

# THE DISTRIBUTION OF METABOLITES IN THE BLOOD AND TISSUES \*

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## INTRODUCTION

With the introduction of simple and reliable microchemical methods of analysis, the determination of the concentration of metabolites in the blood has become an accepted clinical procedure. Consequently, the relation of metabolites in the blood to their distribution throughout the entire organism is a subject of clinical as well as theoretic interest. I wish here to consider the distribution of metabolites in the body as a whole in relation to their concentration in the blood.

Three methods have been applied in studying metabolite distribution. The first, which is used in this report, consists in parallel determinations of the metabolites in the blood and in the various body fluids. The second method consists in the postmortem analyses of tissues to determine their respective metabolite content. The third method is the study of the effect produced by the ingestion of a given quantity of meat, or urea, and the resultant changes in the blood metabolites, controlling the experiments with nitrogen excretion determinations. The limitations of each of these three methods will be discussed later.

The first parallel analyses of urea were made by Javal and Adler <sup>1</sup> in 1906, using the hypobromite method. In four cases they found the urea content of different fluids from the same cases in practical accord. Javal and Boyet <sup>2</sup> reported ten cases with a similar agreement in 1910. In 1911, Javal <sup>3</sup> made parallel urea estimations on the blood and cerebrospinal fluid in eighteen cases, blood and edema fluid in four cases, pleural and edema fluid in one case, blood and pleural fluids in five cases, and pleural and cerebrospinal fluids in five cases. The urea concentrations in the fluids from the same cases were virtually identical. Javal concluded that "when the urea increases in the serum it also increases simultaneously in the organism and diffuses through all the fluids of the organism in the same concentration in which it occurs in the serum. . . . The blood contains from 30 to 35 mg.

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1. Javal and Adler: *Séances et Mém. de la Soc. de Biol.* **61**:235, 1906.

2. Javal and Boyet: *Ibid.* **68**:527, 1910.

3. Javal: *J. de phys. et de path. gen.* **13**:508, 1911.

urea nitrogen per hundred cubic centimeters. Normally, the cerebrospinal fluid contains about the same quantity." Javal's figures are approximately twice those now considered normal for blood urea nitrogen, doubtless because the hypobromite method used gives nitrogen other than urea nitrogen added to the true urea nitrogen figure.<sup>4</sup>

Rosenberg,<sup>5</sup> in 1914, made parallel determinations of urea, creatinin and indican in the blood and in the ascitic, pleural, and cerebrospinal fluids of nephritics. He also used the hypobromite urea method. Normal subjects were not studied. Rosenberg concludes that "in uremia, the urea content of the pleural and peritoneal fluids is from 80 to 100 per cent. of the blood. The creatinin content is up to 20 per cent. of the blood, and the indican is equal to the blood. The cerebrospinal fluid contains from 56 to 96 per cent. of the urea content of the blood, and from 37 to 75 per cent. of the blood creatinin." With the exception of considerably higher creatinin percentages for the body fluids, these findings coincide with those reported here. Using modern microchemical methods, Bernhard<sup>6</sup> found the nonprotein nitrogen, urea nitrogen, sugar and chlorides in eleven transudates and exudates to be comparable to those of normal blood. He did not make parallel analyses of the blood at the same time, and does not state whether or not the fluids were obtained with the patient in the fasting state.

The sugar content of transudates and exudates compared to the sugar content of the blood at the same time has been studied by Hagler and Schumann,<sup>7</sup> using the method of Bang. Of six pleural transudates, all but one had as high a sugar content as the blood, or higher. In twenty pleural exudates, the sugar content was usually lower than that of the blood; in eight peritoneal transudates it was slightly higher, and in seven cases of peritonitis it was slightly lower than the normal blood sugar. The ingestion of 100 gm. levulose or dextrose caused parallel increases in the sugar content of blood and fluids. From parallel analyses on the blood and fluids in five cases with pleuritic, and four cases with ascitic effusions, Dennis and Minot<sup>8</sup> conclude that the urea, uric acid, creatinin and nonprotein nitrogen occur in the same concentration in exudates and transudates as in the blood. They found the sugar content of the four ascitic fluids somewhat higher than that of the blood, contrary to the pleuritic fluids, which had a somewhat lower sugar content.

