AMMONIUM UPTAKE BY THE EXTREMITIES AND BRAIN IN HEPATIC COMA [1, 2]

By LESLIE T. WEBSTER, JR.,[3] AND GEORGE J. GABUZDA

(From the Department of Medicine, Western Reserve University School of Medicine at City Hospital, Cleveland, Ohio)

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Certain compounds containing or liberating ammonium may induce the syndrome of impending hepatic coma in susceptible patients with hepatic cirrhosis or Eck fistula (1–4). This syndrome is often but not always associated with increased ammonium concentrations in the blood (5, 6).

Although the origin and sources of elevated blood ammonium concentrations are not entirely clear, several factors contributing to them have been investigated. Decreased ammonium removal by the liver, resulting from either inadequate urea synthesis or from portal-systemic shunting of blood (7–10), is an important factor since increased arterial blood ammonium concentrations rarely occur if the liver and its circulation are normal. Elevated blood ammonium concentrations from an increased ammonium load are also observed in patients with liver disease. An increased load may result from the oral or intravenous administration of ammonium salts, amino acids and urea (1, 2, 11–13), from protein given orally (3, 14), and from gastrointestinal bleeding (15).

Previous investigations of patients with hepatic decompensation have demonstrated that the extremities and brain, which contain systems active in ammonium metabolism, are important sites for the removal of ammonium from the circulating blood (16–18). The roles of these peripheral sites in ammonium metabolism were evaluated in the present study also. In some instances, the extremities and brain of patients with severe hepatic disease were found to remove significant amounts of ammonium from a given volume of blood. However, in other instances they failed to do so, and thereby contributed indirectly to the increased blood ammonium concentrations observed.

METHODS

Three groups of patients were studied. The first consisted of 24 hospitalized patients without liver disease, the second of 27 patients with hepatic cirrhosis, and the third of 23 patients with hepatic cirrhosis and either impending hepatic [4] coma or coma. The last group is referred to subsequently as the "coma" group. Patients in the "coma" group were divided into one group without an added nitrogen load and a second group of patients with an added nitrogen load in the form of blood in their gastrointestinal tracts (evidence of upper gastrointestinal hemorrhage or massive epistaxis and blood swallowing). Pertinent clinical and laboratory data on all patients are presented in Tables I, II and III.

Patients were observed on the wards of Cleveland City Hospital, Crile Veterans Administration Hospital, and Boston City Hospital.[5] Confusion, coma and "flapping" tremor were graded from first to fourth degree; first degree indicated a mild, and fourth degree a serious, disturbance for each condition as previously described (20). Estimated daily protein intakes ranged from 30 to 100 grams for patients not in the "coma" group. Protein was withheld from confused or comatose patients for at least 24 and usually more than 48 hours before blood sampling.

Control was instituted over most factors known to increase blood ammonium (NH_4–N) concentrations in patients with hepatic disease. No patient received ammonium salts within 72 hours of blood sampling. Blood samples were obtained only when patients had not received nitrogenous foods for the preceding 12 hours (13). Active gastrointestinal bleeding and epistaxis (15) were absent in all patients except some in the "coma" group. Because urea given intravenously may cause prompt increases in blood NH_4–N concentrations (13), patients

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[2] A report of this investigation was presented at the Twenty-Ninth Annual Meeting of the Central Society for Clinical Research, Chicago, Ill., November 9, 1956 (J. Lab. clin. Med. 1956, **48**, 954).

[3] Russell M. Wilder Fellow of the National Vitamin Foundation.

[4] Characterized by mental confusion and a "flapping" tremor (19).

[5] Five patients in the " coma" group were studied at Boston City Hospital. Six patients in the cirrhosis group and one in the " coma" group were observed at Crile Veterans Administration Hospital in Cleveland.

TABLE I

Clinical and laboratory data in 24 patients without liver disease

Patient	Age and sex	Diagnosis	Serum total bilirubin	Serum BSP	B.U.N.	Blood NH_4-N (*micrograms per 100 ml.*) Arm vein	Artery	Jugular bulb	A-V diff. extremities	A-V diff. brain
			mg./100 ml.	%	*mg./100 ml.*					
1	68 M	Remote C.V.A.*	0.2	0	10	48	50	43	+ 2	+ 7
2	67 M	Remote C.V.A.*	0.5		22	47	26	52	−21	−26
3	42 M	Myotonia dystrophica	0.2	2	12	27	46	43	+19	+ 3
4†	65 M	Lues, ?pneumonia	0.6	7	17	55	55	60	0	− 5
5	75 M	Senility	0.1	0	21	73	86	78	+13	+ 8
6	65 M	Peptic ulcer	1.8	2	17	65	54		−11	
7	44 M	Peptic ulcer	0.3	1	12	46	49		+ 3	
8	70 F	Hypertension	0.7	7	22		61	49		+12
9	82 M	Senility	0.2	13	16		40	52		−12
10	74 M	Emphysema	0.3	9	8	46	47	60	+ 1	−13
11†	62 M	?Bronchogenic carcinoma	0.7	2	18	35	28	43	− 7	−15
12	36 F	?Cushing's disease	0.5		10	35	34	50	− 1	−16
13	63 M	Hypertension, fibrosarcoma	0.9	4	21	44	40	44	− 4	− 4
14†	26 M	Pneumonia	0.6	0	11	40	41	43	+ 1	− 2
15	42 M	Peptic ulcer	0.1	9	13	37	45	48	+ 8	− 3
16	52 M	Hypertension	0.5	8	14	43	38	41	− 5	− 3
17	41 M	Hypertension		4	23	32	49	43	+17	+ 6
18‡	42 F	Subsided pyelonephritis		3	20	22	21	23	− 1	− 2
19	28 F	Undiagnosed fever	0.6	8	21	23	22	27	− 1	− 5
20	67 M	?Pulmonary infarct	0.7	7	24	49	43	35	− 6	+ 8
21§	32 M	Lung abscess	0.1	1	10	25	47	44	+22	+ 3
22‖	42 F	Subsided pyelonephritis			10	22	34	30	+12	+ 4
23	35 M	Peptic ulcer		3	14	57	51	54	− 6	− 3
24	45 M	Emphysema	0.3	2	18	60	57	62	− 3	− 5

