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Arginine Deficiency and Orotic Aciduria in Mammals (39020)

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Dietary arginine (Arg) is essential for optimum nitrogen retention by immature rats (1–3); chicks (4); guinea pigs (5), and rabbits (6). Although arginine has not been shown to be essential for positive N balance in man of any age group (7, 8), the need for Arg to support optimum health is not known. It has been reported that adult men (8); dogs (9) and rats (10) do not require dietary Arg for nitrogen equilibrium and it is assumed that adults of other species also meet their Arg needs from endogenous synthesis. Although administration of excess Arg leads to toxicity associated with hyperglycemia (11) it is well established that administration of Arg will ameliorate the signs of ammonia intoxication in man and other mammals (12), if there is sufficient functional liver reserve (13).

Although mammals grow and remain in positive nitrogen balance even if dietary Arg is totally absent from the diet, these criteria fail to delineate other metabolic changes that may occur if Arg availability is marginal. We have previously observed that diets lacking urea cycle amino acids cause metabolic changes including a dramatic rise in orotic aciduria in rats (14). The present experiments were conducted to determine if similar changes in metabolite excretion also occur during Arg deficiency in other species. The data of this communication compare Arg deficiency in hamsters, rats, guinea pigs, dogs, mice, and rabbits.

Materials and methods. Experiments were conducted with rats, hamsters, guinea pigs, mice, dogs, and rabbits fed purified diets containing only L-amino acids (L-AA) (3) or casein as the source of nitrogen. All were adapted to their respective control diet for at least 3 days prior to assignment to a particular experimental dietary treatment. Throughout the experimental feeding, the animals were maintained in individual stainless steel metabolism cages in rooms with controlled temperature and lighting. The rats, mice, and hamsters were purchased from ARS Sprague–Dawley, Madison, Wisconsin. Guinea pigs were random bred and obtained from a local source. Purebred Beagle pups and random bred rabbits of Dutch-belted ancestry came from stock maintained within our university laboratories.

Assignments to dietary treatments were always made randomly. Water was provided *ad libitum*. Supplemental Arg was supplied as the HCl salt. Glycine was used to make the diets isonitrogenous. All diets unless otherwise described, were suspended in 2% agar gel. The percentage compositions of the different diets are shown in Tables I, II, III, and IV. Urine was collected in acid containing receptacles and urinary urea, ammonia, citrate, and orotate were analyzed as described previously (15).

Eight pairs of immature (60–75 g) male, Sprague–Dawley rats (Experiment 1) were pair-fed for 4 days on a diet containing only L-AA with or without Arg (–Arg) but otherwise containing all known essential nutrients (3). Peripheral blood obtained at decapitation was analyzed for NH_4–N and urea (16). In Experiment 2, 10 immature male hamsters (40–45 g) were fed, ad libitum, the L-AA diet with or without Arg as in Experiment 1.

For Experiment 3, 15 mature hamsters (100 g) were conditioned for 4 days to a 12% casein basal diet and then assigned for 7 days to one of three diets: basal casein, the complete L-AA diet, or the L-AA diet minus Arg. In this experiment, the L-AA diets contained the ratio of amino acids provided by the basal casein diet as calculated from published data, Atlas of Nutritional Data on United States and Canadian Feeds (17).

Eight immature male and immature female guinea pigs (95–140 g) were fed an

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TABLE I. FEED INTAKE AND URINARY METABOLITES OF RATS PAIR-FED AN L-AMINO ACID DIET WITH OR WITHOUT ARGININE. [a] [b] [c]

	Control	–Arginine
Feed intake (g/4 days)	50 ± 2*	50 ± 2*
Weight gain (g/4 days)	13 ± 1*	10 ± 1†
Urinary Metabolites[d]		
Urea (mg/24 hr)	30 ± 3*	91 ± 8†
NH_4-N (mg/24 hr)	10 ± 1*	8 ± 1†
Orotate (μg/24 hr)	36 ± 2*	5520 ± 638†
Citrate (μg/24 hr)	72 ± 10*	1535 ± 200†
Blood metabolites[e]		
NH_4-N (μg/ml)	0.51 ± 0.07*	0.84 ± 0.11†
Urea (mg%)	5.9 ± 0.2*	11.2 ± 0.3†

[a] The control diet had the following percentage composition: L-amino acids, Milner *et al.* (3), 14.00; dextrin, 46.37; sucrose, 23.43; corn oil, 10.00; salt mixture, 5.00, Jones and Foster (33); vitamins, 1.0 (Vitamin Fortification Mixture, GBI, Madison, Wisconsin) and choline chloride, 0.20. Glycine was used to make the diets isonitrogenous.