4. Herter and Wakeman: *J. M. Research* **4**:119, 1899; *Johns Hopkins Hosp. Rep.* **9**:69, 1900.

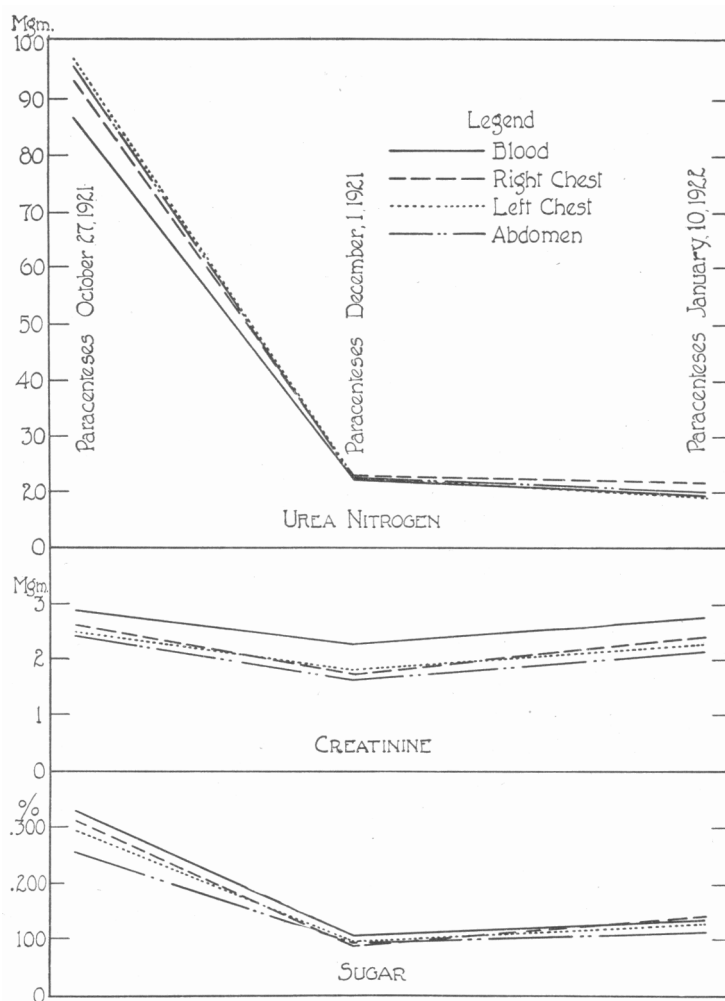
5. Rosenberg: *Berl. klin. Wchnschr.* **49**:1314, 1916.

6. Bernhard: *Interstate M. J.* **49**:188, 1918.

7. Hagler and Schumann: *Med. Klin.* **9**:1810, 1913.

8. Dennis and Minot: *Arch. Int. Med.* **20**:879 (Dec.) 1917.

Seham and Nixon<sup>9</sup> have recently investigated the chemistry of normal and pathologic spinal fluids. Their complete summary of the extensive literature makes further citation unnecessary. They report an average spinal fluid sugar content of 56.2 per cent. of the blood sugar in



Case of chronic nephritis illustrating parallel distribution of urea nitrogen, creatinin and sugar in the blood, ascitic fluid and right and left pleural effusions.

normal cases, with a maximum of 70.3 per cent. and a minimum of 47.8 per cent. Their findings for sugar are comparable to those of previous investigators. In four normal subjects they found the spinal fluid

9. Seham and Nixon: Arch. Int. Med. **28**:561 (Nov.) 1921.

creatinin to average 95.5 per cent. of the blood creatinin, and the diseases with high blood creatinin exhibited a corresponding increase in the creatinin content of the spinal fluid. In four normal subjects the urea content of the spinal fluid averaged 62.15 per cent. of the blood urea, with a range of from 45.5 to 174.6 per cent. in pathologic cases. Their findings for urea differ from those of Cullen and Ellis,<sup>10</sup> who report almost complete agreement between the urea content of the spinal fluid and the blood. Meyers and Fine<sup>11</sup> found in nephritics that the former averages 88 per cent. of the latter. The figures of Seham and Nixon are somewhat higher for spinal fluid creatinin, and somewhat lower for urea, than those reported in this paper.

The various investigators of the metabolite distribution between the blood and other body fluids thus appear in fairly close agreement. They find both the nitrogenous metabolites and the sugar in approximately the same concentration in fluids and in blood. The percentages for the blood are usually slightly higher than for the other fluids, but an increase in the blood values appears to be associated with corresponding increases in the values in the fluids.

#### PROCEDURE

This study is concerned with further investigation of the distribution of metabolites between the blood and other body fluids, primarily in cases in which the blood exhibits no retention of metabolites. A few cases with increased retention are included for comparison.

In all cases the blood and fluids were obtained simultaneously. The patients were kept without food overnight, and the samples were obtained before breakfast, Jacobsen and Edwards<sup>12</sup> having shown that there may be an increase in blood urea, as well as blood sugar, following the ingestion of an ordinary meal. The specimens were immediately sent to the laboratory, where parallel determinations of the sugar, urea nitrogen and creatinin were done. Most of the determinations were made in less than half an hour after withdrawal of the fluids from the patient. The analyses were all made by the same person. Double estimations on the same specimen were frequently made to check the technic, with results well within the limits of experimental error. Urea nitrogen was estimated by Van Slyke and Cullen's modification of Marshall's urease method,<sup>13</sup> creatinin by the method of Folin,<sup>14</sup> sugar by the method of Lewis and Benedict.<sup>15</sup> A Kober colorimeter was

10. Cullen and Ellis: *J. Biol. Chem.* **20**:511, 1915.

11. Meyers and Fine: *J. Biol. Chem.* **37**:239, 1919.

12. Jacobsen and Edwards: *Am. J. M. Sc.* **159**:579, 1920.

13. Van Slyke and Cullen: *J. Biol. Chem.* **24**:117, 1916.

14. Folin: *J. Biol. Chem.* **17**:475, 1914.

15. Lewis and Benedict: *J. Biol. Chem.* **20**:61, 1915.

employed. The percentage concentration of the metabolites in each fluid was obtained by dividing the concentration of the metabolite in the fluid, times 100, by the concentration of the metabolite in the blood.