* Cerebral vascular accident.
† Penicillin discontinued for at least 72 hours in Patients 4, 11 and 14.
‡ Gantrisin® discontinued for three days in Patient 18.
§ Patient 21 receiving penicillin.
‖ Patient 22 receiving Panmycin® and nitrofuridantin.

in the normal and cirrhosis groups were selected so that none had elevated blood urea nitrogen concentrations. Patients having clinical evidence of shock or a systolic blood pressure below 90 mm. Hg were not included because animal experiments indicate that shock may produce increased blood NH_4-N concentrations (21). When steroids, acetazolamide (Diamox®), analgesics or sedatives were given it is so indicated in the tables because some of these drugs have been used in the treatment of impending hepatic coma or have been implicated in its production. The patients studied received neither glutamic acid nor arginine which may lower blood NH_4-N concentrations (20, 22–25). Neomycin and tetracycline antibiotics also may lower blood NH_4-N concentrations in some patients with hepatic disease (26). Accordingly, antibiotics were used only as mentioned in Tables I, II and III.

Ammonium metabolism in extremities and brain was evaluated by analyzing NH_4-N in blood samples obtained within three minutes of each other from a vein located in an extremity, an artery, and a superior jugular bulb. The uptake or release of NH_4-N per given volume of blood circulating through the extremity and brain was obtained by calculating the arteriovenous and arteriojugular bulb blood NH_4-N concentration differences.

Extremity venous blood was obtained from a forearm vein except as indicated for some patients in the coma group (Table III). The jugular vein was punctured, either in its superior bulb or just below this site, by directing a two inch number 20 gauge lumbar puncture needle with the bevel upwards superiorly and posteriorly from a site just under the ear in the space anterior to the mastoid process and posterior to the mandibular ramus.

Ammonium-nitrogen[6] in blood samples was determined by a modified Conway microdiffusion technique (27) with diffusion times of either 10 or 16⅔ minutes. In all but a few instances the values for NH_4-N concentration represent the average of triplicate determinations for a given sample. Concentrations were calculated as recommended by Conway and were expressed as micrograms of NH_4-N per 100 ml. of blood. The percentage of nitrogen recovered from a standard ammonium sulfate solution was used to estimate the per cent recovery of volatile base from blood. A modification was introduced

[6] Whether ammonium normally is present in circulating blood or whether it is formed only after blood is shed has not been established. Volatile base, released from blood upon addition of alkali, is assumed to be nearly all ammonium.

at Cleveland, *i.e.*, the rim of the Conway dish was greased rather than the entire underside of the cover glass. This permitted a greater recovery from an ammonium sulfate standard.

The ranges of blood NH_4–N concentrations obtained in patients with and without liver disease were comparable in Cleveland and Boston. The reproducibility of NH_4–N concentrations in two different blood samples drawn during the day from the same site in a given patient ranged from 0 to 23 micrograms per 100 ml. (mean, 6; S.D., plus or minus 5.2). This range of reproducibility was not significantly different in patients without liver disease compared to those with cirrhosis ($p > 0.7$). Reproducibility in confused or comatose patients with cirrhosis was not tested.

Bromsulphalein concentration was determined in the serum 45 minutes after injection of 5 mg. of this dye per kilogram of body weight (28). Serum bilirubin concentrations were performed by the standard technique (29). The methods of either Myers (30) or of Owings and Mandel (31) were employed for the determination of blood urea nitrogen.

The statistical evaluations presented were derived by the methods described in Snedecor's textbook (32).[7]

RESULTS

Blood ammonium-nitrogen concentrations

The NH_4–N concentrations in blood obtained from different sites in the patient groups studied

[7] Dr. George F. Badger kindly reviewed the application of these statistical methods.

