

## STUDIES IN THE CHEMISTRY OF THE SPINAL FLUID OF CHILDREN \*

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Due in part to the fact that a new method for the treatment of chorea, necessitating the frequent withdrawal of spinal fluid, has been used at the hospital<sup>1</sup> we were fortunate enough, during the past year, to obtain for examination the spinal fluids from a rather large number of children. It appeared of interest to examine these fluids for their nonprotein nitrogenous constituents and their reducing substances, by means of the newer methods of Folin and Denis and their co-workers.

### NONPROTEIN NITROGENOUS CONSTITUENTS

Up to the present, no examinations appear to have been made of the spinal fluid for its nonprotein nitrogenous constituents (total nonprotein nitrogen, urea, uric acid, and creatinin) by means of the accurate and relatively simple methods of Folin and Denis and others.<sup>2</sup> Woods<sup>3</sup> examined the spinal fluid in chronic nephritis for total nonprotein nitrogen and urea. He found that the total nonprotein nitrogen was, as a rule, 25 per cent. lower than that of the blood. The urea content of the spinal fluid approximately equaled that of the blood. Cullen and Ellis<sup>4</sup> found the concentration of urea in the spinal fluid the same as that in the blood. While our work was in progress, Myers and Fine<sup>5</sup> reported the results of their analysis of the spinal fluids from fifteen cases of nephritis in adults. Their conclusions were that the concentration of urea in spinal fluid averaged 88 per cent. of that in the blood; the concentration of creatinin averaged 46 per cent. of that in the blood; the concentration of uric acid averaged 5 per cent. of that in the blood; and the concentration of sugar averaged 57 per cent. of that in the blood.

### REDUCING SUBSTANCE

Very few contributions have been made to the chemistry of the reducing substance of the spinal fluid. According to Mott,<sup>6</sup> Claude

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1. Goodman, A. L.: Arch. Pediat., 1916, **31**, 649.

2. Leopold and Bernhard: AM. JOUR. DIS. CHILD., 1916, **11**, 432.

3. Woods, A. C.: Arch. Int. Med., 1915, **16**, 577.

4. Cullen and Ellis: Jour. Biol. Chem., 1915, **20**, 511.

5. Myers and Fine: Proc. Soc. Exper. Biol. and Med., 1916, **13**, 126.

6. Mott, F. W.: Lancet, London, 1910, **2**, 1, 79.

Bernard demonstrated the existence of sugar in the spinal fluid. Halliburton came to the conclusion that the reducing substance was not sugar, but pyrocatechin. He later abandoned that view, however, and, according to Mott, now agrees with the great majority of other observers, that the reducing substance is glucose, and that it is always present in the spinal fluid in normal conditions. Schloss and Schroeder<sup>7</sup> recently examined normal and pathologic spinal fluids in children for their sugar content, employing the Lewis and Benedict method. They found that the sugar content in normal fluids varied between 0.05 and 0.139 per cent. They also demonstrated that the sugar content is usually reduced in all forms of meningitis, although it may at times be normal in tuberculous meningitis. In infantile paralysis, syphilis, and idiocy the sugar content was normal. Connell<sup>8</sup> considers the absence of sugar in the spinal fluid a certain sign of meningitis, but its presence is no absolute proof that meningitis does not exist. The sugar content of the spinal fluid was investigated by Kopetzky<sup>9</sup> in eight normal cases, by means of the Benedict method; he found that it varied between 0.02 and 0.04 per cent. According to the same observer, in "the estimation of the presence of the carbohydrate body in the spinal fluid, and the determination of its absence, we have one of the earliest and most reliable signs of meningitis, and later a reliable test to afford information as to the progression or retrogression of the infection of the meninges."