#### CLASSIFICATION OF MATERIAL

In all, fifty-five fluids from thirty-six cases were analyzed. As often as possible, more than one fluid was obtained from the same case. Several cases were used more than once, but at each fluid determination a parallel blood analysis was done at the same time. The

TABLE 1.—CLASSIFICATION OF CASES ACCORDING TO GROUPS

Group		Cases
I	Effusions in cases with normal blood metabolites.....	31
	Ascitic transudates .....	13
	Thoracic transudates .....	7
	Ascitic exudates .....	4
	Thoracic exudates .....	7
II	Effusions in cases with increased blood metabolites.....	4
	Ascitic transudates .....	1
	Thoracic transudates .....	3
III	Cerebrospinal fluids in cases with normal blood metabolites.....	15
	Normal fluids .....	7
	Pathologic fluids .....	8
IV	Cerebrospinal fluids in cases with increased blood metabolites.....	5
	Normal fluid .....	1
	Pathologic fluids .....	4
Total	.....	55

TABLE 2.—GROUPING OF FLUIDS ACCORDING TO CLINICAL DIAGNOSES

Diagnosis	Cases	Diagnosis	Cases
Chronic nephritis.....	10	Polyserositis.....	1
Hepatic cirrhosis.....	9	Acute peritonitis.....	1
Carcinoma.....	4	Acute pericarditis.....	1
Tuberculous pleurisy.....	4	Cholecystitis.....	1
Tabes dorsalis.....	3	Neurasthenia.....	1
General paresis.....	3	Dementia praecox.....	1
Myocardial degeneration.....	2	Neurosyphilis.....	1
Tuberculous peritonitis.....	2	Lethargic encephalitis.....	1
Empyema.....	2	Cerebrospinal meningitis.....	1
Hysteria.....	2	Uremia.....	1
Aneurism.....	1	Alcoholism.....	1
Hydrocele.....	1	Normal.....	1
Total.....	55		

cases have been arranged in four groups (Table 1). The clinical diagnoses are arranged in Table 2.

#### EXPERIMENTAL RESULTS

The results of the determinations are given in Tables 3 to 8, and for comparison the average figures for each group are arranged in Table 7. In the cases with normal blood metabolite concentration, the sugar content of the ascitic transudates averaged 96.47 per cent. of the blood sugar, with a minimum of 51 per cent. and a maximum of 112 per cent. In the same cases the average ascitic urea nitrogen was 95.90 per cent. of the blood urea nitrogen, with a minimum of 60

per cent. and a maximum of 180 per cent. In this group the percentage of creatinin averaged somewhat less, from 67.31 per cent., with a minimum of 30 per cent. and a maximum of 91 per cent. of the blood creatinin. The averages for the corresponding group of thoracic transudates, in cases with normal blood metabolites, was quite similar. In this

TABLE 3.—GROUP I. A. ASCITIC AND THORACIC TRANSUDATES WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Carcinomatosis	0.096	0.102	106.25	.....	.....	.....	1.844	1.600	86.00
2	Ascitic	Carcinomatosis	0.104	0.080	76.90	17.85	14.00	78.00	1.416	0.435	30.00
3	Ascitic	Hepatic cirrhosis	.....	.....	.....	.....	.....	.....	1.700	1.250	73.00
4	Ascitic	Hepatic cirrhosis	0.086	0.071	82.50	14.00	9.10	65.00	1.790	1.610	91.00
5	Ascitic	Hepatic cirrhosis	0.093	0.095	102.00	17.85	14.35	79.00	1.950	1.540	78.00
6	Ascitic	Hepatic cirrhosis	0.114	0.105	92.00	10.85	12.60	116.00	1.820	1.000	54.92
7	Ascitic	Hepatic cirrhosis	0.109	0.165	60.00	28.70	28.00	97.50	2.000	1.170	58.50
8	Ascitic	Hepatic cirrhosis	0.123	0.071	51.00	11.55	20.90	180.00	1.807	1.110	61.00
9	Ascitic	Gastric carcinoma	0.100	0.096	96.00	11.80	11.90	100.00	1.860	1.570	84.00
10	Ascitic	Hydrocele	0.102	0.087	85.00	5.25	3.15	60.00	2.360	1.500	63.50
11	Ascitic	Hepatic cirrhosis	0.083	0.093	112.00	9.10	7.14	78.40	1.180	1.400	77.70
12	Ascitic	Hepatic cirrhosis	0.081	0.088	108.00	8.65	8.05	92.80	1.280	1.200	81.00
13	Ascitic	Chronic nephritis	0.100	0.096	96.00	23.00	23.10	100.00	2.250	1.760	78.20
Av.	Ascitic	.....	0.099	0.096	96.47	14.43	13.84	95.90	1.958	1.318	67.31
1	Thoracic	Chronic nephritis	0.133	0.138	103.76	18.88	21.68	114.30	2.770	2.380	85.90
2	Thoracic	Aneurysm of arch	0.098	0.079	80.60	14.00	13.65	97.50	2.110	1.310	62.56
3	Thoracic	Chronic nephritis	0.100	0.086	86.00	23.00	.....	.....	2.250	1.730	76.86
4	Thoracic	Chronic nephritis	0.100	0.088	88.00	23.00	23.80	100.30	2.250	1.790	79.40
5	Thoracic	Myocardic degeneration	0.112	0.091	81.20	15.05	8.40	55.70	1.630	1.110	66.60
6	Thoracic	Myocardic degeneration	0.094	0.082	87.20	14.00	5.25	37.50	1.760	1.320	75.00
7	Thoracic	Chronic nephritis	0.133	0.127	95.48	18.88	18.60	98.64	2.770	2.307	84.00
Av.	Thoracic	.....	0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
Average.....			0.104	0.098	94.23	16.27	13.30	89.30	2.089	1.512	72.38

