URINARY EXCRETION OF AMINO ACIDS IN LIVER DISEASE[1]

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Previous studies from the authors' laboratories have established the range of values for the urinary excretion of 15 amino acids by normal males and females (1, 2). A preliminary survey of the urinary excretion of tryptophane, histidine, and cystine in a variety of disease states, including liver disease, showed that almost one-half of the values were either higher or lower than those observed in the control series (3). Because of the abnormalities encountered in this study, and the known relationship of the liver to amino acid metabolism (4–6), further investigation has been made into the urinary excretion of amino acids in liver disease. The present report is a study of the urinary excretion of amino acids by 25 patients, the majority of whom had subacute or chronic cirrhosis.

METHODS

The previously described methods (1–3, 7, 8) were employed for the preparation of the urine samples and the determination of amino acids by microbiological assay. The probable accuracy of the amino acid data is indicated by average deviations from the mean which averaged 5 (3.7–6.7) per cent for the values at the different levels of the samples. The serum albumin and globulin fractions and total protein were performed by the methods of Kingsley (9); the blood non-protein-nitrogen by the method of Peters and Van Slyke (10); the carbon dioxide combining power by the method of Van Slyke, Stillman, and Cullen (11); the blood sugar by the method of Benedict (12), and the prothrombin time by the Quick method (13).

RESULTS

The results of the studies are given in Tables I through VI. A tabulation of the urinary amino acid values obtained in 22 patients is given in Table I. Tables II and III summarize the significant data from Table I, while more detailed studies of three other patients are given in Tables IV through VI (these patients are not included in Table I).

In Table I, the patients are grouped according to the type of liver involvement, in order to see if any patterns of amino acid excretion occur in different stages of involvement. The diagnosis of the stage of liver disease was made clinically, unless indicated in the chart to be established by autopsy or biopsy. A brief summary of other pertinent laboratory data, and treatment at the time of the study are also listed. It is to be noted that the majority of the patients received the same general type of diet, that is, a high carbohydrate, high protein, and low fat diet. This diet was a measured rather than a weighed diet. Some patients also received oral supplements of high protein mixtures. Only one patient was receiving intravenous amino acid therapy at the time of study. The patients with ascites and edema received ammonium chloride orally and mercurial diuretics parenterally as necessary. Results are arbitrarily indicated to be definitely abnormal in Table I if they were 50 per cent above or below the range found in the control series (1, 2), as there may be wider variations than known at present. It is to be noted that the values obtained in the controls compare well with those found by other workers (14, 15). No patient is included in the series with marked involvement of renal function. In general, it is to be noted from Table I that the patients with jaundice at the time of study or shortly before, whether they were in the subacute or chronic stage of cirrhosis, had increased urinary amino acid levels, while those without jaundice had normal or low urinary excretion rates.

A few specific points from Table I should be mentioned further. Patient 1, M. S., who had very high urinary levels of cystine, histidine, and tryptophane was receiving 1 liter of amigen daily at the time of the study. (In the normal this amount of amigen would not increase the urinary excretion rates to the levels noted [15, 16].) Patient 5, O. W., had a very high 24 hour urinary volume, 5175 ml., with a very high urine histidine

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level. This is too high a level to explain entirely by increased urinary volume. Further support of this idea is the variability in the excretion rates of the other amino acids studied. The cystine level was only moderately increased, the glutamic acid and tryptophane levels were normal and the glycine excretion decreased.

A few patients (Nos. 14. 15, 16, and 18) had relatively low 24 hour urinary volumes (390 to 750 ml.). Both low and high outputs of individual amino acids were found in this group. The high values in the presence of low urine volumes are probably significant. Only two of the patients listed in Table I died primarily of liver failure (No. 1, M. S., and No. 5, O. W.).