[b] Mean ± SEM for eight rats per experimental treatment.

[c] Means with unlike superscripts differ $P < 0.05$.

[d] Day 3 of experimental feeding.

[e] Peripheral blood taken 2 hr after feeding on Day 4.

18% casein diet in dry form with or without 1.0% supplemental Arg for 6 days (Experiment 4). In Experiment 5, 12 mature male guinea pigs (400–500 g) were fed the 20% casein control diet and then randomly assigned for 7 days to either the control diet or the control diet with 1% supplemental Arg.

Twelve purebred 4-month old male Beagle growing dogs, weighing 5–6 kg and reared on a commercial ration (Wayne Bite Size Pellets, Allied Mills, Chicago, Illinois), was randomly assigned to dietary treatments in Experiment 6. Three were assigned to remain on laboratory chow while the remainder were switched to a casein basal diet for three days. Then, of this latter group of nine, three remained on the casein/basal diet, three were assigned to an L-AA diet and three were assigned the L-AA diet minus Arg. Experimental feeding lasted three days.

In Experiment 7, 40 male (BDF SCH) hybrid mice caged in groups of 5 were adapted to the L-AA diet of Experiment 1. After 3 days of adaptation, one-half were switched to the same diet minus Arg for 14 days of experimental feeding.

Six immature male Dutch belted rabbits (300–400 g) were adapted for 4 days to a dry basal 15% casein diet in Experiment 8 and then assigned at random to the basal diet or the basal with 1% Arg added.

All data were analyzed statistically by the methods of Steele and Torrie (18).

Results. Immature rats fed no Arg excreted substantially greater quantities of urea, citric acid and orotic acid than their pair-fed partners given the complete L-AA diet (Table I) which was consistent with previous observations (14–16). The Arg deficient animals had elevated blood NH_4-N and urea concentrations, and their growth was depressed compared to the pair-fed controls (Table I).

Urea excretion in the immature hamsters was not affected by removal of Arg. Urea excretion increased in the –Arg mature hamsters compared to those fed the complete L-AA diet. Compared to controls, growth, feed intake and urinary excretion of ammonia were lower in the immature hamsters fed the –Arg diet (Table II). Citrate and orotate excretion for immature (Experiment 2) and mature (Experiment 3) hamsters were increased following removal of Arg from their diet (Table II). Feed intake was depressed in both age groups. Although not statistically significant at $P < 0.05$, the average citrate and orotate excretion tended to be higher for the casein fed (Experiment 3) hamsters compared to those fed the L-AA diet.

Addition of Arg to the basal casein diet fed immature male or female (Experiment 4) and mature male guinea pigs (Experiment 5) caused a significant decline in urinary orotic acid. No significant effect of Arg supplementation on urinary urea and citrate

TABLE II. FEED INTAKE, GROWTH, AND URINARY METABOLITES OF IMMATURE AND MATURE HAMSTERS AND GUINEA PIGS FED CASEIN OR L-AMINO ACID DIETS WITH OR WITHOUT ARGININE.[a, b]

			Urinary metabolites			
	Intake[c] (g/day)	Growth (g)	Urea (mg/24 hr)	Orotate (μg/24 hr)	NH_4–N (mg/24 hr)	Citrate (μg/24 hr)
Hamsters (7 days growth)						
Immature (Male)						
L-AA[d] (8)	11 ± 1*	14 ± 1*	69 ± 3*	135 ± 8*	10 ± 1*	247 ± 33*
L-AA-Arg[d] (8)	9 ± 1†	10 ± 1†	74 ± 6†	2000 ± 319†	6 ± 1†	1016 ± 247†
Mature (male)		(g/5d)				
Casein[e] (5)	16 ± 1*	4 ± 2*	197 ± 35*	320 ± 65*	10 ± 2*	334 ± 61*
L-AA[e] (5)	14 ± 2*†	3 ± 1*	113 ± 21†	270 ± 29*	11 ± 2*	208 ± 21*
L-AA-Arg[e] (5)	13 ± 1†	−1 ± 3*	183 ± 24*	545 ± 46†	13 ± 2*	292 ± 20†
Guinea Pigs (5 days growth)						
Immature (male)						
Casein (4)	20 ± 3*	6 ± 2*	56 ± 7*	355 ± 38*	3 ± 1*	4292 ± 545*
Casein + Arg[f] (4)	25 ± 2*	15 ± 3†	61 ± 8*	90 ± 4†	2 ± 1*	4083 ± 580*
Immature (female)[e]						
Casein (3)	18 ± 4*	−1 ± 3*	73 ± 13*	262 ± 43*	3 ± 1*	4367 ± 590*
Casein + Arg[g] (4)	26 ± 3*	8 ± 2†	53 ± 8*	78 ± 2†	2 ± 1*	3910 ± 555*
Mature (male)						
Casein (6)	55 ± 7*	8 ± 3*	42 ± 7*	211 ± 18*	47 ± 13*	4620 ± 746*
Casein + Arg[g]	64 ± 7*	2 ± 5†	22 ± 4†	146 ± 19†	39 ± 11†	3200 ± 1040*