group the average sugar content of the fluid was 90 per cent., with a minimum of 80.6 per cent. and a maximum of 103.76 per cent. The urea nitrogen averaged 84.09 per cent., with a minimum of 37.5 per cent. and a maximum of 114.3 per cent. of the blood urea nitrogen. The creatinin averaged 76.89 per cent. with a minimum of 62.56 per cent. and a maximum of 85.9 per cent. (Table 3).

The corresponding exudates showed slightly lower percentages than the transudates. The sugar content of the ascitic transudates with normal blood metabolites averaged 75.55 per cent., with a minimum of 59 per cent. and a maximum of 98 per cent. The urea nitrogen averaged 70.02 per cent., with a minimum of 41 per cent. and a maximum of 113 per cent. The creatinin averaged 48.8 per cent., with a minimum of 35 per cent. and a maximum of 72 per cent. In the corresponding group of thoracic exudates, the sugar content averaged 79.32 per cent., with a minimum of 0 (case of acute empyema), and a maximum of 106.9 per cent. The urea nitrogen in this group averaged

TABLE 4.—GROUP I. B. ASCITIC AND THORACIC EXUDATES WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Tuberculous peritonitis	0.114	0.075	65.00	12.78	5.33	41.00	2.000	0.900	45.00
2	Ascitic	Tuberculous peritonitis	0.126	0.075	59.00	29.65	14.89	50.00	2.550	1.200	47.00
3	Ascitic	Polyserositis	0.102	0.084	82.00	23.55	22.42	95.00	2.850	1.000	35.00
4	Ascitic	Acute peritonitis	0.108	0.106	98.00	8.65	9.80	113.00	2.080	1.500	72.00
Av.	Ascitic	.....	0.113	0.085	75.55	18.66	13.11	70.02	2.370	1.150	48.80
1	Thoracic	Empyema	0.088	0.000	00.00	.....	.....	.....	2.000	1.400	70.00
2	Thoracic	Tuberculous pleurisy	0.083	0.087	104.80	24.05	22.05	91.69	1.740	1.730	99.90
3	Thoracic	Tuberculous pleurisy	0.098	0.102	104.10	28.70	21.30	73.17	2.500	2.050	82.00
4	Thoracic	Tuberculous pleurisy	0.095	0.097	102.20	12.60	13.60	104.00	2.110	1.780	84.32
5	Thoracic	Tuberculous pleurisy	0.101	0.108	106.90	22.20	18.20	81.90	1.880	1.760	93.61
6	Thoracic	Empyema, lues	0.160	0.096	60.00	13.30	10.15	76.31	2.330	1.600	69.53
7	Pericardial	Acute pericarditis	0.100	0.086	86.00	14.00	12.46	89.00	2.000	1.410	70.50
Av.	Thoracic	.....	0.103	0.082	79.32	19.14	16.29	86.01	2.066	1.621	78.41
Average.....			0.108	0.083	77.93	18.90	14.70	78.01	2.212	1.385	62.16

86.01 per cent., with a minimum of 73.17 per cent. and a maximum of 100 per cent. The creatinin figures averaged 78.41 per cent., with a minimum of 69.53 per cent. and a maximum of 99.9 per cent. (Table 4).

The cerebrospinal fluids in cases with normal blood metabolite concentration show consistently lower percentages of metabolites. The figures for the normal and pathologic fluids yield remarkably similar figures. The spinal fluid sugars averaged 60.21 per cent., with a minimum of 40.1 per cent. and a maximum of 89.6 per cent. In the same group the spinal fluid urea nitrogen averaged 66.5 per cent., with a

minimum of 39.9 per cent. and a maximum of 140 per cent. The creatinin averaged 59.8 per cent., with a minimum of 22.03 per cent. and a maximum of 90 per cent. (Table 5).

