THE HYDROGEN-ION CONCENTRATION OF CEREBROSPINAL FLUID

STUDIES IN MENINGITIS. I

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In the course of our investigation of meningitis we found it necessary to study the physicochemical conditions of the spinal fluid. We began this phase of our work with a study of the hydrogen-ion concentration of the fluid. In a previous investigation[1] in which we used methyl red as an indicator, we found that all spinal fluid was alkaline to methyl red, and that the titrable acidity of the fluid varied with different conditions, the fluid of tuberculous meningitis showing the same acidity, or, as we then termed it, the same alkalinity as the normal fluid, and the fluid of epidemic meningitis showing a higher acidity than the normal. We soon discovered, however, that the fluid on which we were working, had been standing too long before examination to give an accurate idea of the acidity. Besides, we were also aware of the fact that the titrable acidity did not represent the true hydrogen-ion concentration of the fluid. We therefore decided to determine whether a similar variation in the free H-ion concentration occurs in different conditions. With this in view, we examined both meningitic and nonmeningitic fluids.

METHOD

At first we made use of the gas-chain method described by Michaelis[2] and the one suggested by Hildebrandt[3] for the determination of the H-ion concentration of spinal fluid. Very early in our work, however, we discovered that acidity measured by the gas-chain method was considerably lower than that determined by the indicator method against standard solutions. This discrepancy was found to be due not to any fault of either method, but to the variations occurring in the H-ion concentration of fluid that had been standing even one-half hour, the time it takes to reach the laboratory and put the gas-chain apparatus in working order. No such discrepancy was apparent when we used the indicator method at the time the readings with the gas-chain became constant. For the immediate determination of the H-ion

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1 Levinson, A.: Arch. Pediat., 1916, 33, p. 241.
2 Die Wasserstoffionenkonzentration, 1914.
3 Jour. Am. Chem. Soc., 1913, 35, p. 847.

concentration we made use of the indicator method and for the old fluid we used either or both methods.

In preliminary experiments with the indicator method we followed the procedure recommended by Sörenson,[4] comparing the spinal fluid to the standard solutions described by Palmer and Henderson.[5] Since we had found that fluid examined immediately after withdrawal from the body was colorless to phenolphthalein, and since we could not use neutral red, the next indicator in the series, because of the difficulty of distinguishing color at night, the time when most of our punctures were performed, we made the phenolphthalein slightly alkaline by adding 1 c.c. of N/10 NaOH to 10 c.c. of phenolphthalein. We used 0.09 c.c. of the alkalinized phenolphthalein to 1 c.c. of spinal fluid, comparing this to 1 c.c. of the standard solutions. This showed a rough distinction between a H-ion concentration expressed in terms of P_H of 8.6, 8.0, 7.4, and 7.1.* To distinguish the reaction of the spinal fluid still further we used the Levy-Rowntree-Marriott[6] standards, adding 0.2 c.c. of the indicator, (0.01% phenolsulphonephthalein) to 3 c.c. of spinal fluid, as recommended by the authors. On checking the standard color tubes against the gas-chain method both with spinal fluid and with borate and phosphate mixtures, we found that with our technic the readings with the colorimetric tubes corresponded to those of the gas-chain method up to a P_H of 8.1. After that point it was difficult to distinguish the quality of the color in the standard tubes, because of the difference in the intensity of the colors. Wherever possible, therefore, we used either the gas-chain method alone or both the gas-chain and the indicator method, on fluids standing for any length of time, placing more credence on the results with the gas-chain.

The spinal fluid we obtained was withdrawn by lumbar puncture in the usual manner, none but perfectly clear fluid being used by us in our work. The test tubes were closed with cotton plugs to conform with the usual clinical methods, except in the case of the special tests noted below. The fluids were kept at room temperature, usually about 20-23 C. The material in these investigations was secured from the Psychopathic Hospital and from the Michael Reese Hospital, both of Chicago. In this connection we wish to express our thanks to Dr. V. Finsand, resident physician of the Psychopathic Hospital, Dr. E. Armstrong of the County Hospital, and the staff of the Michael Reese Hospital for their cooperation in supplying us with material.

The Results with Nonmeningitic Fluids

We examined 177 nonmeningitic spinal fluids drawn from 170 patients, including 20 cases of meningism, that is, cases that presented symptoms of meningitis, although the subsequent course of the disease proved them not to be meningitic in character. Of this number, 5 turned out to be cases of pneumonia, 2 of gastro-intestinal intoxication, 2 of nephritis, 2 of post-diphtheritic paralysis, 2 of poliomyelitis, 1 of tetanus, 1 of Little's disease, and 5 turned out to be meningism accompanying other infectious diseases. All of these occurred in children. Among the other cases there were 24 that proved to be cases of general paresis, 21 of alcoholic psychosis, 3 of dementia praecox,

* P_H, as is well known, is a term recommended by Sörenson indicating the negative exponent of the H-ion concentration. Thus P_H 7.4 = N×10—7.4. H-ions, being a fraction of a normal solution of free dissociated H^+. Therefore the higher the P_H, the lower the acidity.

[4] Ergebnisse der Physiologie, 1912, 12, p. 393.

[5] Arch. Int. Med., 1913, 12, p. 153.

[6] Arch. Int. Med., 1915, 16, p. 389.