[a] Mean ± SEM without a common superscript differ $P < 0.05$.

[b] Number of animals per treatment in parentheses.

[c] Intake as fed in agar gel, 50% dry diet plus 50% H_2O.

[d] Dietary ingredients as listed in Table I. Urinary metabolites for day 7 of experimental feeding.

[e] The diets had the following percentage composition: sucrose, 49.0; corn starch, 16.5; vitamin mixture, 0.5 (Vitamin Mixture 1369, Nutritional Biochemicals Corp.); solka floc, 8.0; cottonseed oil, 10.0; salt mixture, 4.0, Jones and Foster (33); and casein or L-amino acids, 12.0. Urinary metabolites for day 5 of experimental feeding.

[f] Composition of the basal diet, as a percentage: casein, 18.0; L-arginine-HCl, 1.0; corn starch, 37.8; sucrose, 18.0; solka floc, 3.0; corn oil, 10.0; salt mixture, 5.0, Jones and Foster (33); $KC_2H_4O_2$, 2.5; MgO, 0.5; choline chloride, 0.2; vitamin mixture, 1.0 (Vitamin Fortification Mixture, General Biochemicals Corp., Madison, Wisconsin); and ascorbic acid, 0.2. Urinary metabolites for day 5 of feeding.

[g] Composition of basal diet as a percentage: casein, 20; L-arginine-HCl, 1.0; sucrose, 19.77; glucose, 14.98; solka floc, 20.0; soybean oil, 5.0; vitamin mixture, 0.65; mineral mixture, 2.7; $CaHPO_4$, 3.1; calcium gluconate, 10.8; and $KC_2H_4O_2$, 2.0. The composition of the vitamin mixture was (g/kg): vitamin A palmitate (250,000 IU/g), 0.11; vitamin C, 0.30; vitamin D (250,000 IU/g), 0.11; vitamin E, 0.27. It also contained: (mg/100 g/diet): inositol dihydrate, 120.0; thiamine HCl, 1.6; riboflavin, 1.6; pyridoxine-HCl, 1.6; calcium pantothenate, 4.0; niacin, 2.0; biotin, 0.05; folic acid, 1.0; para-aminobenzaldehyde, 5.0; menadione, 2.0; cyanocabalamin, 0.001: rutin, 5.0; choline dihydrogen citrate, 423.0. Composition of mineral premix (mg/100 g/diet): Na_2HPO_4, 463.1; $CaHPO_4$, 163.8; KH_2PO_4, 1080.8; MgO, 580.3; KCl, 276.0; calcium gluconate, 12885.6; ZnO, 12.5; $FeSO_4 \cdot 7H_2O$, 29.9; KIO_3, 0.034; $MnSO_4 \cdot H_2O$, 15.0; Na_2SeO_3, 0.11; $CoCl_2 \cdot 6H_2O$, 0.004; $Cr_2(SO_4)_3 \cdot K_2SO_4 \cdot 24H_2O$, 0.001; $CuCl_2 \cdot 2H_2O$, 1.34. Urinary metabolites for day 5 of feeding.

was observed in immature guinea pigs, although both tended to decrease with supplemental Arg in mature guinea pigs (Table II).

Feed intake was depressed for growing dogs (Experiment 6) consuming the purified diets compared to the commercial ration (Table III). However, weight gains for the short feeding periods were slightly higher in puppies consuming the casein or the complete L-AA diet (C) compared to those consuming the commercial ration (Table III).