Although the bloods from the group of cases with increased metabolite concentration show a decided rise above the normal blood

TABLE 5.—GROUP III. NORMAL AND PATHOLOGICAL CEREBROSPINAL FLUIDS WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Normal	Cholecystitis	0.102	0.055	53.93	12.60	4.65	39.90	1.148	0.253	22.03
2	Normal	Neurasthenia	0.092	0.063	68.48	13.65	8.60	63.00	0.968	0.343	35.33
3	Normal	Gastric carcinoma	0.080	0.037	46.45	.....	.....	.....	1.800	1.300	73.33
4	Normal	Cirrhosis	0.074	0.055	74.32	.....	.....	.....	2.340	1.360	58.12
5	Normal	Hysteria	0.087	0.052	60.00	.....	.....	.....	1.807	1.310	71.80
6	Normal	Dementia praecox	0.097	0.064	66.00	9.80	8.30	84.50	1.720	1.210	70.30
7	Normal	Normal	0.073	.....	.....	10.85	7.00	64.00	2.000	1.200	60.00
Av.	Normal	.....	0.086	0.054	61.53	11.73	7.16	61.00	1.683	0.997	59.20
1	Path.	Neurosyphilis	0.102	0.041	40.10	18.80	9.80	51.60	1.820	1.200	66.00
2	Path.	General paresis	0.166	0.084	50.60	20.30	9.80	48.27	2.000	1.470	73.50
3	Path.	Tabes dorsalis	0.102	0.050	49.00	.....	.....	.....	0.960	0.880	71.68
4	Path.	Enceph. letharg.	0.125	0.074	59.30	.....	.....	.....	1.416	0.843	24.18
5	Path.	General paresis	0.093	0.050	53.76	11.20	15.70	140.00	1.500	0.840	22.80
6	Path.	General paresis	0.105	0.060	57.14	13.48	7.64	56.60	1.000	0.900	90.00
7	Path.	Tabes dorsalis	0.155	0.139	89.60	19.90	16.80	84.42	1.870	1.310	70.00
8	Path.	Tabes dorsalis	0.097	0.055	56.50	7.77	4.90	63.69	1.780	1.030	59.90
Av.	Path.	.....	0.118	0.069	58.90	15.24	10.77	70.60	1.543	0.935	60.00
Average.....			0.102	0.063	60.21	13.48	8.96	66.50	1.613	0.965	59.80

TABLE 6.—GROUP II. ASCITIC AND THORACIC TRANSUDATES WITH INCREASED BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Chronic nephritis	0.325	0.259	76.00	84.20	96.00	114.00	2.88	2.45	85.00
1	Thoracic	Chronic nephritis	0.107	0.152	111.80	.....	.....	.....	4.22	3.98	94.31
2	Thoracic	Chronic nephritis	0.325	0.308	91.69	84.20	98.00	110.45	2.88	2.61	90.62
3	Thoracic	Chronic nephritis	0.325	0.294	90.46	84.20	97.00	115.20	2.88	2.50	86.11
Av.	Thoracic	.....	0.252	0.251	99.70	84.20	95.00	112.00	3.33	3.03	91.10
Average.....			0.288	0.255	88.30	84.20	95.50	113.00	3.10	2.74	88.20

values, the relative concentration of the metabolites in the fluids remains much the same as in the cases without retention. This indicates a corresponding increase in the metabolite content of the fluids. The average sugar content of the effusions with increased blood metabolites was 88.3 per cent. as compared with 90 per cent. in the



cases without retention. The urea nitrogen averaged 113 per cent., as compared with 89.3 per cent. and the creatinin 88.2 per cent., as compared with 76.89 per cent. in the normal group (Table 6).

Similarly, where the blood metabolites are increased, the cerebrospinal fluids show a corresponding increase, so that the percentage concentration remains approximately the same as in the group without retention. This is exclusive of a case of acute meningitis in which no spinal fluid sugar was present. In this group the average sugar content was 27.7 per cent., with a minimum of 0 and a maximum of 98.7 per cent. The urea nitrogen averaged 49.8 per cent., with a minimum of 45.9 per cent. and a maximum of 107.9 per cent. The creatinin 73.57 per cent., with a minimum of 39.74 per cent. and a maximum of 102.6 per cent. (Table 7).

The most significant point shown by the data summarized in Table 8 is the relative uniformity of the findings in the various groups. In

TABLE 7.—GROUP IV. NORMAL AND PATHOLOGICAL CEREBROSPINAL FLUIDS WITH INCREASED BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Normal	Hysteria	0.105	0.069	65.71	27.93	12.78	45.90	3.90	1.35	39.74
2	Normal	Nephritis, tabes	0.099	0.046	44.66	28.70	30.80	107.90	2.21	1.64	74.40
3	Normal	Alcoholism	0.112	0.091	80.80	46.80	49.70	106.00			
4	Normal	Uremia	0.165	0.083	98.70	.....	.....	.....	9.74	9.99	102.60
Av.	Normal	.....	0.120	0.072	60.00	50.53	31.09	61.10	5.28	4.26	80.69
1	Path.	Cerebrospinal meningitis, tabes, nephritis	0.140	0.000	00.00	107.00	45.6	42.61	3.0	2.11	70.33
Average.....			0.130	0.036	27.70	78.76	38.34	49.80	4.14	2.073	73.57

general, the concentration of sugar, urea nitrogen and creatinin in the fluids of all the groups tends to approximate 80 per cent. of their respective concentration in the blood. The spinal fluids are consistently lower than the effusions, approximating 60 per cent. of the blood figures. The concentration of creatinin in all the fluids tends to remain relatively lower than the other metabolites in comparison with their respective blood values.

