

## AMINO ACID EXCRETION IN PRIMARY HYPERURICAEMIA\*

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The demonstration that patients with primary hyperuricaemia are also hyperaminoacidaemic (Kaplan, Bernstein, Wallace, and Halberstam, 1965) has suggested the possibility that the presumptive renal tubular defect in the handling of uric acid by many such patients (Nugent and Tyler, 1959; Seegmiller, Grayzel, Howell, and Plato, 1962) may be only one manifestation of a more generalized defect in renal tubular cell transport that involves substances other than uric acid. For glycine, at least, this has been demonstrated; the renal clearance of endogenous glycine was decreased in subjects with primary hyperuricaemia compared with normouricaemic individuals. Furthermore, after either an oral or an intravenous glycine load, hyperuricaemic subjects failed to increase their renal clearance of glycine as much as did the normal subjects (Kaplan, Wallace, and Halberstam, 1966).

The present report records observations on 26 normouricaemic individuals and 25 subjects with primary hyperuricaemia and normal glomerular filtration rates in whom serum amino acid levels and renal clearances of twelve amino acids were measured. Responses to oral loads of three amino acids and the effects of RNA feeding on these parameters have also been investigated.

### Material and Methods

51 men between the ages of 21 and 67 years were studied; 26 were normouricaemic, and 25 had primary hyperuricaemia (serum uric acid greater than 7 mg. per cent.), of whom all but two had a history of gouty arthritis, though none were tophaceous. None of the subjects was acutely ill at the time of the study. None had taken

any drugs for at least 3 days before the study, except for three gouty subjects who were maintained on their prophylactic colchicine up to the day of the investigation. No subject had known hepatic or gastrointestinal disease. All had glomerular filtration rates higher than 80 ml./min. and normal urinary sediments. The hyperuricaemic subjects were ambulatory clinic patients or hospitalized patients who were convalescent from either an attack of gouty arthritis or some other disease. The normouricaemic subjects consisted of either normal hospital personnel or hospitalized patients in the convalescent phase of their disease.

All observations were made after an overnight fast. To rule out the possibility that serum levels of amino acids might be related to the type of diet before the study, six patients were studied after an *ad lib* diet and again after 2 days on a 40 g. protein diet. No differences in serum levels were observed.

An estimation of glomerular filtration rates was made on each subject by measurement of either inulin clearances or endogenous creatinine clearance. Uric acid and amino acid clearances were measured simultaneously. Urine and serum samples for amino acid analyses were stored at  $-70^{\circ}\text{C}$ . before analysis. Standard techniques were used for the measurement of creatinine (Bonsnes and Taussky, 1945), inulin (Harrison, 1942), uric acid (Praetorius, 1949), and amino acids (Kaplan and others, 1965; Dickinson, Rosenblum, and Hamilton, 1965).

Fourteen normouricaemic and fourteen hyperuricaemic individuals were subjected to oral amino acid tolerance tests. After the overnight fast, a 2-hour urine specimen was collected and blood was drawn so that uric acid, creatinine, and amino acid clearances could be determined. At this point, each subject ingested either 5 g. glycine alone (6 in each group), 5 g. each of glycine, valine, and arginine (7 in each group), 5 g. each of glycine and arginine (1 normouricaemic subject), or 5 g. each of glycine and valine (1 hyperuricaemic subject). Blood was collected at 15, 30, 45, 60, 90, and 120 minutes after the dose of amino acid and another urine specimen was collected 2 hours after the amino acid loading.

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## Results

Pertinent data on these 51 subjects is shown in Tables I and II.

The mean age of the patients with hyperuricaemia was  $42 \pm 11$  years, and that of the normal group  $37 \pm 11$  years ( $0.10 > P > 0.05$ ).

The mean glomerular filtration rate (GFR) of the hyperuricaemic group was  $117 \pm 24$  ml./min., and that of the normal group  $130 \pm 37$  ml./min. ( $0.2 > P > 0.1$ ). One "hyperuricaemic" subject (No. 36) actually had a serum uric acid of 4.5 mg. per cent. He was included here because he had a history of gouty arthritis (several episodes of monarticular