#### PERSONAL STUDIES

We have examined the spinal fluids of fifty-nine children for non-protein nitrogen, urea, uric acid, creatinin and sugar. The reaction of the spinal fluid was tested with litmus paper in every case. A cell count, globulin test, and Wassermann reaction were also done.<sup>10</sup>

#### METHODS

The methods employed for the nonprotein nitrogenous constituents were those of Folin and Denis and their co-workers, as described by us in a previous communication.<sup>2</sup> A modification of the Lewis and Benedict method was used in our sugar estimation.<sup>11</sup>

The results of the examination of ten normal spinal fluids withdrawn for diagnostic purposes are shown in Table 1. The nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average

7. Schloss and Schroeder: *AM. JOUR. DIS. CHILD.*, 1916, **11**, 1.

8. Connell: *Quart. Jour. Med.*, 1909, **3**, 152.

9. Kopetzky: Research Prize, *Am. Laryngol., Rhinol. and Otol. Soc.*, Philadelphia, 1912.

10. Done by Drs. H. Cohen, Saunders, Gordon and Fuller of the house staff of the German Hospital.

11. Myers and Fine: *Essentials of Path. Chem.*, 1915.

amount being 21 mg. The urea varied between 7 and 13.5 mg. per 100 c.c. of fluid, the average amount being 9.9 mg. The creatinin varied between 0.7 and 1.5 mg. per 100 c.c. of fluid, the average amount being 0.9 mg.

*In the normal spinal fluids examined there was a slightly positive reaction present for uric acid in a few cases, but in not a single instance was there enough uric acid present to give a positive quantitative test.* Myers and Fine<sup>5</sup> have shown that in cases of nephritis the concentration of uric acid averaged only 5 per cent. of that in the blood. According to Cushing<sup>12</sup> the cerebrospinal fluid is chiefly secreted by the choroid plexus. The cells of the choroid plexus are relatively impermeable to

TABLE 1. —ANALYSES OF THE SPINAL FLUID IN NORMAL CHILDREN

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Non-protein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
2278	F.	5	24	Alk.	26	8.5	0	0.7	0.07	6	0	0	0
2279	F.	1½	23	Alk.	19	7.5	0	0.7	0.07	3	0	0	0
2334	M.	10	51	Alk.	23	9.5	0	0.7	0.07	25	0	0	0
2461	F.	8	44	Neut.	17	8.5	0	1	0.07	3	0	0	0
2648	F.	9	50	Alk.	19	10.5	0	1.5	0.07	1	0	0	
2615	F.	9	53	Alk.	23	11.5	0	1.5	0.07	2	0	0	
3134	F.	2	19	Neut.	20	7	0	0.7	0.1	41	±	0	
3204	M.	1½	18	Alk.	20	10	0	1	0.08	6	0	0	
3340	M.	5	..	Alk.	22	12.5	0	1	0.09	..	..	0	
3978	M.	4	32	Alk.	24	13.5	0	1	0.07	3	0	0	0
Average.....					21	9.9	0	0.9	0.07				

the passage from the blood stream of drugs and such substances as bile pigments, which in conditions of jaundice quickly stain all body tissues and fluids. From the results of our analysis we must conclude that uric acid, one of the constituents of the blood, does not pass readily through the choroid plexus into the spinal fluid in normal individuals.

The sugar content of the spinal fluid was very constant, and varied between 0.07 and 0.1 per cent., the average content being 0.07 per cent. These figures correspond very closely with those given by Schloss and Schroeder,<sup>7</sup> and are considerably higher than those reported by Kopetzky.<sup>9</sup>

In Table 2 are shown the figures obtained in the analysis of the spinal fluid as compared with the blood of normal children. Our

12. Cushing: Jour. Med. Research, 1914, **31**, 1.

results show that in normal cases lower values for the nonprotein nitrogenous constituents are obtained in the spinal fluid than in the blood. The average concentration of the nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood; the average concentration of urea in the spinal fluid averaged 82 per cent. of that in the blood; and the average concentration of creatinin in the spinal fluid averaged 60 per cent. of that in the blood.