Of special interest is the fact that in Groups II and IV, in which the blood metabolites are increased, the percentage of metabolites in the fluids in relation to the blood is approximately the same as in the cases with normal metabolite levels. This indicates a definite tendency toward equilibrium in the distribution of metabolites between the blood and fluids. This parallelism is well illustrated in Chart I, which shows the findings from a case of chronic nephritis, with ascites and bilateral hydrothorax. On admission the patient's blood urea nitrogen was

87.2 mg. per hundred cubic centimeters, with urea nitrogen values for the pleural effusions and ascitic fluid of 93, 97 and 96 mg. per hundred cubic centimeters, respectively. Five weeks later, under dietary treatment and rest in bed, the blood urea nitrogen had dropped to 23 mg., the right pleural effusion to 23.8 mg., the left pleural effusion to 23.8 mg., and the ascitic fluid to 23.1 mg. per hundred cubic centimeters, respectively. In another five weeks the blood urea had fallen to 18.8 mg., with corresponding drops to 21.68, 18.60 and 19 mg. per hundred cubic centimeters, respectively, in the three fluids. The creatinin and sugar values show equally consistent decreases in the blood and three fluids. Although at the time of the first estimations five liters of fluid were removed, and five and a half liters at the time

TABLE 8.—SUMMARY OF RESULTS. AVERAGE RELATIVE CONCENTRATION OF METABOLITES IN THE BLOOD AND VARIOUS BODY FLUIDS

Classification of Fluids				Metabolite Determinations								
Blood Metabolites	No. Cases	Source	Type	Sugar			Urea Nitrogen			Creatinin		
				Blood	Fluid	Per Cent.*	Blood	Fluid	Per Cent.*	Blood	Fluid	Per Cent.*
Group I Normal	13	Ascitic	Trans.	0.099	0.096	96.47	14.13	13.84	95.90	1.958	1.378	67.31
	7	Thoracic	Trans.	0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
	4	Ascitic	Exud.	0.113	0.085	75.55	18.86	13.11	70.02	2.370	1.150	48.80
Group II Increased	3	Thoracic	Exud.	0.103	0.082	79.32	19.14	16.29	85.10	2.066	1.621	78.41
	1	Ascitic	Trans.	0.325	0.259	76.00	84.20	96.00	114.00	2.880	2.450	85.00
	3	Thoracic	Trans.	0.252	0.251	99.70	84.20	95.00	112.00	3.326	3.030	91.10
Group III Normal	7	C. S. Fl.	Normal	0.086	0.054	62.79	11.73	7.16	61.00	1.638	0.996	59.20
	8	C. S. Fl.	Path.	0.118	0.069	58.80	15.24	10.77	70.60	1.543	0.935	60.60
Group IV Increased	4	C. S. Fl.	Normal	0.120	0.072	60.00	50.53	31.09	61.10	5.280	4.260	80.69
	1	C. S. Fl.	Path.	0.140	0.000	00.00	107.00	45.60	42.60	3.000	2.110	70.33
Total	55											

Sugar in per cent. urea nitrogen and creatinin in milligrams per 100 c.c.

\* Per Cent. =  $\frac{\text{Concentration in fluid}}{\text{Concentration in blood}} \times 100$ .

of the second determination, the metabolite concentration in all the fluids continued to fall. The reaccumulation of effusions appears to bear no relationship to changes in the retention of these metabolites.

No relation between the metabolite figures in the fluids and the clinical diagnoses was apparent.

#### DISCUSSION

As previously mentioned, there are two other methods for studying the distribution of metabolites in the body. Postmortem analysis of the urea content of various tissues was first employed by Schoendorf<sup>16</sup> in 1899. In a well fed dog he found that the liver, spleen, pancreas and

