LXXIV. STUDIES OF THE UREA CONTENT OF CAPILLARY AND VENOUS BLOOD.

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(Received April 7th, 1927.)

THE question as to whether equilibrium exists between the concentrations of urea in the blood and those of the various organs and secretions has been studied by Gad-Andresen [1921]. He arrived at the conclusion that equilibrium exists as far as the secretions are concerned, with the exception of tears and sweat, where the urea content increases with increased secretion. As for the organs, Gad-Andresen's investigations are not conclusive. In muscle he finds a lower urea content than in blood, whereas the ammonia content is higher in such a proportion that the sums of the two substances are identical for muscle and blood. In the liver the concentration of urea is found to be the same as in the blood, while in fatty tissue it is less. For his determinations Gad-Andresen used a micro-method devised by himself.

Tschudi-Madsen [1924], using Van Slyke's urease method for his studies on the distribution of urea, found in all cases higher concentrations of urea in the organs than in the blood. The values for urea in exudates, transudates and cerebrospinal fluid were found to lie very close to those for serum, though slightly lower on an average.

Neither of these authors gives any data with regard to the distribution of urea in arterial and venous blood. This question has been studied by some other investigators, from whose works the following data may be quoted [from Bollman, Mann and Magath, 1924]: Poisseule and Goble found in some cases a higher, in some cases a lower urea content in venous than in arterial blood; Picard found in some cases equal values, in some cases higher values for venous blood; Grehaut and Quincaud found equal values as far as the blood of the extremities was concerned, whilst venous blood derived from the liver and spleen contained more urea than arterial blood from the same organs. Kauffmann did not find any difference.

I. TECHNIQUE.

For my determinations I first tried the micro-method devised by Göthgen [1925]. However, as the results showed too great variations, I resorted to that of Rehberg [1925, 2]. My technique was as follows: 0.5 cc. of distilled water is placed in a test-tube and 0.1 cc. blood, measured in a Hagedorn

pipette, is added. The pipette is washed through three times with the distilled water. Then 0.1 cc. of a fresh 10 % urease solution (Squibb), adjusted to p_H 7 with a phosphate buffer solution, is added. The tube, being closed with a rubber plug, is placed on the water-bath at 40° for 30 mins. Then three drops of octyl alcohol and 1 cc. saturated K_2CO_3 solution are added. Previously, however, 2 cc. $N/600$ H_2SO_4 solution, freshly prepared from $N/10$ solution, should be measured into each titration tube, one drop of octyl alcohol being added. The test-tubes and titration tubes are then connected and aeration takes place for 2.5 hours at a speed moderate enough to avoid spraying the mixture over the walls of the tubes, which gives rise to inaccuracy. One or two blank analyses are set up, and a control with a known urea solution. For the control a 60 mg. % urea solution was used.

When aeration is completed the solution is titrated with $N/30$ NaOH by means of Rehberg's microburette [1925, 1]. Methylene red as indicator was used in a 0.05 % solution. The mean error in my tests was ± 1 mg. urea.

The blood samples were drawn in the morning, while the persons were still in bed and fasting; only in a few cases had they been out of bed for about an hour. The capillary blood was drawn from the ear after it had been rendered slightly hyperaemic by rubbing. Three or four samples were taken in immediate succession with a Hagedorn pipette, which was rinsed in a 3 % citrate solution before each drawing. The venous blood was taken from an arm vein, either without stasis or after a slight stasis had been procured, after I had ascertained that this made no difference to the results. The blood was evacuated into a dry test-tube, from which a number of tests, corresponding to those of capillary blood, were immediately measured off. Addition of anticoagulants proved unnecessary. The tubes were then placed in the ice-box until analysis could be undertaken a few hours later. It was experimentally substantiated that standing did not influence the constancy of the results provided the test-tubes were kept directly surrounded by ice.

II. NORMAL INDIVIDUALS.

(a) *Fasting values.* I have performed analyses with blood from 18 normal persons, altogether 32 sets of analyses with capillary and venous blood. The majority of the persons tested were convalescents after some mild affection not involving metabolism.