TABLE 2.—COMPARISON BETWEEN NONPROTEIN NITROGENOUS CONSTITUENTS AND SUGAR OF BLOOD AND SPINAL FLUID

	Nonprotein N, Mg. per 100 C.c.	Urea N, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Creat- inin, Mg. per 100 C.c.	Sugar as Dextrose, Mg. per 100 C.c.
Blood.....	28	12	1.8	1.5	0.1
Spinal fluid.....	21	9.9	0	0.9	0.07

#### FLUIDS FROM DISEASED CHILDREN

The results of the analysis of the spinal fluid in twenty-one cases of chorea are given in Table 3. It is of interest to note that the figures obtained for the nonprotein nitrogenous constituents and for the reducing substances showed no variation from the normal. The cell count was above normal in only four cases. The globulin reaction was negative in every case but one, in which the result was doubtful. The Wassermann reaction of the spinal fluid was invariably negative. From the negative Wassermann reactions obtained in our cases we conclude with Morse and Floyd<sup>13</sup> that syphilis plays no direct part in the etiology of chorea. In one case of chorea with severe symptoms of long duration the *Streptococcus viridans* was found in the spinal fluid.

Tables 4, 5, and 6 give the results of the examination of the spinal fluid in cases of idiocy, syphilis, epilepsy, and enuresis. The findings showed no changes from the figures obtained in normal cases.

The spinal fluid was examined in two cases of acute nephritis (Table 7). One case without uremic symptoms showed a slight increase in the total nonprotein nitrogen. There was present a trace of uric acid, which was not observed in normal cases. The urea, creatinin and sugar content were normal. In one case of nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased. There was present a trace of uric acid. A comparison of the figures obtained in the spinal fluid and in the blood is shown. The latter were very much higher than those obtained in the spinal fluid.

13. Morse and Floyd: AM. JOUR. DIS. CHILD., 1916, **12**, 61.

We have examined the spinal fluid (Table 8) in one case of serous meningitis secondary to pneumonia, three cases of tuberculous meningitis, two cases of cerebrospinal meningitis, and one case of streptococcus viridans meningitis. In the case of serous meningitis the non-protein nitrogenous constituents and the sugar content were within normal limits, the globulin reaction was negative, and the cell count was normal. In three cases of tuberculous meningitis the total nonprotein

TABLE 3.—ANALYSES OF SPINAL FLUID IN CHOREA

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Non-protein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
1777	F.	8	49	Neut.	24	8.5	0	1.3	0.08	6	0	0	
1889	F.	12	55	Neut.	..	12	0	1	0.08	4	0	0	
2358	M.	8	39	Alk.	22	9	0	1	0.07	3	0	0	
2539	M.	7	41	Alk.	25	11	0	1.5	0.08	—	—	0	
2494	F.	4	35	Alk.	24	11.5	0	1.1	0.08	4	0	0	
2525	F.	5	38	Alk.	21	10	0	0.7	0.07	1	0	0	
1889	F.	12	54	Alk.	25	12.5	0	1	0.06	4	0	0	
2791	M.	6½	45	Alk.	25	10.5	0	1	0.08	3	0	0	0
2746	F.	7	50	Alk.	22	9	0	1	0.07	4	0	0	
3060	F.	8	42	Alk.	24	13	0	1	0.07	7	0	0	
2947*	M.	11	67	Alk.	20	10.5	0	1	0.06	11	0	0	0
3558	F.	13	94	Alk.	21	9.5	0	1	0.07	5	0	0	0
3060	F.	8	42	Alk.	18	9	0	1	0.07	4	0	0	0
3751	M.	7	36	Alk.	24	10.5	0	1	0.08	0	0	0	
3742	M.	8	50	Alk.	25	12	0	1	0.08	31	±	0	
3932	M.	7	50	Alk.	24	14.5	0	1	0.07	4	0	0	±
4153	F.	9	47	Alk.	19	11.5	0	1	0.06	5	0	0	0
4354	M.	6	42	Alk.	25	13.5	0	1	0.07	12	0	0	
4819	F.	10	53	Alk.	24	12.5	0	1	0.05	5	0	0	
4794	M.	11	69	Alk.	30	16	0	1	0.06	3	0	0	
3960	F.	8	52	Alk.	24	11.5	0	1	0.07	28	0	0	

nitrogen and the urea were normal. The creatinin was slightly increased in two cases, and was normal in one case.