TABLE II

Clinical and laboratory data in 27 patients with hepatic cirrhosis

Patient	Age and sex	Biopsy or autopsy	Physical examination*	Serum total bilirubin	Serum BSP	B.U.N.	Blood NH_4-N (*micrograms per 100 ml.*)				
							Arm vein	Artery	Jugular bulb	A-V diff. extremities	A-V diff. brain
				mg./100 ml.	%	*mg./100 ml.*					
1	33 F	No	Angiomata, ascites, edema	1.0	>20	8	47	70	76	+23	− 6
2	68 M	No	Ascites, edema	1.5	32	15	23	35	53	+12	−18
3	55 M	Yes		1.1	35	11	21	30	30	+ 9	0
4	49 M	Yes	Angiomata, edema	1.4	>20	8	19	29	47	+10	−18
5	68 M	Yes	Angiomata, ascites, edema	1.3	>20	17	53	89	75	+36	+14
6	40 M	Yes	Angiomata, ascites, edema	19.7		12	39	65	76	+26	−11
7	54 F	No	Ascites, edema	2.8	30	5	35	59	58	+24	+ 1
8†	39 F	Yes		6.1	27	13	41	66	65	+25	+ 1
9†	41 M	Yes	Ascites	0.4	7	16	23	39	40	+16	− 1
10	48 M	No	Angiomata	6.2	52	9	43	92	95	+49	− 3
11	62 M	Yes	Ascites, edema	1.2	21	17	31	54	53	+23	+ 1
12	68 M	Yes	Ascites, edema	1.3	58	14	64	104	88	+40	+16
13	57 F	No	Ascites, edema	4.9		6	35	87		+52	
14	45 F	No		0.9	16	6	35	60		+25	
15	44 F	No	Splenomegaly	1.2	13	9	78	87	86	+ 9	+ 1
16	58 M	Yes	Angiomata, ascites, splenomegaly	2.0	38	13	59	67	68	+ 8	− 1
17	63 M	Yes	Angiomata	5.6	23	8	36	37	60	+ 1	−23
18‡	72 M	Yes		0.8	9	19	45	49	48	+ 4	+ 1
19	58 F	Yes	Angiomata, ascites	0.3	23	11	78	91	78	+13	+13
20	49 M	Yes	Angiomata, ascites, edema	11.0	53	12	80	86		+ 6	
21	42 F	No	Angiomata, ascites	1.8	22	10	82	93	85	+11	+ 8
22	76 M	Yes	Angiomata, splenomegaly	0.9	34	20	77	79	78	+ 2	+ 1
23	71 M	No	Edema	1.4	23	15	80	94	98	+14	− 4
24	58 M	Yes	Angiomata, splenomegaly	0.9	27	13	83	106	120	+23	−14
25	56 M	No	Angiomata, ascites, edema	2.5		20	84	89		+ 4	
26§	67 M	Yes‖	Ascites, edema	0.9	27	15	69	128	96		+32
27	51 F	Yes	Splenomegaly, edema	1.8	51	8		86	84		+ 2

* All patients had hepatomegaly except Patients 7 and 11.

† Penicillin was discontinued 72 hours prior to blood sampling in Patients 8 and 9.

‡ Patient 18, with miliary tuberculosis, had been receiving streptomycin, isoniazid and *p*-aminosalicylic acid for months.

§ Patient 26, with pulmonary tuberculosis, was receiving streptomycin. The NH_4-N uptake in the extremities was not calculated for Patient 26 because the venous blood sample was not drawn simultaneously with those from the artery and jugular bulb.

‖ Metastatic carcinoma with inferior vena caval obstruction in addition to cirrhosis.