A general summary of the abnormalities found is given in Table II. Thirty-eight per cent of the total number of urinary amino acid values were abnormal, with 20 per cent elevated levels and 18 per cent low values. Sixty-seven and one-half per cent of the high urinary values were found in the patients with acute, subacute, and chronic cirrhosis, with jaundice, while 69 per cent of the low values were in patients in the subacute, or chronic stage of cirrhosis, or healing liver disease of several types, without significant jaundice at the time of study or during hospitalization.

The abnormalities found in the individual amino acids studied are given in Table III. Too few determinations of the urinary levels of glycine, glutamic acid, isoleucine, and phenylalanine were made for comment. Studies of the urinary excretion rates of arginine, aspartic acid, leucine, lysine, methionine, threonine, tyrosine, and valine were made in six to seven patients. Significant abnormalities were found only in the excretion rates of *lysine* (42 per cent of the values low), *methionine* (86 per cent of the unhydrolyzed values high), *tyrosine* (50 per cent of the values high, 17 per cent low), and *valine* (71 per cent of the unhydrolyzed values high).

Urinary outputs of cystine, tryptophane, and histidine were studied more extensively, with determinations in 21 to 22 patients. Fifty-two and one-half per cent of the cystine values were normal, 38 per cent elevated and 9.5 per cent low. The majority of the tryptophane values (77.5 per cent) were normal. Forty-five and one-half per cent of the histidine values were normal, while 42 per cent were low, and 12.5 per cent elevated.

Serial studies were made in three patients (Tables IV, V, and VI) to determine whether or not the rate of urinary excretion of amino acids changed with improvement or progress of the disease.

Urinary amino acid studies were made during three intervals over a 14 month period in A. R., a 43 year old diabetic, with subacute cirrhosis (Table IV). During the first period of study, he had a large liver, with no ascites or edema, and minimal icterus. In the second period of study, there was hepatomegaly with ascites and peripheral edema, but only minimal icterus. The third period of study was made just prior to his death. At this time, he was critically ill with bronchopneumonia, and chest injury, following an automobile accident. The liver was enlarged, but there was no peripheral edema or ascites. Jaundice which was minimal on entry rapidly increased in 24 hours to an icteric index of 68 units. Autopsy performed by the coroner showed a "nodular, fibrotic, fatty liver, with probable areas of necrosis; bronchopneumonia and pericarditis." The complicating infection in the third period undoubtedly increased the liver damage and the rate of tissue breakdown.

The serial studies outlined in Table IV show a striking drop in the average cystine excretion level from 222 to 48 mg. with progress of the disease, with a terminal rise following "Bal" treatment. In contrast to the majority of patients studied, the histidine excretion remained relatively normal throughout. Tryptophane excretion was elevated at each period, but most markedly so in the final entry, with infection and jaundice. On the final entry, a two hour urine was collected before "Bal" was given and a 24 hour urine was collected during "Bal" therapy. "Bal" was given because of its sulfhydril group, although its effect in liver necrosis due to heavy metals is not settled (17). There was little change in amino acid excretion rates after this therapy. The urinary levels of arginine, leucine, lysine, methionine, threonine, valine, and tyrosine were determined in the third period only. The excretion rates of these amino acids were within the normal range except for a marked increase in the output of tyrosine.

A four day period of study of a 47 year old woman with subacute cirrhosis and necrosis just