TABLE 1

H-ION CONCENTRATION OF NONMENINGITIC SPINAL FLUID

Case	Diagnosis	PH			
		Immediate	½ Hour	1 Hour	2 Hours
1	Little's disease	.....	.....	.....	.....
1	Little's disease	.....	.....	.....	.....
2	Tetanus	.....	.....	.....	.....
3	Pneumonia	.....	.....	.....	.....
4	Gastro-enteritis	.....	.....	.....	.....
5	Brain tumor	.....	.....	.....	.....
6	Endarteritis	.....	.....	.....	.....
7	Typhus	.....	.....	.....	.....
8	Brain tumor	.....	.....	.....	.....
9	Tic	.....	.....	.....	8.0 (b)
10	General paresis	.....	.....	.....	8.0 (b)
11	Delirium tremens	.....	.....	.....	.....
12	General paresis	.....	.....	.....	.....
13	Psychosis	.....	.....	.....	.....
14	Tubercle of brain	7.4 (b)	.....	.....	.....
15	Juvenile paresis	7.4 (b)	.....	.....	.....
16	Alcoholic	.....	7.4+(b)	.....	.....
17	General paresis	.....	7.4+(b)	.....	.....
18	Alcoholic	.....	.....	.....	.....
19	Paranoia	7.5 (c)	.....	.....	.....
20	Epilepsy	7.4 (c)	.....	.....	.....
21	Epilepsy	.....	7.5 (c)	.....	.....
22	C. Sp. Lues ?	.....	.....	7.9 (c)	.....
23	Paresis	.....	.....	7.7 (c)	.....
24	Psychosis	.....	.....	7.7 (c)	.....
25	Psychosis	7.5 (c)	.....	.....	.....
26	Psychosis	7.6 (c)	.....	.....	.....
27	Psychosis	7.5 (c)	.....	.....	.....
28	Psychosis	7.5 (c)	.....	.....	.....
29	Brain tumor	.....	.....	.....	8.0 (c) 8.0 (b)
30	Pneumonia	.....	.....	.....	.....
31	Alcoholic	7.4 (c)	7.4 (c)	7.5 (c)	7.9 (c)
32	General paresis	7.4 (c)	.....	.....	.....
33	Psychosis	7.7 (c)	.....	.....	.....
34	Psychosis	7.5 (c)	.....	.....	.....
35	Alcoholic	7.4 (c)	.....	.....	.....
36	Psychosis	7.4 (c)	.....	.....	.....
37	Psychosis	7.5 (c)	.....	.....	.....
38	Alcoholic	7.5 (c)	.....	.....	.....
39	Alcoholic	7.4 (c)	.....	.....	.....
40	General paresis	7.5 (c)	.....	.....	.....
41	Psychosis	7.4 (c)	7.6 (c)	.....	.....
Mixture	.....	7.4 (c)	7.8 (c)	.....	.....
42	Psychosis	7.4 (c)	.....	.....	.....
43	Psychosis	7.5 (c)	.....	.....	.....
Mixture	Psychosis	7.4 (c)	.....	.....	.....
Mixture	.....	.....	.....	.....	.....
44	Poliomyelitis	.....	.....	7.7 (c)	.....
Mixture	General paresis	7.4 (c)	.....	.....	.....
45	.....	.....	.....	.....	.....
46	Pneumonia	7.7 (c)	.....	.....	.....
Mixture	.....	7.4 (c)	.....	.....	.....
47	.....	7.4 (c)	.....	.....	.....
48	Psychosis	7.5 (c)	.....	.....	.....
49	Meningism	7.5 (c)	.....	.....	.....
50	Poliomyelitis ?	.....	7.6 (c)	.....	.....

* Corked.

TABLE 1—*Continued*

H-Ion Concentration of Nonmeningitic Spinal Fluid

PH						
3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days and Over
.....	.....	.....	.....	.....	.....	8.56 (a)
.....	.....	.....	.....	.....	.....	8.14 (a)
.....	.....	.....	.....	.....	.....	8.6 (a)
.....	.....	.....	.....	.....	.....	9.08 (a)
.....	.....	.....	.....	.....	.....	8.3 (a)
.....	.....	.....	.....	.....	.....	7.89 (a)
.....	.....	.....	.....	.....	8.0+(b)	.....
.....	.....	.....	.....	.....	8.6—(b)	.....
.....	.....	.....	.....	.....	.....	8.6— (b)
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	8.0+(b)	.....
.....	.....	.....	.....	.....	.....	8.6— (b)
.....	.....	.....	8.0 (b)	.....	.....	.....
.....	.....	8.6—(b)	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	8.0 (c)	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	8.0 (c)	.....	.....	.....	8.4 (c)
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	8.2 (c)
.....	.....	8.0 (c)	8.1 (c)	8.1 (c)	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	8.1 (a)	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	8.1 (c)	.....	.....	.....	.....	.....
.....	.....	8.1 (c)	8.1 (c)	.....	.....	.....
.....	.....	.....	.....	8.1 (a)	.....	.....
.....	.....	.....	.....	8.1 (c)	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	8.1 (a)	.....	.....
.....	.....	.....	.....	8.1 (c)	.....	.....
.....	.....	.....	.....	7.7 (a)*	.....	.....
.....	.....	.....	.....	7.7 (c)	.....	.....
.....	.....	.....	.....	8.1 (c)	.....	.....
.....	.....	8.1 (c)	.....	.....	.....	.....
.....	.....	8.1 (c)	.....	.....	.....	8.1 (c)
.....	.....	.....	.....	.....	8.2 (a)	.....
.....	.....	.....	8.1 (a)	.....	.....	.....
.....	.....	.....	.....	.....	8.2 (c)	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....