TABLE III. FEED INTAKE, GROWTH, AND URINARY METABOLITES OF DOGS FED PREFORMED PROTEIN OR AMINO ACID DIETS. [a, b]

Diets	Commercial[c]	Casein[d]	L-Amino acids[e]	L-Amino acids–Arg
Initial weight (kg)	5.3 ± 0.2*	5.5 ± 0.3*	5.8 ± 0.4*	5.0 ± 0.1*
Gain (kg/3 days)	0.26 ± 0.02*	0.74 ± 0.44*	0.35 ± 0.22*	−0.16 ± 0.33*
Feed intake (g)				
Day 1	400 ± 0*	325 ± 14†	317 ± 19†	181 ± 16‡
Day 2	421 ± 79*	319 ± 13*	313 ± 9*	128 ± 29†
Day 3	400 ± 0*	241 ± 111†	282 ± 23†	100 ± 48‡
	Urinary metabolites excreted in 24 hr			
Urea (g)				
Day 1	6.5 ± 0*	6.3 ± 1.5*	6.0 ± 1.8*	4.2 ± 0.9†
Day 2	5.1 ± 0.9*	7.5 ± 1.8*	4.1 ± 0.5*	2.0 ± 0.2†
Day 3	4.8 ± 1.7*	9.0 ± 3.0*	3.7 ± 1.0*	2.0 ± 0.4†
Citrate (mg)				
Day 1	10.9 ± 0.7*	1.6 ± 0.2*	3.5 ± 2.0*	2.4 ± 0.1*
Day 2	11.5 ± 2.7*	2.0 ± 0.3*	1.8 ± 0.3*	4.7 ± 2.5*
Day 3	11.3 ± 2.0*	2.1 ± 0.4*	1.1 ± 0.6*	8.3 ± 5.7*
Orotate (μg)				
Day 1	187 ± 82*	92 ± 44*	161 ± 61*	1180 ± 40†
Day 2	72 ± 48*	50 ± 29*	16 ± 8*	1433 ± 807†
Day 3	37 ± 18*	35 ± 11*	43 ± 4*	1579 ± 720†

[a] Mean ± SEM for three Beagle pups per group.

[b] Horizontal values with unlike superscripts differ $P < 0.05$.

[c] Wayne Bite Size Pellets, Allied Mills, Chicago, Ill.

[d] Composition (g/kg): cerelose, 284; sucrose, 284; casein, 250; α-cellulose, 40; corn oil, 80; vitamin mixture 1369 (Nutritional Biochemicals Corp., Cleveland, Ohio), 22; and minerals, Jones and Foster (33), 40.

[e] Composition (g/kg): cerelose, 339; sucrose, 339; L-amino acid mixture, 128.8; arginine, 11.2; α-cellulose, 40; corn oil, 80; vitamin mixture, 1369: (Nutritional Biochemicals Corp., Cleveland, Ohio) 22; minerals, Jones and Foster (33), 40. The amino acid mixture had the following composition (g/kg): arginine, 11.2; alanine, 3.5; asparagine, 6.0; aspartic acid, 3.5; cystine, 3.5; glutamic acid, 3.5; glycine, 42.66; histidine, 3.3; isoleucine, 8.2; leucine, 11.1; lysine, 14.4; methionine, 8.2; phenylalanine, 11.6; proline, 3.5; serine, 3.5; threonine, 8.2; tryptophan, 1.74; tyrosine, 3.5; and valine, 8.2.

Two of the animals consuming the L-AA diet minus Arg lost weight during the 3-day period. The L-AA diet minus Arg caused vomiting which was observed immediately after eating. Removing Arg from the L-AA diet decreased urea excretion when compared to the other dietary regimens. Urinary citrate was consistently higher when the pelleted commercial diet was fed compared to either of the experimental diets. Removing Arg increased citrate excretion compared to the casein or the complete L-AA diets (Table III). Removing Arg increased urinary orotic acid excretion compared to all other treatments. Blood urea concentrations after 3 days of experimental feeding were 42.0 ± 6.6, 42.6 ± 10.8, 15.2 ± 1.0, and 19.8 ± 2.8 mg/100 ml for the groups fed the commercial laboratory chow, casein, L-AA, and L-AA minus Arg, respectively.

Deletion of Arg significantly reduced feed intake and body weight gains in mice (Experiment 7). Urinary orotic and citric acid for the −Arg mice on day 14 were significantly higher than for the controls (Table IV). Removal of Arg depressed urinary urea and ammonia excretion.

Arg supplementation of the 15% casein diet stimulated growth in immature rabbits (Experiment 8) and decreased their urinary orotic acid (Table IV). No significant effect of Arg supplementation on urinary NH_4–N, urea or citrate was observed (Table IV).