TABLE I

Urinary excretion of amino acids in liver disease

Patient Age, color, sex	Death due to liver disease	Treatment						Days in hosp. before study	Laboratory findings					24 hr. urine vol.
									Icteric index					
		High carb. and protein, low fat diet	Regular hospital diet	I.V. Glucose	I.V. Amino acids	Choline	Mercupurin		On entry	At time of study	Alb./Glob.	Prothrombin time	NPN	
				liters/ 24 hr.	*liters/ 24 hr.*	*gms./ 24 hr.*			*units*	*units*	*gms.*	*% normal*	*mg. %*	*ml.*
Acute liver necrosis														
1. M. S., 26, W.F. *Autopsy*	Yes	X		1	1	2		1	8	42	4.4/2.3	28	50	1180
Subacute cirrhosis with necrosis														
2. F. T., 32, W.M.			X			6		14	144	74	4.2/2.8	100	19	2640
3. M. D., 56, W.M.			X			6	X	17	102	31	4.2/3.4	45	45	2500
4. J. B., 50, W.M.		X				6		64	75	13	4.2/4.8	40	22	1300
Chronic cirrhosis with necrosis														
5. O. W., 47, W.M. *Autopsy*	Yes	X		1				5	58	82	3.0/5.0	38	33	5175
6. A. H., 69, W.F.		X				3	X	67	70	21	4.1/5.2	40		1740
7. K. K., 41, W.F.		X		2				11	34	15	4.9/3.3	100	25	3200
8. J. W., 42, W.F.		‖						35	¶	20	2.2/4.0	25	35	1320
									**	15	3.3/4.0	10		1380
Subacute cirrhosis														
9. D. W., 37, W.F. *Biopsy*		X				6		30	6	7	3.5/2.2	100	24	1680
10. W. S., 60, W.M.		X				3		15		6	4.1/3.8	100	29	1340
11. C. R., 41, W.M.		X						4	9		4.7/1.7	100	19	3670
12. D. P., 54, W.M.		X					X	1	16		4.3/2.3	100	34	543
13. H. S., 35, W.M.		X				3	X	75	28–70	13	2.8/4.1			1140
Chronic cirrhosis														
14. R. P., 40, W.M. *Biopsy*		X				2		12		14	3.1/2.7	10		390
15. V. P., 39, W.F.		X				6	X	20	15	4	3.0/2.4	53		640
16. R. T., 57, J.M.††			X				X	30	11	10	3.7/2.6	75	23	560
17. M. F., 59, W.M. *Biopsy*		‡‡					X	4	15		3.4/2.5	80	30	1040
18. J. J., 45, W.M.		X					X	60	8	7	4.0/3.4	100	23	750
Miscellaneous														
19. F. C., 24, W.F. *Viral hepatitis*		X		1		3		7	109		5.1/3.0	100	25	2315
20. C. A., 44, W.F. *Homologous serum jaundice*		X				6		37	§§	8	5.4/2.9			2720
21. L. P., 21, N.M. *Arsenical hepatitis*			X			6	X	30	11	10	4.3/4.0		23	820
22. J. P., 37, W.F. *Nutritional fatty liver*							X	4		3	4.3/4.0	100		1670

‖ Diabetic diet: carbohydrate, 225 gms.; protein, 115 gms.; fat, 60 gms.
¶ Before "Bal" therapy
** After "Bal" therapy
†† Japanese male
‡‡ Diabetic diet: carbohydrate, 250 gms.; protein, 80 gms.; fat, 60 gms.
§§ Patient markedly icteric on entry but icterus index not determined.