In 27 of these 32 cases the urea concentration was found to be higher in capillary than in venous blood, with an average of 10 %. The percentage difference varied, somewhat, from time to time in the same individual as well as from one individual to another. Differences of 4 to 22 % were found. The absolute difference was on an average 2–3 mg., the lowest value being 0.9 mg. and the highest 5.7 mg.

Only in five cases out of the 32 did the venous blood show a higher urea concentration than the capillary blood, the difference being here 1 to 2 % except in a single case, where it was 20.4 % (Nos. 4 c, 5 c, 9, 12 c and 15 b,

Table I). The examination was repeated several times in four of the subjects showing the latter relation, and it appeared that on other occasions these subjects followed the main rule: higher concentration in capillary than in venous blood. The analysis which presented a much higher concentration in venous blood (20.4 %) was one in a set performed during 6 hours of fasting with the purpose of determining the urea level during this period. It appeared that there were only slight variations of the urea concentration. At the beginning and termination of the experiment the venous blood was also examined. The initial sample of venous blood had, as stated, a higher urea concentration than the capillary blood, whilst the final sample of venous blood showed a lower concentration of urea than the capillary blood drawn simultaneously (14 %).

Table I. *Normal individuals.*

No.	Sex	Age	Urea content, mg. per 100 cc.		Difference	
			Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value
1	♂	12	31.6	27.6	4.0	14.4
2	♀	22	35.5	32.7	2.8	8.5
3a	♀	23	27.8	25.0	2.8	11.2
3b	♀	"	32.8	29.8	3.0	10.0
4a	♂	24	20.1	19.2	0.9	4.6
4b	♀	"	24.0	21.0	3.0	14.2
4c	♀	"	22.7	23.3	0.6	2.6
5a	♀	26	16.8	14.3	2.5	17.4
5b	♀	"	17.8	16.8	1.0	5.9
5c	♀	"	19.4	19.7	0.3	1.5
6	♀	27	36.1	33.7	2.4	7.1
7	♀	29	26.7	24.1	2.6	10.7
8	♂	"	27.5	24.2	3.3	13.6
9	♀	"	28.5	29.0	0.5	1.7
10	♀	30	37.9	33.5	4.4	13.1
11	♂	31	40.5	37.3	3.2	8.5
12a	"	34	31.5	30.0	1.5	5.0
12b	"	"	31.5	30.1	1.4	4.6
12c	"	"	23.0	27.7	4.7	20.4
13a	"	35	22.8	18.6	4.2	22.5
13b	"	"	40.7	35.0	5.7	16.2
14	"	36	29.5	25.4	4.1	16.1
15a	"	40	38.9	36.5	2.4	6.5
15b	"	"	39.1	39.9	0.8	2.0
15c	"	"	42.1	38.9	3.2	8.2
15d	"	"	43.8	41.4	2.4	5.7
15e	"	"	47.2	44.3	2.9	6.5
15f	"	"	48.8	45.5	3.3	7.2
15g	"	"	54.3	50.2	4.1	8.1
16	"	42	36.9	33.3	3.6	10.8
17	"	"	42.0	38.0	4.0	10.5
18	"	45	46.2	42.3	3.9	9.2

(b) *Results after ingestion of various substances.* In two normal persons I undertook a series of analyses after the ingestion of various substances. In these cases the blood samples were taken from the ear at an hour's interval, venous blood being drawn two or three times during the course of the experiment.

In one person the substances ingested were (1) urea, 15 g., (2) protein, 35 g., (3) a diet poor in protein, consisting of French beans, butter, coffee with cream, and some rusks.

The fasting blood-urea in this person ranged on an average somewhat higher than the usual value for normals; he was however apparently a perfectly healthy man with normal urine and normal blood-pressure.

With another person analyses were undertaken after the ingestion of 70 g. fat + 70 g. starch, and after 70 g. glucose.

Following the ingestion of 15 g. urea the blood-urea showed a rise from 48 to 74 mg. in the course of 2 hours. After 10 hours the curve had not fallen to the initial level. In these cases the urea content of the capillary blood was 5-7 % higher than that of the venous blood.

Table II. 15 g. urea test.