2 of brain tumor, 1 of solitary tubercle of the brain, 1 of juvenile paresis, 2 of endoarteritis, 1 of epilepsy, and 1 of paronoia. The rest were cases of psychoses, the etiologic diagnosis of which was not established either clinically or by laboratory methods.

We found that the spinal fluids of nonmeningitic cases when examined immediately after withdrawal showed a greater acidity than that reported by other investigators. Our findings showed an H-ion concentration expressed in a P_H ranging from 7.4-7.6 on immediate examination. In only 2 cases of meningism did we get a P_H of 7.7. A positive Wassermann test, brain tumor, or even poliomyelitis seemed to have no effect on the H-ion concentration on immediate examination. The change in the H-ion concentration is so rapid, however, that in fluid examined 2 hours or later after removal from the body, we found the P_H to range from 7.9-8.1—the same as that reported by other investigators. We give in Table 1 cases showing our average results, indicating the method used by the letters a, b, c; "a" represents the gas-chain method, "b" the alkalinized phenolphthalein compared to the Sörenson standards, and "c" the Levy-Rowntree-Marriott[6] indicator compared to the standard colorimetric tubes. A typical change in the H-ion concentration is illustrated in Curve 1, together with the change in meningeal fluids. The results obtained by phenolphthalein compared to the Sörenson standards, are often marked with an additional + and — sign. This means that P_H of the spinal fluid was higher or lower than the figure given, but how high or how low was not determined.

The change on standing of nonmeningitic fluids is quite constant for the first 5 hours, reaching a P_H of 8.1. After that time, however, although the change is still fairly typical, it is not constant, being influenced by such factors as temperature and the amount of fluic in the tube and probably the content of CO_2 in air. Some fluids rise to a P_H of 8.6, and sometimes 9, whereas others retain a P_H of 8.1. The effect of volume on the H-ion concentration we shall discuss later under the subject of mechanism.

Cavazzani[7] and Mott[8] draw attention to the fact that fluid drawn at night is more acid than that drawn during the day. The fluids we drew at night usually showed a P_H of 7.4-7.5, and the fluids drawn during the day generally showed a P_H of 7.5-7.6. Whether this difference is constant or not is a matter that requires further study.

DISCUSSION

Some of the earlier investigators who used the indicator method found the spinal fluid to be more acid than the commonly accepted P_H of 8.1. Cavazzani[7] found the spinal fluid of 2 cases of hydrocephalus to have a neutral reaction. Concetti[9] found the spinal fluid to be alkaline 3 times and weakly alkaline 4 times. Bisgaard[10] found the 2 cases of spinal fluid he examined immediately to be more acid than the borate mixture, 5.7 plus HCl, which is about 8.1. From this, Bisgaard concluded that phenolphthalein was not the proper indicator.

[7] Zentralbl. f. Physiol., 1896, p. 145.
[8] Lancet, 1910, 2, p. 1.
[9] Arch. f. Kinderheilk., 1898, 24, p. 161.
[10] Biochem. Ztschr., 1914, 58, p. 1.

Kopetszky[11] reports that all normal fluids are neutral to litmus paper. The H-ion concentration, according to his findings, must therefore be lower than P_H 8. Especially significant is the work of John Turner[12] who not only knew the high H-ion concentration of the fluid, but was also aware of the fact that the concentration changes on standing. To quote him:

"In all the cases of this series and in 20 examined 15 years ago, I have obtained an alkaline reaction (and not amphoteric) to litmus paper, but with phenolphthalein the great majority have an acid reaction. The degree of acidity, however, is in many cases very slight. A very faint, pink solution of phenolphthalein was poured into two small beakers, so that the tint in both was similar in looking down at them as they stood upon a porcelain slab. A little of the fluid was then added to one beaker and generally the pink color was immediately discharged. I found that the fluid left unstoppered in my room, where gas is constantly burning, rapidly becomes alkaline, whereas similar fluid in stoppered bottles retained its acidity, and that in my later examinations where this source of fallacy was recognized and excluded, the results tend more and more to be uniformly acid with phenolphthalein."

On the other hand, there are a number of observers who employed more modern methods in the determination of the H-ion concentration and who found it to be low. Polyani[13] determined the H-ion concentration of one fluid drawn from a case of hydrocephalus, by the compensation method with the use of the Farkas-Szilisch electrode. He found the H-ion concentration to be 9.084×10^{11}. Hurvitz and Tranter,[14] who used the Levy-Rowntree-Marriott standards, found the P_H of spinal fluids to vary between 8.15 and 8.30 with an average of 8.26, this being somewhat lower when the fluid was dialyzed, the average then being 8.11. Weston[15] found the dialyzed fluid to vary between 7.9 and 8.3 with an average of 8.12.