TABLE I—*Continued*

Patient No.		Urinary amino acids (*mg./24 hours*)*														
		Argi-nine	Aspartic acid	Cystine	Glutamic acid	Glycine	Histi-dine	Iso-leucine	Leu-cine	Lysine	Methi-onine	Phenyl-alanine	Threo-nine	Trypto-phane	Tyro-sine	Valine
Range of values found in controls‡																
	U†	18–21	0	70–115	0	600–800	100–166	2–4	10–12	18–19	2–3	9–10	22–24	18–20	13–24	3–7
	H†	30	15–25		300–400	350–750	190–200	14–16	27–32	75–90	8–14	25–30	63–64		23–26	26–28
Acute liver necrosis																
1.	U			*702*			*292*							*63*		
Subacute cirrhosis with necrosis																
2.	U			172			234									
3.	U						19§									
4.	U	15	1.9	*432*	Trace	520	58	1.9	6.8	14	*15*	10	22	30	25	0.8§
	H	29	34	190	169	252		6.4§	18	38	*26*	18	48		*43*	15
Chronic cirrhosis with necrosis																
5.	U			*392*	Trace	300	*1183*							27		
	H				294	171§										
6.	U	22	8.4§	*220*			24§	0.4§	4.9	4.6§	*8.1*	4.8	23	28	*182*	0§
	H	38	31	122				7.1	21	33§	17	17	60		*185*	19
7.	U			13§			61							*94*		
8.	U	22.4		*182*			172		12	17	*12.5*		*67*	*48*	*71*	6.5
	H	21.8	*59.5*						21	46	16.2		*95*		*65*	
	U	30.4		*476*			*254*		15	31	15.1		*111*	*54*		*11.4*
	H	36.9	33.1						32	100	*25.5*		*128*		*93*	
Subacute cirrhosis																
9.	U			*245*			204							13		
10.	U			77			40§							19		
11.	U			117			68							18		
12.	U			52			23§							11		
13.	U	11	4.4	25§	*53*	54§	Trace§	3.2	2.9§	2.9§	*7.6*	1.3§	11	7.3§	*56*	*17*
	H	26	13	30	101§	74§		7.4	15	21§	12	8§	16§		*56*	13
Chronic cirrhosis																
14.	U			141			39§							18		
15.	U			83			139							16		
16.	U						22§							11		
17.	U	26	*69*	161			29§		7.2	11	4		12	13	10	7.1
	H	33	29						50	58	*33*		48		21	
18.	U			45			111							30		
	H		*119*													
Miscellaneous																
19.	U			79			129							18		
20.	U	9.3		125	*35*	198	Trace§	3.9	6.5	5.4§	*12*	*26*	23	14	6.2§	1.1§
	H	26			513	269		11	19	23§	16	12§	39		28	8§
21.	U			*214*			51							13		
22.	U						51							28.8		

* Numbers in italics represent definitely elevated level.
† U = unhydrolyzed; H = hydrolyzed.
‡ Average per cent deviation from the mean = 3.8%.
§ Definitely low level

TABLE II

Summary of general abnormalities in urinary excretion of amino acids in 22 patients with liver disease

	Numbers	Per Cent
Determinations of urinary amino acids	198	
Abnormal values*	75	38
High values	40	20
Low values	35	18
Distribution of abnormal values		
Acute, subacute or chronic cirrhosis, with necrosis		
High values	27	67.5
Low values	11	31
Subacute or chronic cirrhosis, without necrosis		
High values	13	32.5
Low values	24	69

* 50 per cent above or below range of values found in control series (1, 2).

prior to death is shown in Table V. Except for the terminal period, there was a striking increase in excretion of arginine, methionine, tryptophane, and tyrosine, with slight to moderate increase in the excretion rates of cystine, leucine, lysine, threonine, and valine. The histidine values were within the normal range until the terminal period when they were low. The autopsy confirmed the diagnosis of subacute cirrhosis with acute necrosis.

Values are given in Table VI for the urinary excretion of histidine, cystine, and tryptophane for a 23 day period by M. V., a 49 year old Mexican male, who entered the hospital with acute liver necrosis (probably superimposed on a subacute cirrhosis). This patient made a dramatic recovery after treatment with methionine, intravenous glucose, and amino acids. The early cystine values were low but became normal after several days of therapy. Several high cystine values were noted. There were, however, high average deviations from the mean at different levels in this group of cystine assays. The tryptophane values were high in the first two weeks, but gradually returned to the normal levels. Some, but not all, of the increases during the first 12 days can be accounted for by the parenteral amino acid therapy (15, 16). The histidine levels were normal or only slightly increased during the 12 day period of amino acid therapy. They dropped slightly below normal from the 16th to the 23rd day.