TABLE III

Clinical and laboratory data in 23 patients with cirrhosis and hepatic coma *

Group	Patient	Age and sex	Diagnosis	Biopsy or autopsy	Physical findings†	Mental‡ state	Tremor§	Comment	Serum total bilirubin	Serum BSP	NPN or B.U.N.	Blood NH_4-N (*micrograms per 100 ml.*)‖ Antecubital (A) or femoral (F) vein	Artery	Jugular bulb	A-V diff. extremities	A-V diff. brain
									mg./100 ml.	%	*mg./100 ml.*					
Without hemorrhage	1¶	57 M	Cirrhosis	Yes	Icterus, angiomata, ascites	2° I.C.	0	No G.I. bleeding for 24 hours		39	23 NPN		139	251		−112
	2	62 M	Cirrhosis	Yes	Angiomata, ascites	1° I.C.	1+	11 days after paracentesis; 3 days after Diamox®	1.0	15	42 NPN	(F) 89	153	182	+ 64	− 29
	3¶	65 F	Cirrhosis	Yes	Ascites, edema	3° I.C.	2+	Spontaneous coma	23		28 NPN	(A) 67	120		+ 53	
	4¶	47 F	Cirrhosis	Yes	Angiomata, ascites	3° I.C.	1+	Had phenobarbital and compound F	3.5		42	(F) 107	169	193	+ 62	− 24
	5¶	38 M	Cirrhosis, myocardial infarction	No	Angiomata, ascites	1° I.C.	1+	9 days after paracentesis	1.6	>40	17	(F) 145	226	246	+ 81	− 20
	6	52 M	Cirrhosis	No	Ascites	2° I.C.	3+	Had paraldehyde, ACTH and reserpine	42		14	(A) 167	164	186	− 3	− 22
	7	69 M	Cirrhosis, carcinoma of pancreas	Yes		1° I.C.		4 days after operation	11.9		21	(F) 31	29		− 2	
	8¶	57 M	Cirrhosis	Yes	Angiomata, ascites, edema	1° C.	0	Had Thorazine® and paregoric	1.2	64	21	(A) 266	271	378	+ 5	−107
	9	53 M	Cirrhosis, hypertension, cardiac failure	No	Edema	3° I.C.	3+	Received Diamox®	2.0		34	(A) 28	38	47	+ 10	− 9
	10¶	49 M	Cirrhosis	Yes	Splenomegaly, ascites, edema	3° C.	0	Shock 24 hours previously	3.2	>20	36	(F) 265	297	238	+ 32	+ 59
	11	65 M	Cirrhosis	Yes	Angiomata, ascites, edema	1° I.C.	1+	150 Gm. protein diet previous 4 days	4.3		20	(F) 228	207	235	− 21	− 28
	12	61 M	Cirrhosis	No	Angiomata, ascites	1° I.C.	2+	Had paraldehyde	5.6		9	(A) 118	119		+ 1	
	13	38 M	Cardiac cirrhosis, Cor pulmonale	No	Ascites, edema	1° I.C.	3+	48 hours after Diamox®	1.0	>20	39	(A) 112	121	147	+ 9	− 26
						? I.C.	1+	No further Diamox®			20		113	136		− 23
	14	51 F	Cirrhosis	Yes	Splenomegaly, edema	2° I.C.	2+	No G.I. bleeding for 24 hours	1.8	51	20	(A) 155	156	133	+ 1	+ 23
With hemorrhage	13					1° I.C.	1+	G.I. bleeding			41	(F) 51	112	102	+ 61	+ 10
	14					1° I.C.	3+	Epistaxis			20	(A) 142	185	141	+ 43	+ 44
	15	64 M	Cirrhosis, cholelithiasis	No	Angiomata, splenomegaly, edema	2° I.C.	2+	G.I. bleeding	1.2	24	36 NPN	(A) 62	197		+135	
	16¶	63 M	Cirrhosis	Yes	Ascites, edema	1° I.C.	±	G.I. bleeding	15.2	52	45 NPN	(F) 71	135		+ 64	
						1° I.C.	1+				45 NPN	(A) 70	116		+ 46	
						1° C.	0				28 NPN		203	276		− 73
						2° C.	0				40 NPN		283	275		+ 8
						1° C.	0	Epistaxis				(A) 120	185	145	+ 65	+ 40
	17	64 M	Cirrhosis, peptic ulcer	Yes	Angiomata, edema	2° I.C.	2+	G.I. bleeding	4.4			(A) 78	127	87	+ 49	+ 40
	18	78 M	Cirrhosis	No	Angiomata, ascites, edema	3° I.C.	2+	G.I. bleeding	2.0		37	(F) 150	227	195	+ 77	+ 32
						1° I.C.	1+				37	(F) 83	214	125	+131	+ 89
						3° I.C.	3+		3.2	43	34	(A) 404	625	477	+221	+148
	19	61 M	Cirrhosis	No	Angiomata, splenomegaly, ascites	1° C.	1+	G.I. bleeding	3.5	43	39	(A) 109	175	152	+ 66	+ 23
	20	42 M	Cirrhosis	No	Angiomata, ascites	2° C.	2+	G.I. bleeding	5.1		17	(F) 112	205	172	+ 93	+ 33
	21¶	54 M	Cirrhosis	No	Angiomata, ascites, edema	3° I.C.	3+	G.I. bleeding	7.4	72	22	(A) 211	337	266	+126	+ 71
	22¶	64 M	Cirrhosis, hepatoma	Yes	Angiomata, ascites, edema	1° I.C.	1+	G.I. bleeding	4.9		70	(F) 87	168	115	+ 81	+ 53
	23	47 M	Cirrhosis	Yes	Angiomata, ascites, edema	1° I.C.	2+	G.I. bleeding	6.2			(F) 154	242	185	+ 88	+ 57

* Includes patients with either impending hepatic coma or coma. Patient 8 was the only one receiving an antibiotic (penicillin).
† The liver was palpable except in Patients 2, 3, 5, 11, 15, 20, 21 and 23.
‡ I.C., impending hepatic coma; C, hepatic coma. Both were graded from first to fourth degree (22).
§ "Flapping" tremor graded from 1+ to 4+ (22).
‖ Blood NH_4-N determinations are presented separately when they were done on different days in the same patient.
¶ Expired during hospitalization.

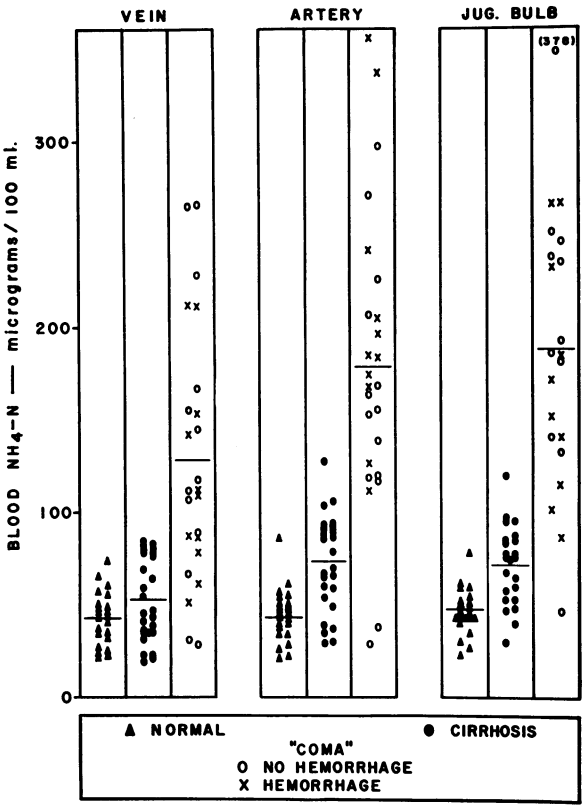

FIG. 1. BLOOD AMMONIUM CONCENTRATIONS

The plotted values represent the concentrations shown in Tables I, II and III. The horizontal line for each group of plotted values indicates the mean concentration for the group.

are charted in Figure 1. Ammonium-nitrogen concentrations in antecubital venous blood of the alert patients with cirrhosis were not significantly higher than those of the group without liver disease ($p = 0.06$). However, NH_4–N concentrations measured in arterial or jugular bulb venous blood were significantly higher in the alert patients with cirrhosis than in those without liver disease ($p < 0.01$).