TABLE I  
DATA ON 26 NORMOURICAEMIC SUBJECTS

Patient No.	Age (yrs)	Diagnosis	GFR* (ml./min.)	Serum Uric Acid (mg. per cent.)	Total Serum Amino Acids ( $\mu$ M/ml.)	Uric Acid/Creatinine Clearance $\times 100$
1	36	Normal	125	5.3	2.354	7.5
2	52	Pneumonia	155	5.9	2.170	4.1
3	22	Normal	115	5.8	2.552	3.0
4	35	Normal	182	5.4	2.128	5.7
5	52	Myocardial infarction	81	6.0	2.707	4.5
6	24	Normal	141	6.4	2.743	4.1
7	29	Normal	82	6.2	2.296	7.1
8	28	Normal	186	4.1	2.143	8.0
9	56	Pneumonia	121	2.9	2.442	6.7
10	45	Coronary artery disease	154	5.4	2.209	3.9
11	29	Normal	138	4.7	2.431	7.1
12	43	Normal	158*	4.8	1.868	8.3
13	50	Coronary artery disease	141	3.7	2.098	6.1
14	30	Pneumonia	104*	3.0	2.371	9.7
15	35	Pneumonia	108*	6.4	2.414	5.9
16	34	Pneumonia	122*	4.1	1.596	7.6
17	34	Normal	121*	5.5	1.717	6.8
18	44	Pneumonia	147*	4.4	1.771	7.3
19	47	Pneumonia	161*	5.1	1.553	9.6
20	58	Coronary artery disease	112	4.9	2.322	5.8
21	38	Normal	119*	5.4	2.181	7.2
22	45	Normal	140*	5.6	1.866	6.0
23	21	Normal	132*	4.0	2.025	11.7
24	25	Normal	104	5.8	2.018	3.6
25	27	Normal	108	4.4	2.262	6.3
26	28	Normal	116	6.0	2.412	7.1

\*Glomerular filtration rate (GFR) is measured either as inulin clearance (\*) or 2-hour endogenous creatinine clearance.

†Total serum amino acids include aspartic acid, threonine, serine, glutamic acid, glycine, alanine, valine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine and histidine.

TABLE II  
DATA ON 25 HYPERURICAEMIC SUBJECTS

Patient No.	Age (yrs)	Diagnosis	GFR (ml./min.)	Serum Uric Acid (mg. per cent.)	Total Serum Amino Acids ( $\mu$ M/ml.)	Uric Acid/Creatinine Clearance $\times 100$
27	45	Gout	172	10.9	2.789	3.8
28	42	Gout	99	10.2	2.945	1.6
29	28	Gout	89	7.8	2.226	1.0
30	23	Hyperuricaemia	125	7.2	2.721	6.7
31	47	Gout	102	9.3	2.538	0.9
32	38	Gout	86	8.2	2.661	5.8
33	54	Gout	83	8.7	2.603	6.2
34	35	Gout	112	11.1	3.284	2.2
35	38	Gout	98	7.9	2.861	6.7
36	48	Gout	142	4.5	2.680	7.5
37	52	Gout	110	10.2	2.232	8.7
38	25	Gout	107	8.1	2.536	6.4
39	35	Gout	123	8.9	2.688	11.8
40	57	Gout	97	7.8	2.547	2.3
41	67	Gout	124	9.8	3.009	4.8
42	56	Gout	88	7.6	2.375	7.6
43	34	Gout	119	8.6	2.675	10.8
44	44	Gout	173	7.4	3.239	9.1
45	43	Gout	98	7.8	3.385	8.4
46	33	Gout	141	7.2	1.614	6.5
47	44	Gout	110	8.3	1.972	4.6
48	53	Gout	141	8.5	2.405	5.6
49	34	Gout	135	8.2	2.650	2.6
50	42	Gout	120	7.3	2.258	2.0
51	44	Hyperuricaemia	120	9.0	2.538	9.2

arthritis responsive to colchicine) and a history of hyperuricaemia (7.4 mg. per cent.) 2 years earlier.

Because of the lower GFR in the hyperuricaemic individuals, urate/creatinine ratios  $\times 100$  are reported rather than urate clearances. While the urate/creatinine clearance ratio is lower in the hyperuricaemic group ( $5.7 \pm 3.2$  compared with  $6.6 \pm 2.0$ ), it is not significantly so ( $0.3 > P > 0.2$ ).

The total serum amino acid levels (where "total" equals the sum of aspartic acid, threonine, serine, glutamic acid, glycine, alanine, valine, isoleucine, leucine, tyrosine, phenylalanine, ornithine, lysine and histidine) show the mean in the hyperuricaemic group ( $2.617 \pm 0.397$ ) to be significantly greater than in the control group ( $2.179 \pm 0.313$ ) ( $P < 0.001$ ) in confirmation of a previous report (Kaplan and others, 1965). In addition, the mean value of

each amino acid is greater in the hyperuricaemic subjects.