	♂ 40 years. (No. 15.)		Difference	
	Urea content, mg. per 100 cc.		mg.	Per cent. in relation to lowest value
	Capillary blood	Venous blood		
Before intake	48.8	45.5	3.3	7.2
1 hr. after intake	69.1	—	—	—
2 hrs. "	74.5	—	—	—
3 " "	69.4	—	—	—
4 " "	72.1	67.0	5.1	7.6
5 " "	68.8	—	—	—
6 " "	68.6	—	—	—
7 " "	62.8	59.7	3.1	5.1
8 " "	59.3	—	—	—
9 " "	57.4	—	—	—
10 " "	60.6	—	—	—

After ingestion of 35 g. protein the urea concentration rose in the course of 5 hours from 39 to 46 mg., falling again to the initial value in the course of 10 hours. The urea content of the capillary blood was from 1 to 6 % higher than that of the venous blood (Table III).

Table III. 35 g. protein test.

Normal individual. ♂ 40 years. (No. 15.)

	Urea content, mg. per 100 cc.		Difference	
			mg.	Per cent. in relation to lowest value
	Capillary blood	Venous blood		
Before intake	38.9	36.5	2.4	6.5
1 hr. after intake	39.1	—	—	—
2 hrs. "	38.6	—	—	—
3 " "	39.6	—	—	—
4 " "	43.3	42.8	0.5	1.1
5 " "	46.1	—	—	—
6 " "	41.9	—	—	—
7 " "	41.5	40.1	1.4	3.4
8 " "	38.4	—	—	—
9 " "	37.6	—	—	—
10 " "	38.4	—	—	—

The results obtained after the person had been on a diet poor in protein (Table IV) showed only slight variations in the blood-urea content, just as was the case after ingestion of glucose (Table V) and fat + starch (Table VI).

The higher value for urea was found in the capillary blood except towards the close of the experiment with glucose, where the venous blood contained 3·4 % more urea than the capillary blood. The experiments thus confirmed the findings with regard to fasting values, the main rule being that the higher concentration of urea is found in capillary blood.

Table IV. *Diet poor in protein.*

	♂ 40 years. (No. 15.)		Difference	
	Urea content, mg. per 100 cc.		mg.	Per cent. in relation to lowest value
	Capillary blood	Venous blood		
Before intake	54·3	50·2	4·1	8·1
1 hr. after intake	52·9	—	—	—
2 hrs. "	52·6	—	—	—
3 " "	52·4	—	—	—
4 " "	51·6	49·1	2·5	5·0
5 " "	50·3	—	—	—
6 " "	51·2	—	—	—
7 " "	50·1	49·9	0·2	0·4
8 " "	48·8	—	—	—
9 " "	51·5	—	—	—
10 " "	49·1	—	—	—

Table V. *70 g. glucose test.*

	♂ 34 years. (No. 12.)		Difference	
	Urea content, mg. per 100 cc.		mg.	Per cent. in relation to lowest value
	Capillary blood	Venous blood		
Before intake	25·6	25·5	0·1	—
1 hr. after intake	30·1	—	—	—
2 hrs. "	28·8	—	—	—
3 " "	31·1	—	—	—
4 " "	30·5	—	—	—
5 " "	30·7	—	—	—
6 " "	29·1	30·1	1·0	3·4

Table VI. *70 g. fat + 70 g. starch test.*

	♂ 34 years. (No. 12.)		Difference	
	Urea content, mg. per 100 cc.		mg.	Per cent. in relation to lowest value
	Capillary blood	Venous blood		
Before intake	31·5	30·0	1·5	5·0
1 hr. after intake	28·9	—	—	—
2 hrs. "	28·7	—	—	—
4 " "	29·5	—	—	—
5 " "	29·7	—	—	—
6 " "	28·5	26·3	2·2	8·3

III. PATHOLOGICAL CASES.

(a) *Fasting values.* I examined three groups of patients in whom one might expect to have found deviations from the normal with regard to the blood-urea relations. They were: 8 cases of icterus, 5 cases of various forms of nephritis and 9 diabetics.

Seven out of the eight analyses of icterus cases showed from 2 to 23 % more urea in capillary than in venous blood and only in one case was the value slightly higher for the venous blood. (No. 22, Table VII, 0.8 %.)