Ammonium-nitrogen concentrations in blood drawn from each site were highest in the "coma" group ($p < 0.01$) but the mean concentrations obtained in patients with and without hemorrhage were not significantly different from each other. Arterial and jugular bulb blood NH_4–N values overlapped less between cirrhosis and "coma" groups than did values found in venous blood obtained from the extremities. Although both arterial and jugular bulb blood NH_4–N concentrations correlated better with the above clinical classification than did those in extremity venous blood, concentrations in blood from all three sites correlated poorly with the depth of impending hepatic coma or coma (Table III).

Arteriovenous ammonium-nitrogen differences for the extremities

Arteriovenous blood NH_4–N concentration differences were calculated for individual patients

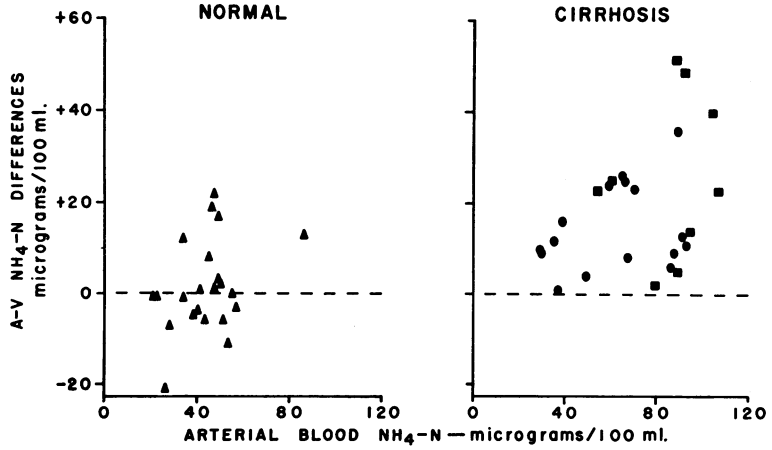

FIG. 2. EXTREMITY A–V AMMONIUM DIFFERENCES

The plotted values are derived from the data in Tables I and II. A positive arteriovenous difference indicates an uptake of NH_4–N; a negative difference indicates a release.

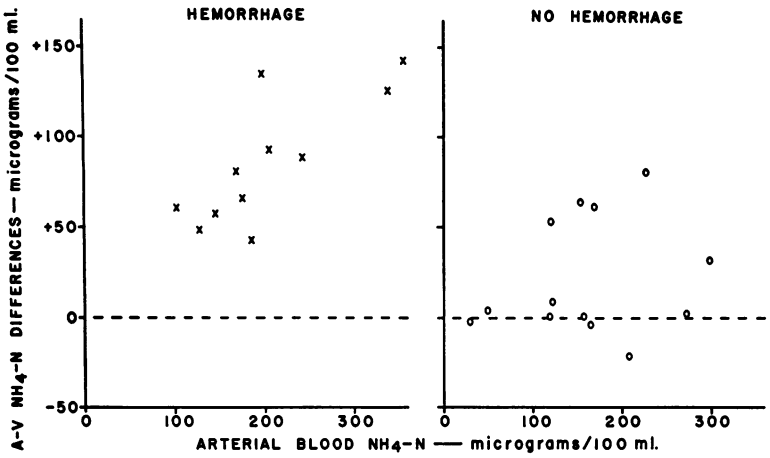

FIG. 3. EXTREMITY A–V AMMONIUM DIFFERENCES IN HEPATIC COMA

The plotted values are derived from data in Table III. Blood NH_4–N concentrations and arteriovenous differences determined on separate days in an individual were averaged. A positive arteriovenous difference indicates an uptake of NH_4–N; a negative difference indicates a release.

(Tables I, II and III). Each arteriovenous NH_4–N difference for the extremities was plotted as a function of its arterial blood NH_4–N concentration. In patients without liver disease, individual arteriovenous NH_4–N differences were within a range of plus 22 to minus 21 micrograms per 100 ml. of blood. There was neither a significant average uptake nor release of NH_4–N per given volume of blood circulating through the extremities. Moreover, there was no correlation between individual arteriovenous blood NH_4–N concentration differences and their respective arterial blood NH_4–N concentrations (Table I, Figure 2).

In contrast to the group without liver disease, alert patients with cirrhosis demonstrated positive arteriovenous NH_4–N differences (uptakes) in their extremities (Table II and Figure 2). When arteriovenous NH_4–N differences obtained for the upper extremities in alert patients with cirrhosis were plotted as functions of their respective arterial NH_4–N values the resulting correlation was not significant (Figure 2) ($r = 0.373$; $p = 0.07$).