In order to determine whether the raised serum levels of amino acids could be accounted for on the basis of renal retention, renal clearances for individual amino acids were calculated, as were amino acid/creatinine clearance ratios. Table III records the range of values obtained for three amino acids: glycine, a purine precursor; valine, a neutral amino acid unrelated to purine metabolism; arginine, a basic amino acid. It is clear that the hyperuricaemic subjects have a decreased clearance of both glycine and valine. Arginine clearance is the same for both groups.

Glutamic acid, glycine, valine, tyrosine, phenylalanine, and histidine all show significantly reduced clearance by the kidneys of hyperuricaemic individuals (Table IV). If the amino acids are separated

TABLE III  
RATIOS OF AMINO ACID/CREATININE CLEARANCE  $\times 100$   
P determined by Student's "t" test

Glycine		Valine		Arginine		
Normouricaemic	Hyperuricaemic	Normouricaemic	Hyperuricaemic	Normouricaemic	Hyperuricaemic	
0.4	0.4	0.02	0.02	0.00	0.06	
0.4	0.7	0.03	0.04	0.07	0.06	
1.0	0.8	0.03	0.04	0.08	0.06	
1.2	0.8	0.08	0.04	0.09	0.10	
1.4	0.8	0.08	0.04	0.09	0.12	
1.5	0.8	0.10	0.06	0.13	0.13	
1.5	0.8	0.11	0.06	0.14	0.14	
1.5	0.9	0.11	0.07	0.16	0.15	
1.7	0.9	0.11	0.08	0.17	0.15	
1.8	1.2	0.11	0.08	0.18	0.21	
1.9	1.2	0.12	0.08	0.21	0.22	
2.4	1.3	0.12	0.08		0.23	
2.5	1.4	0.13	0.08		0.29	
2.6	1.5	0.14	0.09			
2.7	1.5	0.16	0.11			
3.0	1.8	0.19	0.12			
3.2	2.0	0.23	0.12			
5.1	2.1	0.23	0.13			
6.8	2.9	0.26				
7.6		0.31				
Mean	2.5	1.3	0.13	0.07	0.12	0.15
P < 0.01		P < 0.005		P > 0.05		

TABLE IV  
RATIO OF AMINO ACID/CREATININE CLEARANCES  $\times 100$   
P determined by Student's "t" test

Amino Acids	Subject		Probability	
	Normouricaemic	Hyperuricaemic		
Acidic	Aspartic Acid	0.82	1.06	P < 0.25
	Glutamic Acid	0.15	0.08	P < 0.02
Neutral	Glycine	2.46	1.25	P < 0.01
	Alanine	0.34	0.30	P < 0.30
	Valine	0.13	0.07	P < 0.01
	Leucine	0.16	0.12	P < 0.45
	Tyrosine	0.92	0.73	P < 0.05
	Phenylalanine	0.56	0.46	P < 0.05
	Histidine	5.10	2.40	P < 0.01
Basic	Ornithine	0.43	0.37	P < 0.50
	Lysine	0.11	0.16	P < 0.15
	Arginine	0.12	0.15	P < 0.35

into acidic, neutral, and basic on the supposition that each of these groups has its own renal transport mechanism (Christensen, Akedo, Oxender, and Winter, 1962), only the neutral amino acids show consistently reduced clearances in hyperuricaemic subjects. (It may or may not be valid to include glycine as a "neutral" amino acid (Scriver, Efron, and Schafer, 1964)).

In order to test the hypothesis that the kidney of the hyperuricaemic patient has a relative inability to excrete some amino acids and not others, studies with exogenous amino acid loading were performed. Fourteen normouricaemic and fourteen hyperuricaemic subjects received 5 g. glycine orally, either alone or in combination with other amino acids as noted above. Similarly, eight subjects in each group received 5 g. valine orally, either alone or in combination, and six normouricaemic and seven hyperuricaemic subjects received 5 g. arginine orally either alone or in combination. Table V demonstrates that, when the excretion of both glycine and valine is compared before and after the amino acid load, normouricaemic subjects increase their excretion of these two amino acids more than hyperuricaemic subjects. In the 2 hours after the glycine load, normouricaemic subjects excreted a mean of 692  $\mu\text{M}$  more glycine than in the two-hour period prior to the load. Hyperuricaemic subjects increased their excretion by only 137  $\mu\text{M}$ . Similarly, normouricaemic subjects were capable of increasing their valine excretion after a valine load by 9.7  $\mu\text{M}$ ; the hyperuricaemic subjects had a mean increment of only 3.8  $\mu\text{M}$ . There was no significant difference for arginine; this is consistent with the observation that the renal clearance for arginine is the same for normouricaemic and hyperuricaemic subjects.

