THE ABSORPTION OF PHENOLSULPHONEPHTHALEIN
FROM THE SUBARACHNOID SPACE IN DIS-
EASES OF THE CENTRAL NER-
VOUS SYSTEM *

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Since 1842 various observers, beginning with Magendie, have demonstrated that pigments injected into the subarachnoid space eventually appear in the urine. Dandy and Blackfan¹ were the first to apply this knowledge to the study of pathologic conditions. They showed that phenolsulphonephthalein injected into the subarachnoid space is harmless and appears in the urine in normal infants in from four to ten minutes. Their studies were confined to hydrocephalus in infants and to certain animal experiments. As a result of these observations they were led to conclude that there is an active circulation of the spinal fluid; that it is constantly absorbed; and that absorption takes place directly into the vascular supply of the whole subarachnoid space. So far as we know, no other pathologic studies have been made in this way. Cushing and Weed,² using the same dye in connection with their work on the spinal fluid, were convinced that absorption takes place largely by way of the subarachnoid villi into the cerebral sinuses. Motte and Nageotte³ believe that there may be considerable absorption of the spinal fluid by way of the perineural lymphatics.

The following observations were made to determine, if possible, whether there might be some disturbance in the excretion of phenolsulphonephthalein in diseases of the central nervous system other than hydrocephalus. The method adopted consisted, in brief, of doing a lumbar puncture, injecting 1 c.c. of neutral phenolsulphonephthalein,¹ catheterizing the patient and timing the appearance of the dye in the urine.

Certain practical points were soon evident, both from the standpoint of accuracy in results and in maintaining aseptic conditions. In the first place it was noted that there was a tendency for the dye to be

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1. Dandy and Blackfan: Internal Hydrocephalus. *Am. Jour. Dis. Child.*, 1914, **8**, 406.

2. Cushing and Weed: Studies on the Cerebrospinal Fluid. *Jour. Med. Research*, 1914, **31**, 1.

3. Nageotte and Riche: *Tabes Dorsalis*. *Manuel d'Histologie Pathologique*. Cornil and Ranvier, Ed. 3, 1907.

distributed along the path of the needle after withdrawal, giving ample time for it to be absorbed in considerable concentration from the subcutaneous tissues. This would allow it to appear in the urine in practically all cases in ten minutes or less, and would obscure the actual appearance from the subarachnoid space. To overcome this tendency it was found practicable to withdraw 2 or 3 c.c. of spinal fluid in a sterile syringe to be reinjected following the phenolsulphonephthalein so as to leave only clear spinal fluid in the needle. In order that 1 c.c. of phenolsulphonephthalein should replace exactly 1 c.c. of spinal fluid, the following method was devised. This, while extremely simple, was quite as satisfactory as the complicated apparatus with stop-cocks, etc., devised for lumbar puncture that one may find on the market.

The method consists of a needle and syringe adapter joined by three quarters of an inch of small rubber tubing. The first connects with the puncture needle, the latter exactly fits the Luer syringes. When the needle enters the subarachnoid space the obturator is withdrawn and the connecting piece, held with a clamped artery forceps which closes the rubber tubing, is immediately slipped into place. One can then at his leisure attach the manometer for reading the pressure or can withdraw exact amounts of fluid by gradually opening the clamp. Having read the pressure and withdrawn 1 c.c. of fluid to be discarded and 3 c.c. to be held in reserve, exactly 1 c.c. of the neutral phenolsulphonephthalein is slowly injected followed by the 3 c.c. of fluid previously withdrawn. The time of injection is noted. Before withdrawing the needle the patient's legs are slowly straightened (the lateral position is used) so that the changed tissue planes tend to prevent any escape of fluid and phenolsulphonephthalein. Great care should be taken in withdrawing the fluid not to exert suction, the intradural pressure being allowed to push back the piston of the syringe unassisted. It is also well, before introducing the phenolsulphonephthalein, to dilute it by allowing 2 or 3 c.c. of fluid to enter the syringe and then slowly to inject the whole. Obviously the strictest aseptic precautions must be observed at every step of the procedure.