We can account for the low concentration found by these investigators by the fact that their results were obtained on fluids that had been standing for some time. We, too, obtained a low H-ion concentration when we examined fluid that had been allowed to stand, and a high one when we examined fluids immediately on their withdrawal from the body. Very recently, in fact, during the preparation of this paper, Felton, Hussey, and Bayne-Jones[16] also made note of this fact. Their results, however, differ somewhat from our results, in that they

[11] Manhattan Eye, Ear and Throat Hospital Reports, 14, 1913.
[12] Jour. Ment. Sc., 1910, 56, p. 485.
[13] Biochem. Ztschr., 1911, 34, p. 205.
[14] Arch. Int. Med., 1916, 17, p. 828.
[15] Jour. Med. Research, 1916, 35, p. 367.
[16] Arch. Int. Med., 1917, 19, p. 1085.

found the P_H of fluids examined immediately to vary from 7.7-7.9, whereas we found the P_H to range from 7.4-7.6 on immediate determination.

RESULTS WITH MENINGITIC FLUIDS

In examining the fluids from cases of meningitis we employed the methods outlined for nonmeningitic fluids. We examined 74 specimens of 62 cases of tuberculous meningitis, 104 specimens of 62 cases of epidemic meningitis, and 12 specimens of 8 cases of pneumococcus meningitis. Among the cases of tuberculous meningitis we include in our records only those in which diagnosis was established either by the findings of tubercle bacilli in the spinal fluid or postmortem. All cases of epidemic and pneumococcus meningitis reported here were diagnosed by the finding of the respective bacteria in direct smear and culture.

We found that fluid from cases of tuberculous meningitis differed in no respect from that of normal cases, the P_H being 7.4-7.6 immediately after withdrawal and ascending to 8.1 or higher (Table 2). In some tuberculous fluids the H-ion concentration decreased in a much shorter time than in the normal fluid. Whether this rapidity of decrease in the H-ion concentration is generally characteristic of tuberculous fluids further experimentation will tell.

Fluid from cases of epidemic meningitis showed a H-ion concentration slightly higher than that of normal, when examined directly after withdrawal, the P_H being 7.2-7.5, the average being 7.3. The greatest deviation from normal and tuberculous fluid, however, was observed on fluid allowed to stand, the H-ion concentration then decreasing slowly in some cases, remaining stationary in others, and increasing in still others (Table 3). The more turbid the fluid, the longer it retained its acidity. The sicker the patient, the longer the fluid retains its acidity. Administration of serum alters the H^+ concentration only in the cases that are improving (Table 4). The H-ion concentration of fluids of pneumococcus meningitis showed a strong resemblance to that of epidemic meningitis. However, owing to the small number of cases under our observation we shall not include them in our present series.

MECHANISM OF THE CHANGES OCCURRING IN SPINAL FLUID ON STANDING

Nonmeningitic.—That changes in the acidity of spinal fluid occur on standing is not a novel finding. This phenomenon has been pointed out by Bisgaard,[10] Kopetzky,[11] Turner,[12] and Levinson.[1] In this work,

TABLE 2

H+ Concentration of Fluid from Tuberculous Meningitis

Number	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	.....	.....	.....	.....	.....	.....	.....	.....	8.69(a)	8.98(a)	
2	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.9(a)*	
3	.....	.....	.....	7.9(b)							
4	.....	.....	.....	8.0(b)	.....	.....	.....	.....	.....	8.0+(b)	8.6(b)
5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	8.6(b)
6	7.4(b)										
7	7.4(b)										
8	7.4(b)										
9	7.4(b)										
10	7.4(b)	.....	.....	.....	.....	.....	.....	8.0(b)	.....	8.0+(b)	
11	.....	.....	.....	7.6(c)	.....	.....	8.2(c)				
12	7.4(b)										
13	.....	.....	.....	.....	.....	.....	.....	.....	.....	8.2(c)	
14	7.4(c)	.....	.....	.....	.....	.....	.....	.....	.....	8.2(c)	
15	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	8.0(c)*
16	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	8.1(c)
17	.....	.....	.....	.....	.....	.....	.....	8.0(c)			
18	.....	.....	8.1(c)	.....	.....	.....	.....	.....	8.8(a)		
19	7.4(c)	.....	.....	.....	.....	8.1(c)					
20	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.8(c)*	
21	7.4(c)	.....	.....	.....	7.8(c)	.....	7.9(c)				
22	.....	.....	.....	.....	.....	.....	.....	.....	8.1(c)		
23	.....	.....	.....	.....	.....	.....	.....	.....	8.1(c)		
									8.4(a)		
24	.....	.....	.....	.....	.....	.....	.....	7.7(c)			
25	7.6(c)										
26	7.4(c)	7.6(c)	7.6(c)	7.8(c)	7.8(c)	.....	.....	.....	.....	8.1(c)	
										8.5(a)	
27	.....	.....	.....	7.75(a)							
				7.7 (c)							
28	7.4(c)	.....	7.6(c)	.....	.....	.....	.....	.....	.....	8.2(c)	

* Corked.