DISCUSSION

Few quantitative determinations of the urinary excretions of individual amino acids in liver disease have been made previously. Previous data on urinary excretion, covering almost all of the amino acids, have only qualitative significance due to the low specificity of the gravimetric and colorimetric methods employed. The urinary excretion of 10 "essential" amino acids in eight normal subjects, seven patients with liver disease, and five patients with Wilson's disease (hepato-lenticular degeneration) has been reported (15). The seven patients with liver disease showed about the same

TABLE III

Summary of abnormalities in individual amino acid

		No. of determinations	High values	Low values	Normal values
			per cent	*per cent*	*per cent*
Glutamic acid	U	4	50		50
	H	4		25	75
Glycine	U	4		25	75
	H	4		50	50
Isoleucine	U	4		25	75
	H	4		25	75
Phenylalanine	U	4	25	25	50
	H	4		50	50
Arginine	U	7			100
	H	7			100
Aspartic acid	U	7	14	14	72
	H	7	28		72
Leucine	U	7		14	86
	H	7			100
Lysine	U	7		42	58
	H	7		42	58
Methionine	U	7	86		14
	H	7	43		57
Threonine	U	7	28		72
	H	7	28	14	58
Tyrosine	U	6	50	17	33
	H	7	71		29
Valine	U	7	71		29
	H	4		25	75
Cystine	U	21	38	9.5	52.5
	H				
Tryptophane	U	22	18	4.5	77.5
	H				
Histidine	U	24	12.5	42	45.5
	H				

TABLE IV

*Subacute cirrhosis with necrosis (autopsy)**

Period	Diet in gms.	Blood chemistry					24 hr. urine vol.	24 hour excretion in mg.														
		Icter. index	Albumin	Globulin	Prothrombin	NPN		Cystine	Histidine	Tryptophane	Arginine		Leucine		Lysine		Methionine		Threonine		Valine	Tyrosine	
	C. P. F.†	Units	*gms.* %	*gms.* %	% *normal*	*mg.* %	*ml.*	U	U	U	U	H	U	H	U	H	U	H	U	H	U	U	H
12-13-45 to 12-23-45	225–90–60 to 300	16	3.2	3.5	30–48	22	2240–3140 Average 2785	6–395 A‡-222	156–230 A-194	42–86 A-59													
1-16-46 to 1-22-46	300–125–60	13	2.3	3.3	58	21	1920–4300 Average 2664	3–109 A-48	125–343 A-189	33–70 A-48													
2-7-47	Intravenous glucose only +	18				55	82§	44.4	103.2	92.4	36	38.4	11	73	30	118	14.4	31	22	74	13.2	402	185
2-7-47 to 2-8-47	"Bal" therapy	68	3.9	3.3	18		1575	97.3	159	113	76.5	40.5	13.9	78.2	30.8	111	17.3	31.3	17	79.2	15.2	406	360

* A. R., white male, aged 43, 940–933 (diabetic)
† C—carbohydrate, P—protein, F—fat
‡ A—average
§ Values calculated for 24 hours from values obtained on two hour urine sample.

TABLE V

*Subacute cirrhosis with acute hepatic necrosis (autopsy)**

Hospital	Diet in gms.	Blood chemistry					Urobilinogen in urine	24 hr. urine vol.	24 hour excretion in mg.																	
		Ict. index	Alb.	Glob.	Prothrombin	NPN			Arginine		Cystine	Histidine	Leucine		Lysine		Methionine		Threonine		Tryptophane	Tyrosine		Valine
									U	H	U	U	U	H	U	H	U	H	U	H	U	U	H	U
Day	C. P. F.†	units	gms. %	gms. %	% normal	mg. %		ml.																		
1	300–150–50	122	3.8	4.4	40	33	trace undil.																			
to																										
9		160	3.3	2.8		95	neg.	2680	71	63	175	155	17	73	24	103	60	86	52	120	84	147	163	9.6
10	‡						+1/80	2675	84	75	203	115	12	76	22	96	70	124	34	117	102	141	241	10.8
11								2840	86	74	286	149	15	98	30	125	60	131	56	128	71	198	350	15.3
12							+1/160	420	52	51	163	59	7.1	70	12	83	58	70	22	78	72	114	160	12.4
13§																										

