aminogram, urinary aminogram, and renal clearances were measured in the fasting state. Lysine supplement improved the hypolysinemia; hyperargininemia and hyperornithinemia remained unchanged; and rate of urinary excretion and renal clearance of lysine increased (Tables II, III, and IV). Arginine supplement caused: partial correction of hypoargininemia and hypoornithinemia with increased urinary excretion and renal clearance of both substances; simultaneously hyperlysinemia and lysinuria intensified. Arginine plus lysine caused simultaneous improvement in plasma arginine, lysine, and ornithine levels with simultaneous increase in urinary excretions and renal clearances of all three amino acids; meanwhile hyperaminoacidemia of remaining amino acids showed moderate improvement. Best improvement of Patient M. W.’s plasma aminogram was achieved by citrulline plus lysine, the supplement which most nearly corrected the deficiencies of lysine, arginine, ornithine, and citrulline, and the excesses of the remaining amino acids (Table II). Simultaneous with this improvement, her urinary excretions and renal clearances of lysine, arginine, and ornithine increased to a greater extent than under any other type of dietary supplementation (Tables III and IV).

Effect of amino acid supplements on blood NH₃. While the patient ate a 10 gm protein diet, her fasting blood NH₃ was moderately elevated to 80 to 120 μg/dl. Ingestion of one glass of chocolate Nutrament containing 12.5 gm of protein at 8 A.M. caused severe and prolonged hyperammonemia. In normal children, blood NH₃ did not rise under these conditions. Fasting and postprandial hyperammonemia after protein ingestion was now studied after 5 to 8 days’ supplementation of the 10 gm protein diet with lysine, arginine, citrulline, or combinations. Arginine, arginine plus lysine, citrulline, or citrulline plus lysine improved the fasting and postprandial hyperammonemia, the latter two supplements seeming more effective (Table II).

LONG-TERM TREATMENT WITH AMINO ACID SUPPLEMENTS

The observations up to this point were consistent with the hypothesis (Fig. 3) that deficiencies of lysine, arginine, and ornithine were responsible for the patient’s growth...
failure, hyperammonemia, and aversion to protein. The one-week experiments, moreover, suggested that the deficiencies of these amino acids could be corrected by feeding sufficiently large supplements of lysine plus arginine, since the block to intestinal absorption of these two amino acids was known to be only partial, and since a fraction of absorbed arginine would be converted to ornithine. The short-term data also indicated that we could replace arginine by feeding the normally absorbed, monobasic amino acid citrulline, which would be converted to arginine in the hepatic Krebs-Henseleit cycle. The two options (lysine plus arginine and lysine plus citrulline), were tested separately in the following 2-year study (Fig. 1):

- **Period I:** 6 months' observation without treatment.
- **Period II:** 6 months' arginine + lysine (3 gm daily for each).
- **Period III:** 6 months' citrulline + lysine (3 gm daily for each).
- **Period IV:** 6 months, no treatment.

The following variables were monitored: height and weight (every 2 weeks); plasma amino acid pattern (monthly); fasting blood NH₃ (every 2 months); electroencephalogram (every 2 months); spontaneous food intake (every 3 to 6 months). During Period I, gain in height was retarded to 0.31 cm/month, and gain in weight to 0.11 kg/month (Fig. 1). Electroencephalogram continued to exhibit generalized slowing and frequent periods of high voltage activity. She ate only 8 to 12 gm of protein daily (Table I). Plasma amino acid pattern showed the same abnormalities observed during the initial evaluation (Table II). During Period II, gain in height accelerated to 0.80 cm/month, and gain in weight to 0.39 kg/month. Electroen-
GENETIC DEFECT IN EPITHELIAL TRANSPORT OF LYSINE, ARGININE AND ORNITHINE

DECREASED INTESTINAL ABSORPTION
OF DIETARY LYSINE AND ARGININE

INCREASED RENAL EXCRETION
OF LYSINE, ARGININE AND ORNITHINE

DEFICIENCY OF
ORNITHINE (non-essential)
ARGININE (non-essential)
LYSINE (essential)

IMPAIRED UREA CYCLE
HYPERAMMONEMIA + HYPERAMINOACIDEMIA

SEIZURE DISORDER
INFANTILE POST-PRANDIAL EMESIS
PROTEIN AVERTION

PROTEIN MALNUTRITION
OSTEOPOROSIS,
KYPHOSCOLIOTOSIS
GROWTH FAILURE
HEPATOMEGALY

Fig. 3. Postulated sequence of events in Patient M.W.

cephalogram remained unchanged. The protein intake rose to 18 gm daily (Table I). Plasma amino acid pattern showed partial normalization in terms of higher levels of arginine, lysine, ornithine, and citrulline, and lower value of glycine (Table II). Fasting blood NH₃ however, remained elevated.