Following the injection, the patient is catheterized and the urine allowed to drop into a series of test tubes containing small amounts of sodium hydroxide. These are placed in order in a rack and the time of drawing off each is noted. The first tube to show a definite pink color is an indicator of the excretion time. On the following day, provided the phenolsulphonephthalein has disappeared from the urine, 1 c.c. is injected intramuscularly according to the usual technic for kidney function test, and the time of the appearance in the urine noted. Practically, it is rarely necessary to catheterize the patient on this examination, merely having him void at the end of ten minutes, at which time the dye is in most cases present in the urine. This, with careful urine analysis, was done to rule out any delays due to kidney disease.

Quantitative estimations were made in a considerable number of cases, but these were found to vary so greatly as to be of little value. The dye is apparently absorbed very slowly from the subarachnoid space and in many instances may suffer considerable reduction before complete elimination can take place.

Apparently the observations reported by Kendall⁴ had not been

4. Kendall: The Fate of Phenolsulphonephthalein When Injected Into the Animal Organism, *Jour. Am. Med. Assn.*, 1917, **68**, 343.

extended to include the cerebrospinal fluid. A series of fluids were therefore tested for their reducing ability. Eighteen different fluids were incubated with measured quantities of phenolsulphonephthalein for varying lengths of time. Some of these showed a reduction of from 10 to 20 per cent., others no reduction whatever. While there are certain features about this reduction (percentage) that have not yet been explained, it is safe to say that the decrease in the recoverable dye is not sufficiently great to interfere with qualitative tests.

The series discussed below consists of fifty-nine individuals who were selected from the neurologic and medical clinics of Stanford University Medical School so as to include a reasonable number of supposedly normal persons (neurologically), the others representing as great a variety as possible of organic central nervous system diseases. The series may be divided into five groups.

Group I includes twelve persons whose symptomatology, physical signs and spinal fluid analyses suggested no organic disease of the central nervous system or disease of the urinary tract. These are shown in the table. It will be observed that this group contains persons ranging in age from 27 to 54 years. While it is probable that old age, especially when associated with considerable arteriosclerosis, tends to prolong the appearance time, still the results in this group may be taken as fairly well representing the normal appearance. The time in this series averages practically nine minutes. In these individuals there is no apparent relationship between age and appearance time, neither can a definite relationship between spinal fluid pressure and appearance time be established.

Group II is definitely pathologic. It includes thirty-one persons having both physical and laboratory evidence of organic central nervous system disease. Of this number thirty were syphilitics, nine having been diagnosed tabes dorsalis, five paresis, one juvenile paresis, eleven cerebrospinal syphilis, one pachymeningitis hypertrophica cervicalis syphilitica, one Erb's spastic paraplegia, one syphilitic amyotrophic lateral sclerosis, one gumma of parietal bone with meningeal involvement. The other case was one of tuberculous meningitis. In this group the appearance time ranged from five to seventy-four minutes. In tabes the appearance time ranged from fifteen to sixty minutes, with one exception it was thirty minutes or over, averaging forty-two minutes. Again, one finds no direct relationship between the length of the appearance time and the age, but in this group the average spinal fluid pressure was definitely increased. The five paretics ranging from eighteen to fifty minutes, with one exception, all ran thirty minutes or over, averaging thirty-eight minutes. In this group there was more of a correspondence between age and appearance time.

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—
Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System.