Uric acid was present in every case of tuberculous meningitis. In one instance there was a trace of uric acid, and in the other two cases 0.7 and 1.2 mg., respectively, per 100 c.c. of fluid. The sugar content was normal in one case and reduced in two. The globulin reaction was invariably positive. The cell counts were much increased. In two cases of cerebrospinal meningitis, in which the meningococcus was

TABLE 4.—ANALYSES OF SPINAL FLUID IN IDIOCY

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Oreat-inin				Spinal Fluid	Blood	
1353	F.	2	25	Neut.	21	9	0	1.5	0.06	14	+	0	0	Idiocy
662	M.	1	19	Alk.	21	10.5	0	2.4	0.08	4	+	0	0	Idiocy
1775	M.	6	33	Alk.	..	11	0	1	0.08	6	+	0	0	Idiocy
2445	F.	5	23	Alk.	21	11.5	0	1	0.06	5	0	0	—	Idiocy, mongolian
2665	F.	2	22	Neut.	23	11.5	0	1	0.06	3	0	0	0	Idiocy
2680	M.	6	51	Alk.	25	10.5	0	1.5	0.07	1	0	0	0	Idiocy, mongolian *
3244	M.	8	46	Alk.	21	9	0	1	0.06	4	0	0	0	Idiocy

TABLE 5.—ANALYSES OF SPINAL FLUID IN SYPHILIS

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Oreat-inin				Spinal Fluid	Blood	
7961	M.	10	55	Neut.	15	5	0	1.5	0.06	4	0	0	4+	Syphilitic synovitis
815	F.	14	61	Neut.	24	13	Faint trace	0.5	0.07	4	0	0	4+	Bone syphilis
8633	F.	7	44	Alk.	21	10.5	0	1	0.07	22	0	10+	4+	Syphilis
4024	M.	11	61	Alk.	19	9.5	0	1	0.07	4	0	0	4+	Syphilis

TABLE 6.—ANALYSES OF SPINAL FLUID IN MISCELLANEOUS CASES

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Non-protein N	Urea N	Uric Acid	Creatinln				Spinal Fluid	Blood	
2144	F.	8	62	Alk.	24	10.5	0	0.5	0.08	4	0	0	—	Eneursis
1136	M.	6	46	Neut.	25	9.5	0	1.5	0.07	40	+	—	—	Epilepsy
1611	M.	11	73	Neut.	21	12.5	0	1	0.08	5	0	0	—	Epilepsy

TABLE 7.—ANALYSES OF SPINAL FLUID IN ACUTE NEPHRITIS

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Remarks
					Non-protein N	Urea N	Uric Acid	Creatinln				Spinal Fluid	Blood	
2208	F.	7	33	Alk.	33	13	Trace	0.8	0.08	8	0	0	—	Albumin in urine with many hyaline and granular casts; few coarse granular casts and red blood cells; phenolsulphone-phthalein output 85 per cent. McClean ratio 57; blood pressure 120 mm.; severe edema; condition improved
2674	M.	3	26	Alk.	93	46	Trace	2.4	0.12	60	0	0	—	Albumin in urine 0.15 per cent.; many red blood cells and coarse granular casts; phenolsulphone-phthalein output 4 per cent.; blood pressure 88 mm.; mercury; uremia; condition improved
2674	Blood.....				170	116	2.5	5	0.15					