16. Schoendorf: Arch. f. d. ges. Phys. **74**:307, 1899.

brain contained approximately the same concentration of urea as the blood (from 0.1115 to 0.1228 per cent.), while the heart contained slightly more and the muscle slightly less. Marshall and Davis<sup>17</sup> criticized these findings as being too high for the blood, and probably even less correct for the tissues. They introduced the more accurate urease method of urea estimation, and studied the urea content of normal dogs' tissues, postmortem. They found that the percentage of urea was practically constant throughout the body, except the urinary tract, averaging from 28 to 30 mg. per hundred grams. Similar results were obtained in postmortem analyses of various human organs. By killing dogs soon after the ingestion of urea per os, they were also able to show that it diffused very rapidly into all the tissues, and whether the urea concentration in the body was normal or increased, it was distributed with remarkable uniformity throughout the various tissues. In similar experiments, Foster and Davis<sup>18</sup> found that the amounts of retained nitrogen could not be accounted for by the total nonprotein nitrogen of the total blood of the body. Postmortem analyses of the tissues led them to conclude that more of the nitrogenous metabolites are retained in the tissues than in the blood. Becker<sup>19</sup> studied the total nonprotein nitrogen in nephrectomized dogs. The relatively greatest increase was in the blood, but the absolutely greatest increase was in the muscles. The increase in the other organs was slight in comparison with the musculature. He found a much closer agreement between the urea nitrogen of the tissues and blood than in the total nonprotein nitrogen. Becker also showed that the increase in total nonprotein nitrogen in the various tissues of dead bodies was related to their respective total nitrogen content, with a fairly constant nonprotein nitrogen: total nitrogen ration of 1:10. Becker states that postmortem analyses of blood nitrogen are more nearly comparable to postmortem tissue analyses than blood analyses obtained antemortem.

Rosenberg<sup>20</sup> estimated the metabolites in the blood and thigh muscle of nine normal men, eleven chronic nephritics and seven acute nephritics. The blood was taken either just before or immediately after death, and the thigh muscle as soon as possible postmortem. He extracted the musculature with trichloracetic acid, and determined the total rest nitrogen by Kjeldahl's method, urea by the hypobromite

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17. Marshall and Davis: *J. Biol. Chem.* **18**:53, 1914.

18. Foster and Davis: *Proc. Soc. Exper. Biol. & Med.* **8**:33, 1915.

19. Becker: *Deutsch. Arch. f. klin. Med.* **128**:1, 261, 1918, *ibid.* **129**:1, 8, *ibid.* **134**:325, 1920, *ibid.* **135**:331, 1920. Becker and Strauss: *Zentralbl. f. Inn. Med.* **42**:345, 1921.

20. Rosenberg: *Arch. f. exper. Path. u. Pharmacol.* **86**:1, 1920, *ibid.* **87**:86, 1920, *ibid.* **87**:153, 1920.

method, creatinin by Folin's method, and indican by the method of Jolles. Rosenberg's average figures for normal blood and muscle are as follows:

	Blood		Muscle
Rest nitrogen.....	0.025 per 100 c.c.....	0.307	per 100 gm.
Urea nitrogen.....	0.020 per 100 c.c.....	0.232	per 100 gm.
Creatinin .....	0.0015 per 100 c.c.....	0.00355	per 100 gm.

In two cases in which the normal musculature of the thigh was obtained at amputations for disease below the knee, and analyzed immediately, the results were virtually identical with those for muscle analyzed postmortem. Although the hypobromite method which he used gives figures for urea nitrogen approximately twice those obtained by the urease method,<sup>4</sup> it is difficult to reconcile Rosenberg's figures of 232 mg. per 100 gm. for the urea content of normal musculature with Marshall and Davis of from 28 to 30 mg. per 100 gm. On the other hand, the proportion of rest nitrogen made up of urea nitrogen in Rosenberg's figures is about that generally accepted as normal. His figures for normal blood metabolites, also, are within the generally accepted limits. Rosenberg found similiar values for the musculature of rabbits.

From a comparison of the blood chemistry and the postmortem muscle analyses Rosenberg concludes:

In uremia the muscle rest nitrogen begins to increase when the blood level rises above 170 mg. per hundred cubic centimeters. There is no difference between acute and chronic cases. . . . It is probable that there is a reciprocal relation between the blood and tissues and not, as von Monakow<sup>21</sup> thought, that the tissues fill with metabolites and then overflow into the blood. . . . In the muscles of chronic nephritics it is found not only that the urea nitrogen increases to a relatively higher degree than the other nonprotein nitrogenous metabolites, but that these may even diminish, possibly through the conversion of amino-acids into urea. . . . The muscle urea shows an increase when the blood urea rises above 150 mg. per hundred cubic centimeters. . . . In all cases showing increased muscle urea the absolute increase of urea in the blood was considerably less than in the musculature. . . . The muscle creatinin increase was inconstant, and occurred only with severe creatininemia.

According to Rosenberg, then, normal muscle values for the rest nitrogen and urea are over ten times their concentration in the blood, and are not increased until the blood level rises above approximately two thirds of the normal muscle concentration. Retention of urea in the musculature occurs earlier than the other metabolites and its disproportionate increase in the muscles is probably due to the conversion of other nonprotein metabolites into urea.

Weiss and Vaughn<sup>21</sup> recently reported a case of severe nephritis in which the blood urea twelve hours before death was 304 mg., and the nonprotein nitrogen 401 mg. per hundred cubic centimeters. Post-

21. Weiss and Vaughn: J. Lab. & Clin. Med. 7:229, 1921.

mortem, the pericardial fluid contained 374 mg. of urea nitrogen, the muscle 352 mg., and the liver 335 mg. per hundred grams, respectively. Their technic is not given, but the results show a close approximation of the urea content of the blood, fluid and tissues. Andresen<sup>22</sup> reports an equal distribution of urea, between the blood, organs and secretions, with the exception of tears and sweat, where a value three times that of the blood was found.