In the 11 "coma" patients with an added nitrogen load in the form of blood in their gastrointestinal tracts the extremities removed more NH_4–N from the blood with increasing arterial NH_4–N concentrations as expressed by the regression $\hat{Y} = 0.343X$ plus 15.5 (Figure 3) ($r = 0.77$; $p < 0.01$). In contrast, only 4 of 11 patients in the "coma" group without evidence of an added nitrogen load removed ammonium efficiently from a given volume of blood at increased arterial NH_4–N concentrations (Figure 3). Thus, at a given arterial blood NH_4–N concentration there was a greater removal of NH_4–N from a given volume of blood circulating through the extremities of the group of confused or comatose patients with blood in their gastrointestinal tracts than in the group without hemorrhage.

Arteriovenous ammonium-nitrogen differences for the brain

Arteriovenous NH_4–N differences for brain, as for the extremities, were plotted as functions of

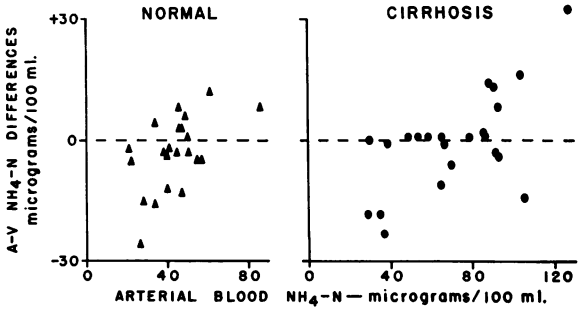

FIG. 4. BRAIN A–V AMMONIUM DIFFERENCES

The values plotted are derived from data in Tables I and II. A positive arteriovenous difference indicates an uptake of NH_4–N; a negative difference indicates a release.

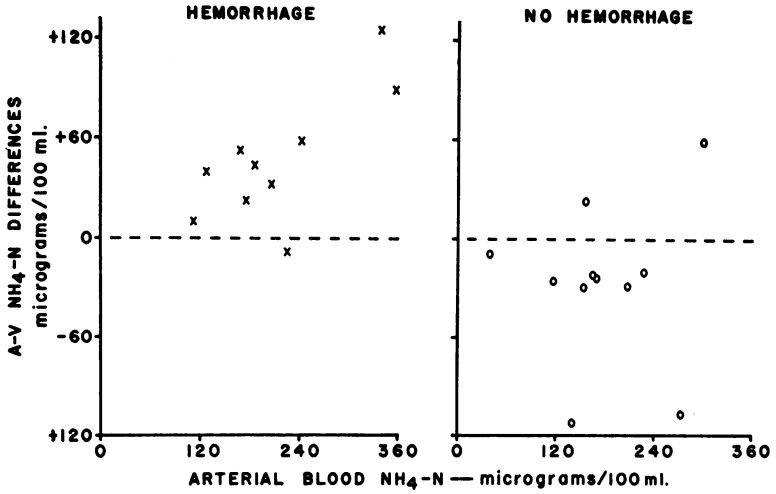

FIG. 5. BRAIN A-V AMMONIUM DIFFERENCES IN HEPATIC COMA

The plotted values are derived from the data in Table III. An average difference is plotted when these differences were determined for the same patient on separate days. A positive arteriovenous difference indicates an uptake of NH_4–N; a negative difference indicates a release.

their corresponding arterial blood NH_4–N concentrations (Figures 4 and 5).

Arteriovenous differences across the brains of patients without liver disease or of alert patients with cirrhosis were neither consistently positive nor negative, although there was some correlation between this variable and arterial NH_4–N concentrations in both groups (Figure 4). In the "coma" group with blood in their gastrointestinal tracts, 9 of the 10 patients showed increasing removal of NH_4–N from a given volume of blood circulating through the brain with increasing arterial NH_4–N concentrations ($r = 0.74$; $p = 0.01$) as expressed by the regression $\hat{Y} = 0.355X$ minus 28.8 (derived from all values shown in Figure 5). The uptake of NH_4–N from a given volume of blood circulating through the brain which occurred in this "coma" group was significant ($p < 0.01$).

A significantly greater removal of NH_4–N per given volume of blood circulating through the brain occurred in those patients with hemorrhage than in those without ($p < 0.01$). Most of the patients belonging to the latter group displayed a release of NH_4–N into blood circulating through their brains (Figure 5). However, although the average arteriojugular bulb blood NH_4–N difference for this group indicated an NH_4–N release into the blood, this was not statistically significant ($p = 0.1$).

DISCUSSION

The removal or release of ammonium from a given volume of blood circulating through the extremities or the brain was obtained by calculating the arteriovenous concentration differences for patients without liver disease, for alert patients with cirrhosis, and for patients with hepatic coma. Although, as discussed below, the interpretation of arteriovenous blood ammonium differences is beset with some difficulties, the NH_4–N levels and arteriovenous NH_4–N differences in these peripheral sites differed in the groups of patients with cirrhosis when compared with values obtained for patients without hepatic disease. In the patients with liver disease the findings for the extremities differed in some respects from those for the brain.