The differences in renal excretion for glycine and valine could not be accounted for by differences in gastrointestinal absorption as measured by the peak serum level reached, by the time at which the peak was reached, or by the rate of disappearance of the amino acid from the bloodstream. There were no significant differences between the two groups for any of these parameters. The Figure (overleaf) shows examples of the curve of serum concentration against time after the load for glycine and valine in four subjects.

Even though the normal subjects excreted a greater proportion of the administered amino acid, one would not expect any obvious difference in the rate of disappearance of the amino acid from the serum. Only about 1 per cent. of the administered glycine was excreted in the urine during the 2-hour study period, and less of the valine.

To rule out the possibility that the observed differences in renal handling of some amino acids was secondary in some way to high levels of uric acid in the hyperuricaemic group, two normal subjects and one hyperuricaemic subject were subjected to "glycine-valine-arginine tolerance tests" before and after a 2-day feeding of 4 g./day RNA. The data in Table VI (overleaf) indicate that increasing the serum uric acid concentration did not produce a decrease in the glycine or valine excretion after the oral load of amino acids. Endogenous amino acid clearances were similarly unchanged after ingestion of RNA.

In thirteen subjects (five normal subjects and eight hyperuricaemic subjects) uric acid clearance was measured both in the 2-hour control period and in the 2-hour post-amino acid feeding period (nine received glycine alone and four received glycine,

TABLE V  
INCREMENT IN AMINO ACID EXCRETION ( $\mu\text{M}$ ) AFTER AMINO ACID LOADING  
P determined by Student's "t" test

Glycine		Valine		Arginine	
Normouricaemic	Hyperuricaemic	Normouricaemic	Hyperuricaemic	Normouricaemic	Hyperuricaemic
87	24	4.7	0.0	0.0	0.0
151	51	5.6	1.1	0.4	0.0
199	60	6.4	2.2	0.6	0.4
305	69	6.9	2.3	2.1	1.0
321	73	8.5	2.4	5.2	3.0
379	76	10.1	3.6	6.4	3.2
580	78	13.3	4.1		3.5
638	142	21.9	14.5		
951	144				
997	153				
1063	225				
1597	243				
1711	449				
Mean	692	137			
		9.7	3.8	2.5	1.6
		P < 0.01	P < 0.01	P > 0.2	

The increment equals the number of micromoles of the amino acid excreted in the 2-hour period following the ingestion of 5 g. of the amino less the amount of the amino acid excreted in the 2-hour period before ingestion.

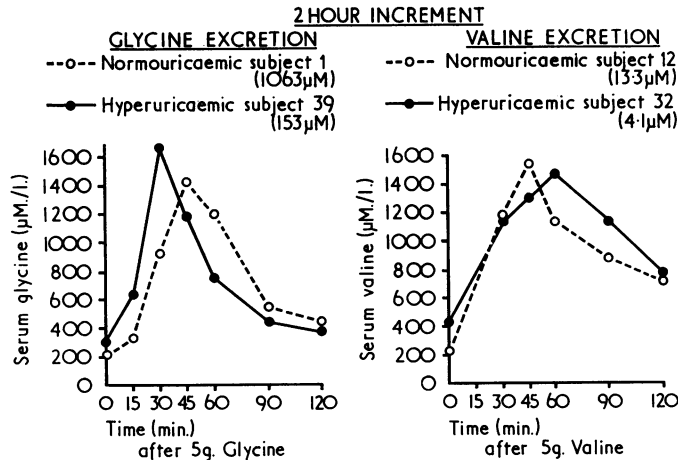


Figure.—Examples of serum concentration curves of glycine and valine in two normouricaemic and two hyperuricaemic subjects. The control concentrations and the serum concentrations after a 5 g. oral dose of glycine or valine are shown plotted against time.

TABLE VI  
EFFECT OF RNA INGESTION ON EXCRETION OF GLYCINE AND VALINE AFTER A 5 g. ORAL DOSE

Subject No.	Serum Uric Acid (mg. per cent.)		Glycine Increment ( $\mu$ M)		Valine Increment ( $\mu$ M)	
	Before	After	Before	After	Before	After
25	4.4	6.5	199	234	6.4	6.2
21	5.4	7.1	321	364	4.7	4.8
50	7.3	11.2	73	66	1.1	6.6

The increment is the excretion in micromoles of the amino acid after the amino acid load less the excretion before the load, as in Table V.

valine, and arginine). The mean uric acid clearance in these thirteen subjects before receiving oral amino acid was 6.3 ml./min., but after the amino acid feeding, the mean uric acid clearance was 9.7 ml./min. The mean difference was thus 3.4 ml./min. (S.E. =  $\pm 1.4$ ) giving a P value of less than 0.05 ("t" = 2.5 using the Fisher Test). This increase in renal clearance of uric acid is matched by a fall in the mean serum uric acid value over the 2-hour period from 7.2 to 6.7 mg. per cent. The mean difference of 0.5 mg. per cent. gave a P value of less than 0.01 ("t" = 3.3 by the Fisher test).