TABLE 3

H+ Concentration of Fluid of Epidemic Meningitis Before Administration of Serum

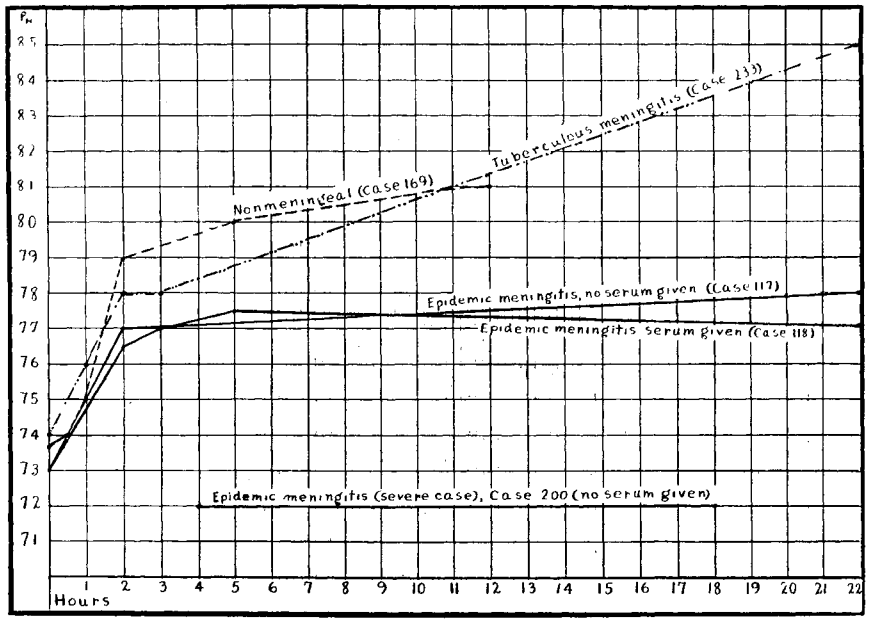
Number	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	.....	.....	.....	.....	.....	.....	.....	.....	7.4(b)		
2	7.4(b)										
3	.....	.....	.....	.....	.....	.....	7.0(b)				
4	7.1(c)	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.8(c)
5	7.3(c)	.....	.....	7.7(c)	.....	.....	.....	.....	.....	7.8(c)	
6	.....	.....	.....	.....	.....	.....	.....	7.4(c)			
7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.2(c)
8	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.1(c)
9	.....	.....	.....	.....	.....	.....	.....	.....	7.9(c)		
10	.....	.....	.....	.....	.....	.....	.....	.....	7.9(c)		
11	.....	.....	.....	.....	.....	.....	.....	7.4(c)			
12	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.8(c)	
13	.....	.....	.....	.....	.....	7.2(c)	.....	.....	7.2(c)	.....	7.1(a)
14	.....	.....	.....	.....	.....	7.3(c)					
15	.....	.....	.....	.....	.....	7.3(c)	.....	.....	.....	7.4(c)	7.2(c)
16	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.7(c)	7.8(c)
17	.....	.....	.....	.....	7.7(c)						
					7.7(a)						
18	7.3(c)	7.4(c)	.....	.....	.....	.....	.....	.....	7.6(c)	7.6(c)	7.9(c)
19	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	6.6(c)
											6.0(a)
20	7.4—(c) 7.5	.....	.....	.....	.....	.....	.....	.....	8.1(c)		
21	7.3—(c) 7.4	.....	.....	.....	.....	.....	.....	.....	7.8(c) 7.8(a)	7.8(a)	
22	7.3(c)	.....	.....	.....	.....	.....	.....	.....	.....	7.9(c)	

TABLE 4

H-ION CONCENTRATION OF FLUID OF EPIDEMIC MENINGITIS AFTER ADMINISTRATION OF SERUM*

Number	PH										
	Immediate	½ Hour	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	12 Hours	18 Hours	24 Hours	2 Days or Over
1	7.4—(b)										
2	7.4—(b)										
3	7.4—(b)										
4	.....	.....	.....	.....	.....	7.0(b)					
5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.4(b)
6	.....	.....	.....	.....	.....	.....	.....	.....	7.4(b)		
7	.....	.....	.....	.....	.....	.....	.....	7.0(b)			
8	.....	7.1(b)	.....	.....	.....	.....	.....	.....	7.4(b)		
9	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.1(c)	
10	.....	.....	.....	.....	.....	.....	7.4(c)				
11	7.3(c)										
12	.....	.....	.....	7.7(c)							
13	.....	.....	.....	.....	.....	.....	.....	7.6(c)	7.8(c)		
14	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.2(a)
15	7.1(c)	.....	.....	.....	.....	.....	.....	.....	7.9(c)		
16	.....	.....	.....	.....	.....	.....	.....	.....	8.1*		
17	7.3(c)	.....	.....	7.6-7(c)	.....	7.7—(c)	7.7—7.8 (c)	.....	.....	7.7(c)	
18	.....	7.4	.....	.....	.....	.....	.....	.....	8.2		

* Diagnosis was not settled.



Curve 1. Change in H^+ concentration of 3 types of spinal fluids.

however, we were interested principally in finding the causes underlying the change. As spinal fluid is drawn into ordinary test tubes, we at first thought it possible that changes in acidity on standing might be due to the glass rather than the fluid. We discarded this idea, however, when we found that fluids left in nonsol glass also showed quantitatively the same degree of change. Having eliminated this possibility, we sought the cause of the change in the fluid itself.