Arteriovenous NH_4–N differences across the extremities ranged from plus 1 to plus 52 mg. per 100 ml. of blood (NH_4–N removed) for alert patients with cirrhosis, but were distributed within the range of minus 21 to plus 22 mg. per 100 ml. of blood for patients without liver disease (Figure 2). Arteriovenous NH_4–N differences across the brains were not significantly different in the control subjects compared to the values for the alert patients with cirrhosis (Figure 4). Thus there were differences in NH_4–N removal for: 1) the extremities of alert patients with cirrhosis

compared to those of the control subjects; and 2) the extremities as contrasted to the brains of the alert patients with cirrhosis.

The alert patients with cirrhosis had arterial NH_4–N concentrations that were elevated as compared to the values obtained for control subjects (Figure 1). The elevations of arterial blood NH_4–N concentrations in patients with cirrhosis were apparently sufficient to stimulate an enhanced removal of NH_4–N by the extremities but not by the brain. Further support for this hypothesis was obtained by comparing the arteriovenous NH_4–N differences for brain with those for the extremities in the group of patients in coma with hemorrhage (Figures 3, 5). Positive arteriovenous NH_4–N differences (uptakes) for both extremities and brain correlated with the arterial NH_4–N concentrations in these patients, but the uptakes of NH_4–N occurred at lower arterial concentrations in extremities than they did in brain. In addition, individuals in the coma group who demonstrated positive arteriovenous NH_4–N differences for extremities did not always have positive differences for brain (Table III). The explanation for these differences in the metabolism of ammonium in extremities compared to that in brain of the patients with cirrhosis studied is not known. However, ammonium disposal is known to differ in these sites (17), and other dissimilarities might exist as well, *e.g.*, in ammonium transport mechanisms.

The data obtained in comatose patients with hemorrhage suggest that both extremities and brain removed ammonium from a given volume of blood with about equal efficiencies once removal was initiated, since the regression of arteriovenous NH_4–N differences upon the arterial concentrations for these two sites was similar (0.343 for extremities and 0.335 for brain). This is at variance with the finding of Bessman, Fazekas, and Bessman (16), that at a given arterial NH_4–N concentration the extremities of patients with hepatic coma had twice as large an arteriovenous NH_4–N difference as the brain (17).

As predicted by Bessman and Bessman (17), arterial and jugular bulb blood NH_4–N concentrations correlated better with the classification of patients into normal, cirrhosis and "coma" groups than did the concentrations in antecubital and femoral venous blood (Figure 1). However, even when arterial and jugular bulb venous blood was analyzed, there was considerable overlap of concentrations between different patient groups and a poor correlation between blood NH_4–N concentrations and coma depth in patients belonging to the "coma" group. Actually, an excellent correlation between coma depth and blood NH_4–N concentration might not be expected because of the many factors which may affect both variables.

Patients in the coma group were classified clinically according to the presence or absence of associated gastrointestinal bleeding. This classification was made because experience suggests that the prognosis of hepatic coma is better for patients with coma precipitated by a nitrogen load than for patients in whom mental symptoms occur without an associated precipitating factor. Whether or not arteriovenous NH_4–N differences increased with increasing arterial NH_4–N concentrations varied according to this clinical classification. Arteriovenous blood NH_4–N differences for extremities and brain usually increased with increasing arterial NH_4–N concentrations in confused or comatose patients with cirrhosis who had blood in their gastrointestinal tracts, *e.g.*, an added nitrogen load. In contrast, NH_4–N was not removed efficiently from a given volume of blood circulating through the extremities and brains in most of the patients in the "coma" group who did not have gastrointestinal bleeding. In fact, the brains of some of the latter patients released NH_4–N into the circulating blood. The difference in prognosis for the patients with, as contrasted to those without, an added nitrogen load might be related to these observed differences in NH_4–N metabolism.

The presence or absence of an added ammonium load (*e.g.*, gastrointestinal bleeding) probably did not *per se* account for the variations in arteriovenous NH_4–N differences because high arteriovenous differences were noted for the extremities of some alert patients in the cirrhosis group and for the extremities and brains of others in the "coma" group in whom no evidence of an extra ammonium load was detected. Furthermore, if an increased ammonium load to the systemic circulation were to initiate NH_4–N removal in the extremities only by increasing the arterial NH_4–N concentration, one would expect large arteriovenous NH_4–N differences across the extremities and brains of all patients having markedly ele-

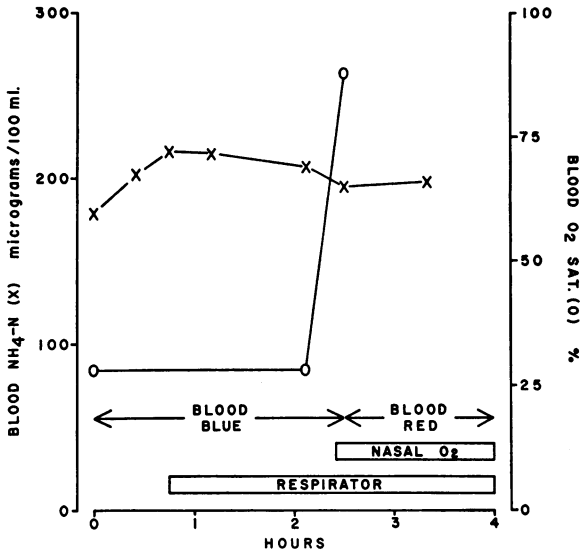

FIG. 6. EFFECT OF ARTERIAL BLOOD O_2 SATURATION ON BLOOD AMMONIUM CONCENTRATION

vated arterial NH_4–N concentration. This did not always occur (Figures 3, 5). The observed variations in peripheral arteriovenous NH_4–N differences might be explained more plausibly by an alteration in the ability of the peripheral intracellular systems either to metabolize ammonium or to initiate ammonium removal at elevated arterial NH_4–N concentrations. The negative arteriovenous NH_4–N difference across the brains of certain individuals in the coma group might only reflect an inability of their brains to cope with ammonium which is normally produced (33). For example, in animals ammonium concentrations in the brain may increase if fluoroacetate, an agent effective in blocking the tricarboxylic acid cycle, is administered (34). These possibilities require further elucidation.