During Period III, the patient’s favorable progress continued. Protein intake now averaged 29 gm daily. Gains of height and weight, 1.33 cm/month and 0.54 kg/month, respectively, were 1.7 times and 1.4 times greater than during Period II, and 4.3 times and 4.9 times greater than during Period I. Plasma amino acid pattern showed further correction of deficiencies of arginine, lysine, ornithine, and citrulline, and of excesses of most other amino acids; fasting blood NH₃ moreover, was now within normal range (Table II). Electroencephalogram was generally similar to Period II.

In Period IV, Patient M.W.’s growth rate declined to that of Period I. Anorexia and protein aversion returned, spontaneous protein intake averaging only 13 gm daily. The patient’s mother reported the child was lethargic and slept frequently during the day, but a consistent change in electroencephalogram was not apparent. Plasma amino acid pattern was similar to that during Period I (Table II).

DISCUSSION

Patient M.W.’s clinical manifestations and abnormal laboratory data were similar to those of affected individuals in the previously reported pedigrees: hyperdibasic-aminoaciduria, gastrointestinal symptoms, and growth retardation. The hyperdibasicaminoaciduria and hypodibasicaminoacidemia in this patient were comparable in degree to those of the Finnish and Japanese subjects, who were more severely affected than the Canadian ones. She also had hyperammonemia and hypermonobasic-aminoacidemia as did the Finnish patients.

Three aspects of her clinical picture merit special comment. (1) The physical findings of hyperelastic skins and hypermobile joints, not mentioned in previous reports on this syndrome, resemble manifestations of type VI Ehlers-Danlos syndrome. In the latter disease, the skin
and joint abnormalities are attributed to a deficiency of hydroxylysine which results in collagen of low tensile strength. Consequently skin, ligaments, joint capsules, and other connective tissues are abnormally stretchable. Similar findings in Patient M. W. suggest that she too may have abnormal collagen due to lifelong intestinal malabsorption and renal wasting of the essential amino acid, lysine. (2) Previous reports on hyperdibasicaminoaciduria concurred on defective renal tubular reabsorption of dibasic amino acids but disagreed in respect to impairment of intestinal transport. The data of Patient M. W. indicate that transport of arginine and lysine is impaired not only in the renal tubule but also in the small intestine. (3) Patient M. W. illustrates a practical point in the diagnosis of hyperdibasicaminoaciduria: amino acid analysis of random urine samples showed only lysinuria without argininuria or ornithinuria (Table III). Apparently, in the untreated state, the combination of intestinal malabsorption of dibasic amino acids and reduced intake of these substances because of aversion to protein (Table I) caused such severe hypoargininemia and hypornithinemia that urinary excretion of these two amino acids was only slightly elevated. When protein intake was increased to 40 gm daily, however, or when the 10 gm protein diet was supplemented with arginine or citrulline, there was excessive argininuria and ornithinuria (Table III). Analyses of amino acids in plasma as well as in urine are thus essential when a patient is being evaluated for the hyperdibasicaminoaciduria syndrome.

Fig. 3 suggests how a transport defect can lead to all the chemical and clinical abnormalities observed in Patient M. W. On the basis of this scheme, two approaches to therapy seemed logical: (1) Since the block to intestinal absorption of arginine and lysine is incomplete, large oral doses of these two amino acids could be given. (2) In the case of arginine, the block to absorption could be bypassed by feeding the neutral amino acid citrulline, which was absorbed by the patient with > 90% efficiency (as shown with 14C citrulline test), conserved normally by the kidneys (Tables III and IV), and converted within the body to arginine and ornithine. Theoretically citrulline could serve as a repository form of arginine and ornithine, perhaps leading to more prolonged correction of arginine and ornithine depletions. Another possible advantage of supplementation with citrulline rather than with arginine would be to facilitate absorption of lysine by avoiding an arginine-versus-lysine competition for intestinal absorption. In support of this idea, administration of either arginine or citrulline corrected hypoargininemia (Table II); administration of arginine, however, accentuated the hypolysinemia whereas citrulline improved this abnormality (Table II).

The 5 to 8 day trials provided chemical evidence of effectiveness for the amino acid supplements. It was evident, however, that citrulline plus lysine was more beneficial than arginine plus lysine: the former combination more nearly normalized the plasma aminogram and corrected the postprandial hyperammonemia. This could be explained, as suggested above, by better absorption of lysine when not subject to competition by a simultaneous supplement of arginine. Perhaps more prolonged availability of arginine generated endogenously from fully absorbed citrulline, as compared to intermittent and partial absorption of exogenous arginine, was also a factor.

The two-year experiment bore out these impressions. Both regimens of supplements resulted in an acceleration of growth rate, an increased appetite, including that for protein, partial normalization of plasma aminogram, and decrease in hyperammonemia. In most respects, the citrulline plus lysine combination was more effective than arginine plus lysine.

Miss Bettye M. Hollins performed the amino acid analyses. Mrs. Delores Fegan supervised the nursing, and Miss Irma O’Beirne and Mrs. Elaine Quiter supervised the dietary aspects of the study.

REFERENCES