Discussion. Our previous work (2, 14–16) shows that a deficiency of dietary Arg causes significant increases in the excretion of the

TABLE IV. GROWTH AND URINARY METABOLITES OF IMMATURE MICE AND RABBITS FED DIETS WITH OR WITHOUT SUPPLEMENTAL ARGININE.

	L-AA[b]	L-AA-Arg
Mice[a]		
Growth (g/2 week)	6.6 ± 0.3*	2.9 ± 0.4†
Feed intake[c] (g/day)	5.1 ± 0.2*	4.0 ± 0.1†
Urinary metabolites[d]		
Urea (mg/24 hr)	170 ± 20*	106 ± 14†
NH_4-N (mg/24 hr)	23 ± 3*	13 ± 3†
Orotate (μg/24 hr)	88 ± 11*	1052 ± 216†
Citrate (μg/24 hr)	556 ± 167*	2862 ± 450†
Rabbits		
Growth (g/4 days)	45 ± 7*	79 ± 5*
Urinary metabolites		
Urea (mg/24 hr)	341 ± 25*	319 ± 15*
NH_4-N (mg/24 hr)	1.9 ± 0.1*	1.1 ± 0.3*
Citrate (μg/24 hr)	3935 ± 669*	5317 ± 1098*
Orotate (μg/24 hr)	4618 ± 1879*	953 ± 487†

[a] Mean ± SEM of five mice per cage with four replicates per treatment.

[b] Composition of diet as for rats in Table I.

[c] As fed 50% dry diet plus 50% H_2O in agar gel.

[d] Mean with unlike superscripts differ $P < 0.05$.

[e] Percentage composition of diet: casein, 15.0; arginine-HCl, 1.0; corn starch, 43.0; cerelose, 24.0; solka floc, 3.0; mineral mixture, Jones and Foster (33), 5.0; $KC_2H_4O_2$, 2.5; MgO, 0.5; vitamin mixture (Vitamin Fortification Mixture, General Biochemicals Corp., Madison, Wisc.), 1.0; corn oil, 5.0.

primary end products of nitrogen metabolism in urine of immature and mature rats. The significant rise in citrate and orotate occurred within 24 hr in rats and persisted for a feeding period of 35 days (19, 20). The present experiments show that similar changes in urinary metabolites also occur in mice, growing dogs, hamsters, guinea pigs and rabbits but their magnitude varies with species, age and the diet. Most importantly, all diets marginal or deficient in arginine resulted in excessive loss of urinary orotic acid independently of species, age or diet fed. It is important to recognize that all of the Arg deficient diets also lacked the other amino acids which are intermediates of the urea cycle. In practical terms, however, the metabolic changes are those of an Arg deficiency because ornithine and citrulline are virtually absent from native proteins.

Ornithine or citrulline fed isonitrogenously fail to completely prevent the growth depression and changes in urinary metabolites seen with Arg deficient rats (14). Based upon these observations we have concluded that Arg deficiency decreases the ability of the urea cycle to detoxify ammonia and that there is increased shunting of intramitochondrial carbamyl phosphate into pyrimidine synthesis (14, 16). These responses were independent of the source of dietary nonessential amino acids (14). This evidence agrees with Kennan and Cohen (21) who concluded from data for rats that the urea cycle normally operates near its maximum capacity for ammonia detoxification.

Quantitative variations between species in the excretion of metabolites during Arg deficiency may in part be due to differences in digestive processes. For instance, bacteria in the pregastric pouch of hamsters and in the ceca of guinea pigs and rabbits can incorporate ammonia nitrogen into proteins resulting in a net synthesis of amino acids and a variety of other essential nutrients. Although neither proteolytic activity nor ammonia production appear to have been studied in the pregastric pouch of the hamster, rumen type microorganisms have been demonstrated (22), and the pouch has anatomic and histologic features similar to those of the forestomach in ruminant animals (23). Volatile fatty acid production (23) and utilization of urea, both microbial processes, have been demonstrated in hamsters (24). These observations argue strongly for rumenlike bacterial digestive processes capable of altering the quality of dietary protein in this species. It is impossible from present data to determine if the quanti-

tative differences in excretion of orotate and citrate between immature and mature hamsters were a response to the diet as fed or if they resulted from significant influences of the microbial flora. Regardless, it is clear that endogenous or bacterial synthesis of Arg was unable to meet the requirements for normal growth in hamsters and to maintain the normal concentrations of urinary metabolites for immature or mature hamsters under these conditions.