There are only two possible sources for the changes taking place in the fluid on standing; one is the loss of volatile substances, such as CO_2, and the other is the formation of alkaline substances in the fluid, such as ammonia. To determine which is the factor responsible for the change, we instituted the following experiments:

We took a fluid immediately after its withdrawal from the body and divided it into 2 parts, 1 of which we examined directly and found its P_H to be 7.4, and the other portion we put in a beaker and introduced immediately into a desiccator containing 20% NaOH. We allowed the fluid to remain in the

TABLE 5

CHANGES IN H^+ CONCENTRATION ON REMOVAL OF CO_2 BY EXPOSURE TO ALKALI IN DESICCATOR

Case	Fluid Drawn	PH Immediately	Exposed to Alkali	Exposed to Air	Examined	PH
190	6:55 p. m.	7.4	12 minutes		7:07 p. m.	7.7 - 7.8
190	6:55 p. m.	7.4	20 minutes		7:15 p. m.	7.8
190	6:55 p. m.	7.4	20 minutes	7 minutes after 20 minutes exposure to alkali	7:22 p. m.	7.8 - 7.9
190	6:55 p. m.	7.4	27 minutes	38 minutes after 27 minutes exposure to alkali	7:55 p. m.	7.8 - 9
190	6:55 p. m.	7.4	20 minutes	13 hours	11:22 a. m.	8.1
188	7:08 p. m.	7.4	10 minutes		7:13 p. m.	7.7 - 7.8
188	7:08 p. m.	7.4	30 minutes		7:38 p. m.	7.8
188	7:08 p. m.	7.4	30 minutes	3 minutes	7:36 p. m.	7.8
186	7:45 p. m.	7.4	6 minutes		7:51 p. m.	7.6 - 7.7
186	7:45 p. m.	7.4	25 minutes		8:10 p. m.	7.9

desiccator for periods varying from 10 to 30 minutes. After each removal from the desiccator we examined the fluid and found its acidity to be greatly decreased, from a height of 7.6-7.7 attained in 6 minutes to 7.8 in 20 minutes and 7.9 in 25 minutes, showing clearly that the removal of CO_2 from the fluid has the effect of causing a decrease in the H-ion concentration in a short time (Table 5). We may state here that the fluid which had been left in the vacuum without NaOH also showed a rapid decrease in the H-ion concentration showing that the loss of CO_2 thus accelerated under this condition decreased the H-ion concentration of the fluid in a similar way.

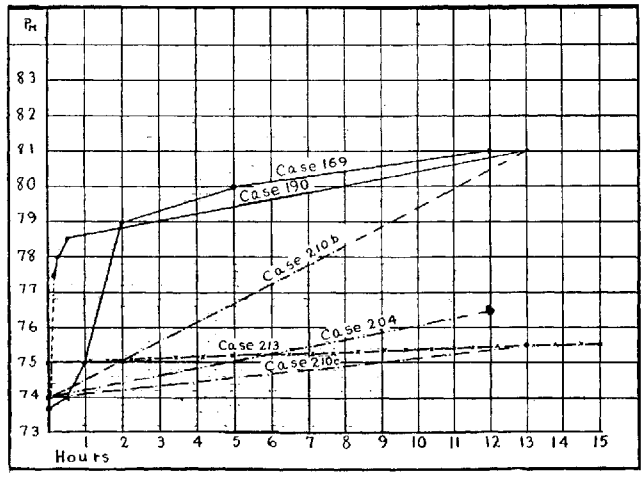
In order to ascertain whether the decrease in the H-ion concentration is due entirely to CO_2 and no other factor, we corked the fluid tightly directly after its removal from the body. If the loss of CO_2 is the sole cause of the decrease in the H-ion the tightly corked fluid ought to retain the original P_H