* L. M., white female, aged 47, #1007–599
† C—carbohydrate, P—protein, F—fat. In addition to diet, received 1–2 liters of 10 per cent glucose in water intravenously daily.
‡ Stopped eating regular diet after the ninth day. Given 1 liter of protein milk by stomach tube, and 1 liter of 10 per cent glucose in water intravenously daily.
§ Values calculated for 24 hours from six hour sample, as patient died on this date.

range of urinary amino acid excretion rates as the normals, while the five patients with Wilson's disease showed a definitely increased excretion. The exact state of liver function in these patients is not indicated. Urinary excretion of amino acids after intravenous administration in four of the patients with "active cirrhosis" varied little from the levels obtained in eight control subjects.

Earlier studies demonstrated normal urine values in chronic hepatitis, cirrhosis, infectious and toxic jaundice (18, 19). In the advanced stages of acute yellow atrophy a rise in the blood amino acid level and urinary excretion rates has been reported (18–21). It was suggested that this was presumably due to lack of deamination. It is to be noted in this connection that deamination and urea formation are not demonstrably impaired in the rabbit until 90 per cent of the liver has been removed (22). With complete hepatectomy in the dog, blood and urine amino acid levels rise, with a drop in blood urea levels (4, 5).

Increase in urinary amino acid levels can conceivably be due to several factors, each of which may operate separately or in combination:

1. Decreased deamination and transformation to other compounds by the liver
2. Increased rate of tissue breakdown
3. Decreased oxidation and utilization by the liver and tissues
4. Decreased reabsorption by the renal tubules
5. Lack of one or more amino acids (essential or non-essential).

The fact that 67 per cent of the elevated urinary amino acid levels in our series were found in patients with clinical or histologic evidence of hepatocellular damage strongly suggests difficulty in deamination or transformation by the liver as the major cause of increased urinary excretion. What is less easy to explain on this basis is the fact that all the urinary amino acid values did not rise. It is a well established fact, however, that in the normal some amino acids are conserved more rigorously than others and renal clearances vary (23). The liver, also, frequently shows alteration of separate functions or enzyme systems.

As the majority of our patients presumably ate a high carbohydrate, high protein diet, the changes in urinary amino acid levels in some cannot be

TABLE VI

*Subacute cirrhosis with acute necrosis (biopsy)**

Hospital Day	Blood								Urine				Therapy
	Ict. index	Alb.	Glob.	Prothrombin	NPN	Sugar	CO_2	White count	Vol.	Histidine	Cystine†	Tryptophane	
	Units	*gms.* %	*gms.* %	% *normal*	*mg.* %	*mg.* %	*vol.* %		*ml.*	*mg.*	*mg.*	*mg.*	
1	40	4.7	2.5	40	108	28	16	25,000	Oliguric				Digitalis, I.V. glucose.
2					115	75	29		Oliguric				I.V. glucose, Amigen, 10 gms. methionine oral.
3	58	3.2	1.3	10	110	264	49		4,000	112	36	145	I.V. glucose, Amigen, 6 gms. methionine oral.
4	75	3.2	1.5	38	49	142	55		5,040	157	30	91	I.V. glucose, Amigen, 4 gms. methionine oral.
5	65	2.9	1.3	29	36	145	62		2,240	96	70	67	I.V. glucose, 5 gms. methionine oral.
6	39	2.9	1.5	52	36	112	53	9,150	1,710	217	151	69	I.V. glucose, Parenamine, 5 gms. methionine oral.
7									1,820	137	154	56	I.V. glucose, Parenamine, Amigen, 5 gms. methionine oral.
8‡									2,120	160	180	86	I.V. glucose, Parenamine, 5 gms. methionine oral.‡
9	20	3.0	1.5	58					1,610	170	121	57	5 gms. methionine oral.
10	16	2.7	1.9	70					2,550	204	158	64	I.V. glucose and Parenamine.
11									2,780	179	150	56	I.V. glucose and Parenamine.
12	10	2.5	1.8	N§	34				2,880	190	188	45	I.V. glucose and Parenamine.
13	11	3.2	1.8	N					2,600	168	275	43	
14	10	3.7	2.8	N					2,460	114	210	41	
15									2,100	100	189	33	
16									1,820	84	146	27	
17									1,320	54	87	19	
18									1,640	80	114	25	
19									1,620	93	100	29	
20	6	3.9	2.4						1,360	65	104	23	
21									1,800	84	160	31	
22									1,480	74		22	
23									1,560	48		18	
24									1,930	70	62	17	
25									2,080	90	165	21	