### Discussion

Hyperuricaemia is of heterogeneous origin. There is good evidence for polygenic inheritance for this trait (Hauge and Harvald, 1955). Recent studies have shown that one form of familial hyperuricaemia and gout, characterized by marked overproduction of uric acid, is due to a partial deficiency of the enzyme, hypoxanthine-guanine phosphoribosyl transferase (Kelley, Rosenbloom, Henderson, and Seegmiller, 1967). Environmental factors also play a role. Hyperuricaemia is related

to obesity (Shapiro, Klinenberg, Peck, Goldfinger, and Seegmiller, 1964; Křížek, 1966), to diet (Shapiro and others, 1964), and to drugs (Sorensen, 1962), among other factors.

The precise relationship between hyperaminoacidaemia and hyperuricaemia is not clear. In the work reported here, there was some degree of overlap in the serum amino acid levels of the controls and those with hyperuricaemia, but the mean level in the hyperuricaemic subjects was significantly higher ( $P < 0.001$ ). In addition, renal clearances of the neutral amino acids were consistently lower in the hyperuricaemic subjects. Renal handling of exogenously administered glycine and valine similarly differed in the two groups; the hyperuricaemic subjects were unable to excrete as much of the two amino acids as did the controls. These differences in renal handling of amino acids were clearly not the result of hyperuricaemia *per se*, because they were not influenced by ingestion of RNA, inducing rises in serum urate levels.

It has been suggested by Wyngaarden (1966) that there may be a defect in the kidney of the hyperuricaemic subject which causes decreased secretion of uric acid at the tubular cell. The data presented

here suggest that such a hypothetical defect in some patients with hyperuricaemia may actually involve a group of substances, including the neutral amino acids, rather than just uric acid alone.

It is not surprising that there is a concordant relationship in the renal handling of uric acid and amino acids. The most pertinent data relating to this point are that glycine and protein feeding in humans produces uricosuria (Christman and Mosier, 1929; Leopold, Bernhard, and Jacobs, 1925; Folin, Berglund, and Derick, 1924). This is confirmed by the present studies demonstrating an increased uric acid clearance after amino acid ingestion, accompanied by a fall in the serum uric acid concentration.

Such evidence suggests that uric acid and some amino acids compete for reabsorption by the renal tubule. While there is no direct evidence that amino acids are secreted by the kidney, competition between uric acid and other weak organic acids is

well described in other syndromes (*e.g.* hyperbeta-hydroxybutyricacidaemia (Scott, McCallum, and Holloway, 1964; Goldfinger, Klinenberg, and Seegmiller, 1965), starvation (Pabico, Canfield, and Barry, 1965), and von Gierke's disease (Howell, Ashton, and Wyngaarden, 1962). It may be that tubular transport of amino acids is affected by the same renal abnormality leading to decreased uric acid excretion in some hyperuricaemic subjects.

#### Summary

This study has demonstrated that the clearance of several amino acids by the kidneys of hyperuricaemic subjects is diminished. Hyperuricaemia alone does not appear to be the cause of the altered amino acid clearance. It is suggested that the renal tubular cells in hyperuricaemic persons have a defect in transport mechanisms leading to a reduction in secretion of both uric acid and certain amino acids.

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#### L'excrétion des acides aminés dans l'hyperuricémie primaire

##### RÉSUMÉ

Cette étude a démontré que l'élimination de plusieurs acides aminés par les reins de sujets atteints d'hyperuricémie est diminué. L'hyperuricémie seule ne semble pas être la cause de l'élimination des acides aminés altérés. Il est suggéré que les cellules des tubes urinifères chez les personnes atteintes de l'hyperuricémie ont un défaut dans l'appareil d'élimination conduisant à une réduction de la sécrétion de l'acide urique ainsi que celle de certains acides aminés.

#### Excreción de aminoácido en la hiperuricemia primaria

##### SUMARIO

Este estudio ha demostrado que la eliminación de varios aminoácidos por los riñones de sujetos con hiperuricemia es reducida. La hiperuricemia, por sí sola, no parece ser la causa de la alterada eliminación de aminoácido. Se sugiere que las células tubulares renales en personas hiperuricémicas tienen un defecto en los mecanismos de transporte, que conducen a una disminución en la secreción tanto de ácido úrico como de ciertos aminoácidos.