Aside from difficulties inherent in measuring blood NH_4–N,[8] interpretation of arteriovenous NH_4–N differences is difficult for several reasons. An arteriovenous difference for a given tissue only determines whether or not there is an overall ammonium removal or release in that tissue; it provides no information concerning the ammonium transport mechanisms involved. The composition of the blood analyzed (arterial as contrasted to venous) might affect the amount of ammonium recovered during analysis. For instance, some investigators suggest that the ammonium concentration in blood is proportional to its oxygen content (35, 36). However, a patient with cor pulmonale studied in this laboratory did not demonstrate significant fluctuations in arterial blood NH_4–N concentrations when his arterial oxygen saturation was increased *in vivo* from 28 to 88 per cent (Figure 6). When the quantity of blood circulating through the tissue is not known, arteriovenous differences can provide only semiquantitative estimates of tissue uptake or release. Abnormalities of blood flow do occur in patients with cirrhosis of the liver (37–40), but it seems unlikely that variations of blood flow through the extremities and brain solely accounted for the variations in arteriovenous NH_4–N differences noted in the present study. The magnitude of changes in arteriovenous differences observed is probably too great to be explained by changes in blood flow alone. The incidence of clinical findings often associated with altered blood flow through peripheral tissues, *i.e.*, hypotension, palmar erythema, and spider angiomata, was similar for individuals having high or low NH_4–N uptakes per given volume of circulating blood. In addition, preliminary studies in this laboratory indicate that the rate of cerebral blood flow, found to be decreased in patients with hepatic coma (39, 40), does not correlate with the arteriovenous NH_4–N difference across the brain. In accord with the above reservations, data concerning arteriovenous blood NH_4–N differences for peripheral sites have been discussed only in reference to the results obtained for the control group of hospitalized patients without liver disease.

Considering the present findings and assuming that abnormal ammonium metabolism is important in hepatic coma, one might explain this disorder in several ways. The removal of ammonium occurring in the brains of patients with an added nitrogen load suggests that hepatic coma might result because the brain had to metabolize increased quantities of ammonium presented to it by the arterial blood. This process of ammonium disposition might deprive the brain of reactants that are required for other essential metabolic processes. The release of ammonium from the brains of some patients in coma not associated with an

[8] Since ammonium ion is not measured directly by methods devised to date, it is possible that volatile base released from other substances present in blood is also being measured.

added nitrogen load suggests that the confusion or coma associated with hepatic disease might ensue because certain metabolic functions of the brain concerned in ammonium disposal were affected adversely by an abnormally functioning liver. These mechanisms operating simultaneously in a patient with hepatic coma would make the identification and evaluation of each difficult.

SUMMARY

Ammonium nitrogen was determined in blood obtained practically simultaneously from an extremity vein, an artery and a superior jugular bulb in fasting patients without liver disease, with cirrhosis, and with cirrhosis and either impending hepatic coma or coma.

Arterial and jugular bulb blood ammonium concentrations were least in the group without liver disease, higher in the group with cirrhosis, and highest in the group with impending hepatic coma or coma. Ammonium concentrations in blood obtained from these sites correlated better with the above clinical classification than did those found in extremity venous blood. However, the correlation was not good enough to permit prediction of the clinical state in individual cases.

As judged by arteriovenous blood NH_4–N differences alone, there was no significant uptake or release of NH_4–N across the extremities and brains of patients without hepatic disease. In patients with liver disease, sufficient increases in arterial blood ammonium concentrations were usually associated with a removal of ammonium from a given volume of blood circulating through these peripheral sites. The extremities of some patients in both the cirrhosis and "coma" groups removed ammonium from a given volume of blood in proportion to the arterial blood ammonium concentrations. A similar removal of ammonium also occurred in the brains of some patients in the "coma" group. This was roughly proportional to the arterial blood ammonium concentration.

Ammonium was not always removed efficiently from a given volume of blood in the extremities and in the brain. Some patients in the cirrhosis group and some in the "coma" group demonstrated a poor ammonium removal for the extremities. Furthermore, not only did the brains of some patients in the latter group remove ammonium poorly but others showed significant releases. In alert patients with cirrhosis the extremities removed ammonium from a given volume of circulating blood when the brain did not.

Confused or comatose patients with hepatic cirrhosis were classified into two groups according to the presence or absence of an added nitrogen load, *i.e.*, blood in the gastrointestinal tract. Although there was overlap between individual values, ammonium removal from given volumes of blood circulating through the extremities and brain was significantly greater in the group with an added nitrogen load than in the group without hemorrhage.

The status of peripheral ammonium removal may be important in the genesis and outcome of hepatic coma.

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