TABLE 6

H+ Concentration of Fluids Standing in Corked Tubes

Number	Age	Diagnosis	Date Drawn	Date Examined	Interval	Stoppered With	PH
Mixture			p.m.	p.m.			
210a	27	Alcoholic	6/25/17 – 7:15	6/25/17 – 7:15	Immediately		7.4
	38	Alcoholic	6/25/17 – 7:20	6/25/17 – 7:20	Immediately		7.4
				a.m.			
210b	27	Alcoholic	6/ 5/17 – 7:15				
	38	Alcoholic	6/25/17 – 7:20	6/26/17 – 8:00	13 hours	Cotton	8.1
210c	27	Alcoholic	6/25/17 – 7:15	6/26/17 – 8:00	12 hours	Paraffined cork (few bubbles below cork)	7.5-7.6
	38	Alcoholic	6/25/17 – 7:20				
211a	43	Alcoholic	6/25/17 – 7:28	6/25/17	Immediately		7.5
	46	Alcoholic	6/25/17 – 7:37	6/25/17	Immediately		
211b	43	Alcoholic	6/25/17 – 7:28	6/26/17 – 8:10		Cotton	
	46	Alcoholic	6/25/17 – 7:37		12½ hours		8.1
211c	43	Alcoholic	6/25/17 – 7:28	6/26/17 – 8:10	12½ hours	Paraffined cork	7.5-7.6
	46	Alcoholic	6/25/17 – 7:37				
211d	43	Alcoholic	6/25/17 – 7:28	6/26/17 –11:17	15½ hours	Paraffined cork replaced after 3 c.c. removed for exam. at 8:10, leaving 3 c.c. space in 6 c.c. tube	
	46	Alcoholic	6/25/17 – 7:37				7.6
212	55	Alcoholic	6/25/17 – 7:48	6/25/17 – 7:52	4 minutes		7.4
b	55	Alcoholic	6/25/17 – 7:48	6/26/17 –11:05	15 hours	Paraffined cork	7.5-7.6
c	55	Alcoholic	6/25/17 – 7:48	6/26/17 –11:30	15 hours	Cotton	8.2
				p.m.			
d	55	Alcoholic	6/25/17 – 7:48	6/28/17 –12:30		Cotton	7.9
213	39	Alcoholic	6/25/17 – 8:00	6/25/17 – 8:02	2 minutes		7.5
b	39	Alcoholic	6/25/17 – 8:00	6/26/17 –11:25	15½ hours	Paraffined cork	7.5-7.6
218	1 yr.	Pneumonia	6/26/17 – 1:30	6/26/17 – 1:30	Immediately		7.5-7.6
b	1 yr.	Pneumonia	6/26/17 – 1:30	6/28/17 –12:30	47 hours	Paraffined cork	7.5-7.6
c	1 yr.	Pneumonia	6/26/17 – 1:30	6/28/17 –12:30	47 hours	Cotton	8.2
204	46	Pulmonary tuberculosis	6/18/17 – 7:15	6/18/17 – 7:30	15 minutes		
	42	Alcoholic	6/18/17 – 7:20		10 minutes		7.4
	38	General paresis	6/18/17 – 7:30		Immediately		
				a.m.			
b	38	General paresis	6/18/17 – 7:30	6/19/17 – 7:30	12 hours	Cotton	8.1
c	38	General paresis	6/18/17 – 7:30	6/19/17 – 7:30	12 hours	Paraffin; left 3 c.c. space above volume of liquid	7.6-7.7
				p.m.			
205	29	Alcoholic	6/18/17 – 7:40	6/18/17 – 7:53	11 minutes		
	34	Alcoholic	6/18/17 – 7:45		8 minutes		7.4
	36	Alcoholic	6/18/17 – 7:53		Immediately		
				a.m.			
b	36	Alcoholic	6/18/17 – 7:53	6/19/17 – 7:55	12 hours	Cotton	8.1
c	36	Alcoholic	6/19/17 – 7:53	6/19/17 – 7:55	12 hours	Paraffined; 1 c.c. of space left on top of fluid	7.5-7.6

or be only slightly above it. If ammonia formation is responsible for the change the H-ion concentration ought to decrease. We found that fluid in tightly corked tubes with all the air excluded (no bubble on the top) retained its original P_H, proving that CO_2 is the only factor responsible for the change (Table 6). We followed the experiment up further by filling the test tubes with different amounts of fluid, leaving various amounts of space between the fluid and the cork. In examining for the P_H we found that the greater the space above the fluid, the higher the P_H (Table 6). There is still a possibility that the increase in the P_H of fluid standing in a tube with cotton stopper may be due to the absorption of ammonia from the air. That this factor, if present, is negligible is shown by the following experiment: We divided a fluid into 2 portions, 1 of which we exposed to ammonia-free air in a desiccator, and the other we left in the ordinary laboratory air. After 30 minutes we examined the 2 fluids for their H-ion concentration and found it to be the same in both cases, showing that the usual decrease in the H-ion concentration of a fluid is not due to absorption of ammonia from the air (see Curve 2).



Curve 2. Change in H^+ concentration of nonmeningitic fluids on standing at room temperature under various conditions. Case 169. Plugged with cotton. Case 190. Immediately after withdrawal, exposed to CO_2 free air in desiccator (dotted line) and later left with cotton plug. Case 210b. Plugged with cotton; Case 210c, the same fluid as b, but corked with cork—a few bubbles at the top. Case 204. Six c.c. tube, half filled, and tightly corked; cotton plugged fluid was same as Case 210b (8.1). Case 213. Almost perfectly sealed with cork, without any air bubble above the fluid.

From these experiments it follows that if the spinal fluid is corked tightly the determination of the H-ion concentration can be made even hours after standing, provided no space is left for the escape of CO_2. When the tube is cotton-stoppered the amount of fluid in the tube and the portion taken must be ascertained.

Tuberculous Meningitis.—For the study of tuberculous fluids we tried similar experiments as those we had used for normal and we found, as we had in

the case of normal, that fluid in a tightly corked tube retained its original P_H (Table 7), indicating that the escape of CO_2 is the principal factor determining the change on standing.