Table VII. *Icterus.*

No.	Sex	Age	Urea content, mg. per 100 cc.		Difference		Diagnosis
			Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value	
19 a	♂	19	25.2	23.9	1.3	5.4	Icterus catarrhalis
19 b	"	"	29.0	24.7	4.3	17.4	"
19 c	"	"	33.6	30.1	3.5	11.6	"
20 a	"	20	25.1	23.6	1.5	6.3	"
20 b	"	"	27.1	26.5	0.6	2.2	"
21	♀	43	12.3	10.0	2.3	23.0	"
22	♂	63	33.9	34.2	0.3	0.8	Cholelithiasis
23	"	66	25.9	23.8	2.1	8.8	"

The five cases of nephritis, some of which had a considerably increased concentration of blood-urea, all showed higher values for the capillary blood.

Table VIII. *Renal diseases.*

No.	Sex	Age	Urea content mg. per 100 cc.		Difference		Diagnosis
			Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value	
24	♂	8	20.2	19.2	1.0	5.2	Glomerulonephritis
25	"	"	77.8	74.1	3.7	4.9	"
26	"	12	55.9	49.4	6.5	13.1	"
27	"	22	52.3	52.2	0.1	0.2	Nephrosis
28	♀	56	103.0	101.9	1.1	1.0	Nephrosclerosis

Eight of nine diabetics followed the main rule; only in one case the reverse relation was found. (No. 30, Table IX.)

Table IX. *Diabetics.*

No.	Sex	Age	Urea content, mg. per 100 cc.		Difference	
			Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value
29	♀	24	32.2	31.5	0.7	2.2
30	♂	39	35.7	36.3	0.6	1.6
31	"	48	44.2	42.0	2.2	5.2
32	"	49	34.9	31.1	3.8	12.2
33	"	"	23.7	22.6	1.1	4.8
34	♂+♀	55	25.4	24.6	0.8	3.2
35	♂	58	26.3	21.2	5.1	24.0
36	♂+♀	60	87.3	83.2	4.1	4.9
37	♂	66	24.7	23.1	1.6	6.9

(b) *Results after ingestion of various substances.* One of the icterus cases was examined after the intake of 35 g. protein and 15 g. urea. The curves resembled very much those found for normals: an abrupt rise following the ingestion of urea (Table XI) and a slow rise after the ingestion of protein with maximum after 5 hours (Table X). In these cases also the main rule was followed with one single exception (Table X, 3 hours after ingestion).

Table X. 35 g. protein test.

Icterus, ♂ 19 years. (No. 19.)		Urea content, mg. per 100 cc.		Difference	
		Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value
Before intake		25.2	23.9	1.3	5.4
1 hr. after intake		28.9	—	—	—
2 hrs.	"	29.7	—	—	—
3 "	"	28.1	28.4	0.3	1.0
5 "	"	32.8	—	—	—
6 "	"	29.0	27.1	1.9	7.0
8 "	"	27.1	—	—	—

Table XI. 15 g. urea test.

Icterus, ♂ 19 years. (No. 19.)		Urea content, mg. per 100 cc.		Difference	
		Capillary blood	Venous blood	mg.	Per cent. in relation to lowest value
Before intake		29.0	24.7	4.3	17.4
1 hr. after intake		66.2	—	—	—
2 hrs.	"	55.7	—	—	—
4 "	"	49.2	47.6	1.6	3.3
6 "	"	43.4	—	—	—
8 "	"	52.0	—	—	—
10 "	"	45.9	43.2	2.7	6.2

SUMMARY.

Twenty-seven out of 32 sets of analyses of blood from 18 fasting normal individuals showed a higher concentration of urea in capillary blood (from ear-lobe) than in venous blood (from vena mediana cubiti), 10 % higher on an average. The percentage difference varied from individual to individual and also in the same individual from one day to another. Percentage differences of from 4 to 22 were found. The absolute difference was 3 mg. on an average.

In four cases the values were slightly higher for venous blood, only in a single case as much as 20 % higher.

Following the ingestion of protein, urea, diet poor in protein, fat + starch, and glucose, the main rule was again a higher concentration of urea in capillary than in venous blood in the course of the day.

Examinations of patients with diabetes, nephritis and icterus showed similar relations to those observed in normals. Only in 2 out of 22 cases was the urea content higher in venous blood.

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