With the exception of Rosenberg, all of these investigators appear in fair agreement in regard to the uniform distribution of urea. He diverges considerably in regard to the urea value for normal musculature, but agrees with the others that the urea accounts for most of the nonprotein nitrogen retention in the body.

The distribution of ingested nitrogen was first studied by Soetbeer<sup>23</sup> in 1909. Four and one-half hours after a heavy meal of meat he found the total nitrogen in a dog's blood had increased 132 per cent., in the liver 41 per cent., and in the brain and muscles only 5 or 6 per cent. Seventy-two hours after nephrectomy, the total nitrogen in a dog's blood had increased 873 per cent., in the liver 144 per cent., in the brain 40 per cent., and in the muscles only 35 per cent. This would indicate a heaping up of the retained nitrogen in the blood before its accumulation in the tissues.

Von Monakow<sup>24</sup> showed that after a single ingestion of 20 gm. urea per os, in normal men, the blood urea rose in fifteen minutes and reached its peak in two hours, remaining slightly increased at twenty-four hours and returning to normal on the second day. If one day after the first ingestion, a second 20 gm. was given, the blood urea level still returned to normal within two days. In other words, it was impossible to raise the blood level by repeated small doses of urea per os. Von Monakow assumes that most of the ingested urea passes into the tissues.

Lichtwitz<sup>25</sup> repeated these experiments, controlling them with simultaneous estimations of nitrogen elimination in the urine. After the ingestion of 20 gm. urea per os, he found widely varying percentages of the retained urea in the blood. He concludes that the rest nitrogen is very unequally divided between the blood and other organs, and that it need not be increased in the blood, although the amount of nitrogen eliminated indicates a definite nitrogen retention.

Nonnenbruch<sup>26</sup> has recently repeated similar experiments on urea ingestion, retention, and elimination. He finds that the variations in

22. Andresen: *Biochem. Ztschr.* **116**:266, 1921.

23. Soetbeer: *Verhandl. 26 Cong. f. inn. Med.*, 1909.

24. Von Monakow: *Deutsch. Arch. f. klin. Med.* **115**:47, 224, 1914; *ibid.* **116**:1, 1914.

25. Lichtwitz: *Klinische Chemie*, 1918.

26. Nonnenbruch: *Arch. f. exper. Path. u. Pharmacol.* **89**:200, 1921.

blood urea nitrogen following the oral ingestion of 20 gm. urea, do not parallel its elimination. For the most part the nonprotein nitrogen of the blood does not increase sufficiently to account for the urea ingested and falls much more rapidly than it is eliminated in the urine. In some cases, blood urea nitrogen was still increased after the ingested urea had all passed out through the kidneys. Several cases showed two peaks and two troughs in the blood rest nitrogen curves. On the basis of these findings, Nonnenbruch concludes that there is a marked difference of distribution between the blood and other tissues; that a normal blood rest nitrogen does not indicate the absence of nitrogen retention, nor, on the contrary, does an increased blood nitrogen indicate nitrogen retention in the tissues. He thinks that immediately after its ingestion urea is carried to the tissues and afterward returned to the kidneys for elimination.

#### SUMMARY

Although the studies with ingested urea indicate that during the period of its elimination there is no constant parallelism in the concentration of nitrogenous metabolites of the blood and tissues, both the estimation of the body fluid metabolites and the comparison of metabolites in the blood and tissues, strongly suggest a tendency to equilibrium throughout the organism. This does not necessarily mean that a normal concentration of metabolites in the tissues approximates that in the blood, but that the metabolites are distributed between them in a fairly constant proportion, and that an increase in one is paralleled by a proportionate increase in the other. No account, of course, is taken here of any but the simple metabolites; available sugar in the form of glycogen, or available rest nitrogen, urea nitrogen, creatinin or uric acid in more complex chemical forms, are incalculable factors. The distribution of creatinin and sugar throughout the body is for the most part unknown.

The distribution of metabolites between the blood and all the body fluids is fairly consistent. For clinical purposes, it appears justifiable to deduce from the concentration of metabolites in the blood, an approximately proportional concentration throughout the whole body. Nevertheless, until the distribution of metabolites for all the tissues is quantitatively determined, it will remain impossible to deduce accurately from the blood chemistry alone the degree of retention in the whole body.

#### CONCLUSIONS

1. In cases in which the blood metabolite level was not increased above normal, the concentration of sugar in serous effusions averaged 83.42 per cent. of the sugar concentration in the blood. The urea nitrogen averaged 80.08 per cent., and the creatinin 67.28 per cent.

2. No characteristic difference in the metabolite concentration of exudates and transudates was observed.

3. In cases in which the blood metabolite level was normal, the average concentration of sugar in the spinal fluid was 44.24 per cent. of the blood sugar. Urea nitrogen averaged 58.15 per cent., and creatinin 68.3 per cent.

4. Except for the absence of sugar in acute meningitis, no difference was present between normal and pathologic spinal fluids.

5. In cases in which the blood metabolite level was increased, the metabolite concentration in the fluids varied *pari passu* with the changes in the blood.

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