Epidemic Meningitis.—The slight but constantly higher H-ion concentration of the fluid in epidemic meningitis as compared to normal, on immediate examination, we believe, can be explained by the fermentation of the dextrose in

TABLE 7

TUBERCULOUS FLUID, CORKED

Fluid	Date Drawn	Date Examined	Interval	How Stoppered	PH
B.	6/28/17 9:10				7.4
B.		6/28/17 3:05	5 hours	Cork	7.4
B.		6/28/17 3:05	5 hours	Cotton	7.9
A. C.	7/13/17 11 a. m.	7/13/17 11 a. m.	Immediately		7.5–6
	7/13/17	7/14/17 11 a. m.	24 hours	Cork	7.5–6
	7/13/17	7/14/17 11 a. m.	24 hours	Cotton	8.0

TABLE 8

FLUID FROM EPIDEMIC MENINGITIS, WITH CORK AND COTTON STOPPER

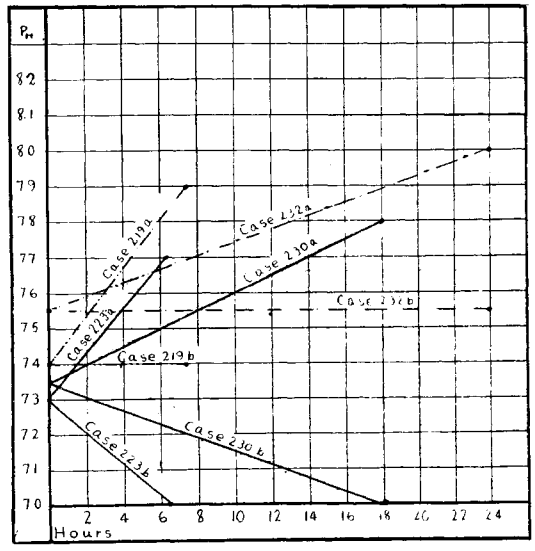
Diagnosis	Date Drawn	Date Examined	Interval	Stoppered With	PH
Epidemic meningitis	6/30/17 12:20 p.m.	6/30/17 12:20 p.m.	Immediate		7.3
		6:35 p.m.	6¼ hours	Paraffined cork	7.0
		6:35 p.m.	6¼ hours	Cotton plug	7.7
Epidemic meningitis	7/ 6/17 2:30 p.m.	7/ 6/17 2:30 p.m.	Immediate		7.4
		7/ 7/17 8:30 a.m.	18 hours	Paraffined cork	7.3
		7/ 7/17 8:30 a.m.	18 hours	Cotton	8.2
Epidemic meningitis	7/11/17 11:30 a.m.	7/11/17	Immediate		7.4-7.5
		7/12/17 4:30 p.m.	17 hours	Paraffined cork	7.4
		4:30 p.m.	17 hours	Cotton	8.1
Epidemic meningitis	7/11/17 1:30 p.m.	7/11/17 1:30 p.m.	Immediate		7.3-7.4
		7/12/17 7:30 a.m.	18 hours	Paraffined cork	7.0
			18 hours	Cotton	7.8
Epidemic meningitis	7/14/17	7/14/17	Immediate		7.3
		7/15/17	22 hours	Paraffined cork	7.1
			22 hours	Cotton	7.9

the spinal fluid by the bacteria—a fact that has been brought out by several investigators. As for the mechanism underlying the slow decrease in the H-ion concentration of epidemic fluid, there are several possibilities to be considered, such as a slower loss of CO_2 in the fluid on standing; a constant CO_2 production by the cells present in the sediment of the fluid; lactic acid for-

mation due either to further fermentation of sugar by the bacteria in the test tube or to a destruction of cells on standing.

We found that the H-ion concentration in these fluids increased on standing in tightly corked tubes, from 7.4 to 7.0. This indicates that there is not only no loss of CO_2, but that there is also a formation of certain acids on standing, a fact quite different from nonmeningitic and tuberculous fluids (Table 8).

In order to study the cause of this increase of acidity the following experiments were made: We put 1 c.c. of tuberculous meningitic fluid in 1 chamber of the biometer (Tashiro[17]), and exactly the same amount of epidemic fluid in the other chamber of the biometer. We found that the tuberculous fluid gave off more CO_2 than the epidemic, showing that although both tuberculous and epidemic fluids give off CO_2 constantly, tuberculous fluid loses more CO_2 than does epidemic. This would suggest that the increased acidity in epidemic meningitis is not due to a greater production of CO_2, but probably to the production of some other acid, very likely lactic acid (Curve 3).



Curve 3. Different effects of corking on tuberculous and epidemic meningeal fluids. Case 219a, tuberculous meningitis, cotton-plugged; b, same fluid, tightly corked (no air above). Case 232a, tuberculous meningitis, cotton-plugged; b, same fluid, corked (no air above). Case 223a, epidemic meningitis, cotton-plugged; b, same fluid, tightly corked (no air above); Case 230a, epidemic meningitis, cotton-plugged; b, same fluid, tightly corked (no air above).

SUMMARY

Spinal fluid of nonmeningitic cases covering a variety of conditions, is almost neutral, the P_H varying between 7.4-7.6 if the fluid is examined immediately on withdrawal from the body. The H-ion concentration of this fluid decreases steadily on standing. If the fluid is put into tightly corked tubes it does not change its H-ion concentration.

[17] A Chemical Sign of Life. 1917.

The decrease of acidity is most probably due to an escape of CO_2 from the fluid.

Fluid from cases of tuberculous meningitis acts exactly like normal fluid, except that frequently the H-ion concentration shows a more rapid fall than the normal.

The H-ion concentration in epidemic meningitis varies according to the severity of the disease. Usually it is 7.3-7.4 immediately on withdrawal, decreasing very slowly. In some cases it even increases on standing with cotton plug. Put into a tightly corked tube, the fluid shows an increase in the H-ion concentration. The increase of the H-ion concentration of the fluid on standing is most likely due to a production of lactic acid in the fluid.