Number	Age	Clinical Diagnosis	Phthalein Ap- pearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intra- spinal, Min.	Intra- muscular, Min.	Blood	Spinal	Pres- sure, Mm.	Nonne	Noguchi	Cells	
48128	27	Gastritis.....	7	Under 10			100	+		1	0000000000
48471	26	Constipation.....	5	Under 10			170			2	1000000000
48528	39	Normal.....	10	Under 10			120			1	0000000000
24669	52	Normal.....	10	Under 10			110	+	+	2	0000000000
46098	24	Mediastinitis.....	14	Under 10			130			1	0000000000
47225	29	Normal.....	10	Under 10			150			1	1100000000
16410	50	Broken nose.....	10	Under 10			150			2	1110000000
46944	57	Manic depressive.....	5	Under 10			90			2	0000000000
40629	26	Neurasthenia.....	6	Under 10			100			1	0011000000
48043	41	Epilepsy.....	4	Under 10			120			1	0000000000
50680	31	Manic depressive.....	6	Under 10			130			1	0000000000
50643	33	Normal.....	7	Under 10			150	+		1	0110000000

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

42103	29	Tabes dorsalis.....	30	6	+++	+++	200	+++	+++	30	1222332000
37034	51	Tabes dorsalis.....	45	7	+++	+++	230	++	++	11	2233320000
43842	26	Tabes dorsalis.....	55	5	+++	+++	150	++	+	50	1221100000
44850	37	Tabes dorsalis.....	15	4		+++	210	++	+	26	1233310000
27433	47	Tabes dorsalis.....	34	10	+++	+++	250	++	++	74	0122110000
45495	45	Tabes dorsalis.....	42	7	+++	+++	310	+++	+++	34	2234310000
30882	35	Tabes dorsalis.....	55	6		+++	165	++	+	44	3332210000
43409	44	Tabes dorsalis.....	60	10	+++		180	+	+	12	1123320000
26336	40	Tabes dorsalis.....	40	6		+++	160	+	+	86	1123100000
34057	52	Paresis.....	52	6	+++	+++	270	+	+	28	1110000000
N.S.H. 1	46	Paresis.....	43	8	+++	+++	200	+++	+++	22	5555554433
N.S.H. 2	28	Paresis.....	18	7	+++	+++	190	+++	+++	75	5555554332
N.S.H. 3	40	Paresis.....	32	7	+++	+++	210	++	++	50	
34457	34	Paresis.....	45	5	+++	+++	200	+++	+++	150	5544400000
48870	10	Juvenile paresis.....	23	5	+++	+++	140	+++	+++	42	5333200000
76067	25	Cerebrospinal lues.....	45	7	+++	+++	170	+++	+++	48	3333300000
46220	39	Cerebrospinal lues.....	25	11	+++	+++	200	+++	+++	160	1223321000
47383	46	Cerebrospinal lues.....	74	5	++	+++	190	+++	+++	33	2234320000
48759	33	Cerebrospinal lues.....	26	4	+++	+++	150	+++	++	56	3444430000
48889	44	Cerebrospinal lues.....	65	6	+++	+++	150	++	+++	45	1112320000

—GROUPS OF NORMAL PERSONS AND PERSONS WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM

Group I.—Individuals Having Neither Physical Nor Laboratory Evidence of Organic Disease of the Central Nervous System.

Urine	Subjective Symptoms	Physical Signs					
		Eyes	Knee Jerk	Ankle Jerk	Bladder	Dysarthria	Ataxia
Trace alb.	Pain in the epigastrium.....	Normal	Normal	Normal	Normal	None	None
Normal	Nervousness	Normal	Normal	Normal	Normal	None	None
Normal	Worry	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None
Normal	Pain in the chest.....	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None
Normal	Headache.....	Normal	Normal	Normal	Normal	None	None
Normal	Flight of ideas.....	Normal	Normal	Normal	Normal	None	None
Normal	Palpitations.....	Normal	Normal	Normal	Normal	None	None
Normal	Epileptic attacks	Normal	Normal	Normal	Normal	None	None
Normal	Depression.....	Normal	Normal	Normal	Normal	None	None
Normal		Normal	Normal	Normal	Normal	None	None