* M. V., white male, aged 49, #559–043
† High mean deviations from the mean at the different levels in the assays.
‡ High protein diet started, in addition to intravenous therapy.
§ N—Normal

explained on the basis of increased oral or parenteral protein or amino acid intake. Increased intake of protein or the addition of crystalline methionine in the normal has not significantly altered urinary amino acid levels (24), although there is disagreement about the effect of low protein diets on urinary amino acid levels (14, 24). The problem of the total caloric intake as a factor in excretion rates is still an unsettled problem (24). Whether these factors, level of protein intake, and total caloric intake, operate similarly in patients with liver disease as in normals has not been studied. The role of nitrogen balance (rate of tissue anabolism or catabolism [25]) was not studied in our patients. The problem of whether increased urinary excretion was due to decreased utilization in protein formation, transformation to other compounds, or oxidation, cannot be answered by our studies. The majority of the patients studied had no significant change in renal function to explain altered urine amino acid levels (26). Lack of one or more essential amino acids has been shown to increase urinary amino acid excretion (27). With the high protein diet given (if it was actually eaten and absorbed), this factor should not be operative in our studies. The additional possibility exists that with severe liver damage it may be impossible for the liver to synthesize the so-called non-essential amino acids. This might cause decreased utilization for protein formation, due to lack of essential building stones.

Low urinary excretion rates of amino acids can be due to:

1. Increased rate of deamination and transformation by the liver
2. Increased utilization or requirement by the tissues
3. Decreased excretion due to renal disease.

Possibility of increased rate of change of the amino acids in the liver cannot be excluded as a factor in our low results, but was not studied. As previously mentioned, the majority of the patients did not have renal failure to explain variabilities in urine levels. What is significant is the fact that 69 per cent of the low values in our series were in patients with chronic liver disease. Many of these patients had low plasma albumin

levels or total protein levels and the possibility of increased tissue requirement due to protein depletion exists.

In addition to the general pattern of urine levels discussed, significant changes occurred in individual excretion rates. The three amino acids which were studied most extensively were cystine, histidine, and tryptophane. Forty-two per cent of the urinary histidine values were significantly below normal. Seventy-seven per cent of these low values were found in patients with subacute or chronic cirrhosis with jaundice. This suggests increased tissue demand as a possible mechanism. Another possibility is increased activity of the liver enzyme histidase which converts histidine to 1 glutamic acid, which is then converted to glycogen. Increased histidine values were found only in patients with liver necrosis, suggesting here decrease in histidase activity. This has been suggested as a possible mechanism for the increased urinary excretion of histidine in pregnancy (28). Decreased histidase activity has been noted in hepatomas (29).

Tryptophane studies showed that 77.5 per cent of the values were within the normal range. It has previously been shown (30) that compared with other amino acids the body has little tendency to conserve tryptophane. (The values found in this study were far higher than those found in our control series.)

The sulfur containing amino acid cystine was elevated in 38 per cent of the determinations made. Seventy per cent of the elevated urinary levels were in patients with liver necrosis. This suggests difficulty in oxidation to inorganic sulfur by the liver in advanced liver disease.