Diets containing 18–22% casein as the only source of nitrogen fail to provide adequate intakes of Arg for guinea pigs since they require approximately 1.56% in their total diet (25). Our data also show that Arg deficiency increased orotic acid excretion in both immature and mature guinea pigs. Clearly, marginal intakes of Arg in the present studies caused a significant loss of orotic acid in the urine. More dramatic effects would be expected during total Arg deprivation.

Wretland (26) concluded that Arg is required for intravenous feeding of dogs to optimize utilization of other amino acids and to counteract the toxic effects of ammonia arising from high concentrations of glycine. The present results argue strongly that immature dogs require Arg because their excretions of metabolites are similar to those of the other species deficient in Arg. The episodes of vomiting observed in these studies might occur in other species having a vomiting reflex. Compared to the puppies fed other diets, citrate excretion was considerably higher for the Beagle puppies fed laboratory chow. This may be due to appreciable quantities of citrate contained in this commercial product, Milner and Visek (unpublished data).

Others have concluded that Arg is not required by mice (27). Our data show that endogenous synthesis of Arg was inadequate for normal growth in mice and that the changes in urinary metabolites were characteristic of other species. Published data dealing with amino acid requirements for immature rabbits give little evidence to base conclusions about Arg requirements. McWard *et al.* (6) found that Arg supplementation of semipurified casein diet stimulated their growth. Our present data show that dietary arginine was required for optimal growth and maintenance of normal excretion of metabolites in their urine.

Antibiotics in the drinking water or feed have been shown to reduce requirements for Arg in rats (19, 20). This suggests that determinations of Arg requirements with antibiotics in the diet may be erroneous. Mertz *et al.* (28) estimated that pigs can synthesize sufficient arginine to sustain growth rates equivalent to about 60% of controls. However, an antibiotic was included in the basal diet. Our preliminary data show that ammonia intoxication in 15 kg pigs causes greatly elevated urinary orotic acid excretion. Such evidence indicates that metabolites similar to those of other species are excreted by swine when the capacity of their urea cycle is exceeded during ammonia intoxication (15) or there is a lack of essential urea cycle intermediates (14). Easter *et al.* (29) have concluded that on the basis of growth and urinary metabolites that female swine do not require dietary Arg for postpubertal growth and pregnancy. Their evidence may be the result of species differences or the composition of the diets fed.

Bigwood (30) found that as much as 46% of the dietary arginine is destroyed by microflora in the rumen of the sheep. It is possible that Arg supplies to the absorptive surfaces of ruminants are inadequate when urea or other forms of nonessential nitrogen are fed and demands for ammonia detoxification are increased. Whenever urea or other forms of nonamino nitrogen are fed or there is an Arg deficiency the quantity of urea hydrolyzed in the bowel by bacteria is increased substantially (31). This further increases the utilization of Arg for ammonia detoxification and would enhance the severity of an Arg deficit for meeting other requirements.

Both sexes of rats show increases in urinary orotate and citrate when there is a deficiency of urea cycle amino acids (32) and the present data show that these changes occur regardless of total feed intake. The present studies also show that increased excretion of orotic acid occurs during Arg deficiency in rats, hamsters, guinea pigs, mice, dogs, and rabbits. Although urinary

citrate generally increases, it is a less reliable indicator of Arg nutrition because of its usual concentrations in the urine and its variation due to other dietary conditions. Orotic acid on the other hand is present in very small quantities unless there is a deficit of Arg, hyperammonemia, altered pyrimidine synthesis or treatment with certain drugs (3, 16). Urinary orotic acid, shown to rise during pregnancy, declines when additional Arg is fed (32). In view of the similarities in intermediary metabolism, studies in other ureotelic species including man, are indicated. Based upon available data, the authors suggest that urinary orotic acid is a reliable indicator of Arg deficiency in ureotelic mammals.

Summary. Dietary arginine deficiency in rats causes significant increases in urinary excretion of urea, citric acid and orotic acid independently of feed intake. Urea excretion during arginine deficiency depends upon the diet, sex, age, and species. Thus urea excretion has limitations as an indicator of arginine availability. Although elevated urinary citric acid during arginine deficiency is more consistently observed, it may be influenced by citric acid in natural dietary ingredients. Orotic acid excretion, however, appears to be a reliable indicator of available dietary arginine based upon studies in rats, mice, hamsters, guinea pigs, rabbits, and dogs.

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