TABLE 8.—ANALYSES OF SPINAL FLUID IN MENINGITIS

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.			Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis and Remarks
					Non-protein N	Urea N	Uric Acid				Spinal Fluid	Blood	
1845	M.	8	44	Neut.	11	6.5	0	0.1	8	0	0	...	Serous meningitis; lobar pneumonia; recovered
1778	F.	1½	18	Neut.	15	6.5	0.7	0.05	50	2+	0	...	Tuberculous meningitis; died
2851	F.	2	..	Neut.	10	4	Trace	0.08	900	4+	...	...	Tuberculous meningitis; died
2778	F.	5	30	Alk.	30	15	1.2	0.04	200	4+	...	...	Tuberculous meningitis; died
3303	F.	11	50	Neut.	21	9.5	0	0.04	100,000	4+	...	...	Tuberculous meningitis; died
4031	F.	9	54	Alk.	21	9.5	0	0.06	4,400	4+	...	...	Cerebrospinal meningitis (diplococcus); improved
2925	F.	6	39	Alk.	15	7.5	0	0	420	4+	...	...	Cerebrospinal meningitis (diplococcus); recovered
													Streptococcus viridans; died

TABLE 9.—ANALYSIS OF SPINAL FLUID IN INFANTILE PARALYSIS

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Non-protein N	Urea N	Uric Acid	Oreatin				Spinal Fluid	Blood
4404	F.	1½	19	Alk.	25	12	0	1.7	0.07	24	2+	0	0
4523	F.	3	30	Alk.	33	14.5	Faint trace	1.8	0.08	564	0	0	0
4908	F.	2½	26	Alk.	21	10.5	0	1.5	0.06	6	1+	0	0
5049	F.	3	..	Alk.	26	10.5	0	0.5	0.05	14	0	0	0
5106	M.	2½	..	Alk.	..	13	0	0.5	0.09	50	0	0	0



found, the nonprotein nitrogenous constituents were normal, there was no uric acid present, the sugar content was reduced in both cases, the globulin reaction was positive, and the cell counts were enormously increased. Both patients recovered. In one case of meningitis in which the *Streptococcus viridans* was found, the nonprotein constituents were normal, but sugar was entirely absent from the spinal fluid. The cell count was markedly increased, and the globulin reaction was positive. The patient died.

Five cases of infantile paralysis were examined (Table 9), all in the early stages of the disease. The nonprotein nitrogenous constituents were within normal limits, but a trace of uric acid was found in one case. The sugar content was normal. The cell count was increased in all but one instance and the globulin reaction was positive in two patients, and negative in three.

#### SUMMARY

Chemical examination of the spinal fluid in ten normal cases in children gave the following results: The total nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average being 21 mg.; the urea nitrogen varied between 7 and 13.5 mg., the average being 9.9 mg.; the creatinin varied between 0.7 and 1.5 mg., the average being 0.9 mg. In no case was there enough uric acid present in the spinal fluid to give a positive quantitative test. The sugar content varied within very narrow limits (0.07 and 0.1 per cent), the average being 0.07 per cent. The figures for the nonprotein nitrogenous constituents and the sugar content were lower in the spinal fluid than in the blood, in normal children. The concentration of total nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood, the urea 82 per cent. of that in the blood and the creatinin 60 per cent. of that in the blood.

The chemical examination of the spinal fluids from diseased children showed the following conditions:

1. In chorea the chemical examination of the spinal fluid for its nonprotein nitrogenous constituents gave results closely paralleling those obtained in normal children.
2. Chemical examination in cases of idiocy, syphilis, epilepsy, and enuresis gave similar results.
3. In acute nephritis without uremic symptoms the total nonprotein nitrogen was slightly increased and uric acid was present in small amounts. In acute nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased and uric acid was present in slight amounts. The sugar content was also increased. The figures obtained in the analysis of the spinal fluid were lower than those from the blood.

4. In serous meningitis the nonprotein nitrogenous constituents, as well as the sugar content were within normal limits. In tuberculous meningitis the total nonprotein nitrogen and the urea were normal, but the creatinin was slightly increased. Uric acid was present in every case, but the sugar content was normal or slightly reduced. In cerebro-spinal meningitis the nonprotein nitrogenous constituents were normal, but the sugar content was reduced. In a fatal case of meningitis in which the streptococcus was found, the nonprotein nitrogenous constituents were normal and sugar was absent.

5. In the early stages of infantile paralysis the nonprotein nitrogenous constituents, as well as the sugar content, were within normal limits.

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