Although fewer determinations were made, the changes in urinary methionine levels were more striking than those found for cystine. Eighty-six per cent of the unhydrolyzed urinary levels were elevated, with 66 per cent of these values in patients with jaundice. The increased excretion rate for both cystine and methionine may be due to inability of the liver to use these amino acids for lipotropic purposes (31) as well as to difficulty in oxidation. DL-methionine given intravenously in liver disease has been reported to show diminished rates of removal from the blood, but little change in the urinary excretion of L-methionine (32). Another study (33) showed slight prolongation of high urinary methionine levels after an oral dose of DL-methionine, in adults with hepatic disease. Homburger (34), using a method which gives very high urinary methionine values compared to our controls, reported a marked increase in methionine excretion in two patients with liver disease during the stage of activity, with a decrease during improvement. He suggested that the increased excretion could be due to lack of utilization of methionine by the damaged liver.

Fifty per cent of the tyrosine values were elevated, despite the fact that tyrosine is treated under ordinary circumstances with great economy by the body, possibly due to its important role as a precursor of such substances as epinephrine, melanin, and diiodotyrosine. Our results quantitatively confirm the fact long established qualitatively that tyrosine crystals may be present in the urine in advanced liver disease. Elevation of free tyrosine in the blood in liver disease has been reported (35).

Although there were few studies on glycine (50 per cent of the hydrolyzed values low) it may be suggested that the excretion of glycine and some other amino acids was below normal due to the reduced ability of the liver to form hippuric acid, glycocholic acid, nicotinuric acid, ornithuric acid, phenyl-acetyl glutamine, phenaceturic acid, and other amino acid-organic conjugates. It is recognized that hippuric acid synthesis is impaired in certain types of liver disorder as first suggested by Quick (36) and confirmed by others (37–39). According to Snapper and his associates (40–42) the decreased hippuric acid synthesis is balanced, at least in part, by increased excretion of benzoyl glucuronate.

The problem arises concerning the role of urine volume and renal function in interpreting urinary amino acid levels. In several studies on controls (2, 23) where no attempt was made to have a constant fluid intake or urine output there was little change in excretion rates even with variations in urine volume. Any renal lesion which causes decreased glomerular filtration, if advanced, may cause a rise in blood amino acid levels (10, 26, 43). What is less well understood is the problem of tubular reabsorption of amino acids, as some amino acids are conserved more rigorously than others (23, 44, 45). Competition for tubular reabsorption may exist between certain

amino acids at high plasma levels but not at the plasma levels usually found, and a common mechanism for reabsorption is postulated (44, 45). Increased or decreased excretion of one amino acid may alter tubular reabsorption of other amino acids. The interpretation of results of urinary amino acid levels in liver disease is further complicated by the fact that tubular damage is frequently associated with liver damage and jaundice.

No implications regarding therapy can be drawn from these results.

SUMMARY

Urinary excretion rates of three to 15 amino acids were studied in 25 patients with liver disease. The majority of the patients had subacute or chronic cirrhosis.

Thirty-eight per cent of the total number of urinary amino acid determinations were abnormal, with 20 per cent elevated and 18 per cent low values in 22 of the patients studied. Sixty-seven and one-half per cent of the high urinary values were found in the patients with the acute, subacute, or chronic stage of cirrhosis associated with hepatocellular damage and jaundice. Sixty-nine per cent of the low values occurred in patients with subacute, chronic, or healing liver disease without significant jaundice at the time of study.

Serial studies in three patients demonstrated changes in excretion levels with improvement or progression of the disease.

The urinary excretion rates in general were not of prognostic significance.

The majority of the values obtained for arginine, aspartic acid, threonine, and tryptophane were normal.

Fifty per cent or more of the excretion rates of methionine, tyrosine, and valine were high.

Almost half the lysine and histidine values were low.

Changes in rates of deamination, conjugation, or utilization were suggested as possible mechanisms in the changes encountered.

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