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease

Normal	Gastric crises; pains in the legs....	Pupils unequal; fixed to light	Absent	Absent	Normal	None	Present
Normal	Poor vision; pains in the legs....	Pupils fixed; optic atrophy	Present	Present	Incontinence	None	Slight
Normal	Poor vision; pains in legs and arms	Pupils unequal; fixed; optic atrophy	Present	Absent	Normal	None	Slight
Normal	Paresthesias in arms and legs....	Pupils unequal; fixed	Absent	Absent	Normal	None	Present
Normal	Photophobia; pains in legs; impotency	Pupils unequal; fixed	Present	Present	Normal	Slight	Absent
Normal	Paresthesias; pains in the legs....	Pupils unequal; fixed; irregular	Absent	Absent	Dribbling	None	Present
Normal	Pains in legs; severe gastric crises	Pupils sluggish	Absent	Absent	Normal	None	Absent
Normal	Shooting pains in legs; trophic ulcer	Pupils fixed	Present	Present	Normal	None	Slight
Trace alb.	Pains in legs; difficult urination...	Pupils sluggish	Absent	Absent	Dribbling	None	Present
Normal	Euphoric; elated; grandiose.....	Pupils unequal	Exaggerated	Exaggerated	Normal	Slight	Absent
Normal	Euphoric; partially demented.....	Pupils fixed	Increased	Increased	Normal	Present	Slight
Normal	Euphoric; violence	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Demented	Pupils unequal; fixed	Increased	Increased	Incontinence	Present	Present
Normal	Irritability; headaches	Pupils sluggish	Increased	Increased	Incontinence	Present	None
Normal	Spastic paralysis; mental retrogression	Pupils fixed	Increased	Increased	Dribbling	Present	Slight
Normal	Headache; diplopia	Iritis	Increased	Increased	Normal	None	None
Normal	Headache; vertigo; paresthesias...	Pupils unequal	Increased	Increased	Normal	None	Present
Normal	Depression; paresthesias	Pupils sluggish	Increased	Increased	Normal	None	None
Normal	Depression; paresthesias; headache	Unequal; sluggish; irregular pupils	Absent	Absent	Normal	None	None
Normal	Vertigo; pains in legs.....	Normal	Increased	Increased	Dribbling	None	None

TABLE SHOWING ABSORPTION OF PHENOLSULPHONEPHTHALEIN FROM THE SUBARACHNOID SPACE IN VARIOUS—
Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Number	Age	Clinical Diagnosis	Phthalein Ap- pearance Time		Wassermann		Spinal Fluid Analysis				Colloidal Gold Reaction (Lange)
			Intra- spinal, Min.	Intra- muscular, Min.	Blood	Spinal	Pres- sure, Mm.	Nonne	Noguchi	Cells	
48881	44	Cerebrospinal lues.....	60	6		+++	170	++	++	73	2334210000
43315	31	Cerebrospinal lues.....	60	14	+++	+++	190	+++	++	31	2233322000
32271	36	Cerebrospinal lues.....	30	6	+++	+++	160	++	++	21	3355321000
29145	39	Cerebrospinal lues.....	15	5		+++	150	++	++	175	1122100000
40131	40	Cerebrospinal lues.....	40	7	+++	+++	200	+++	++	94	2233000000
39268	32	Cerebrospinal lues.....	36	6	+++	+++	220	+++	+++	32	2233300000
40478	43	Pachymeningitis cervicalis syphilitica	40	11	+++	+++	200	++	++	42	1122331000
31351	22	Erb's spastic paraplegia syphilitica	5	5	+++	+++	200	++	++	3	3332220000
30747	39	Amyotrophic lateral sclerosis, syphilitic	14	5	+++	+++	170	+++	++	15	0112210000
49721	35	Gumma of parietal bone	30	8	+++		150	++	+++	9	0011000000
48183	24	Tuberculous meningitis....	55	8			200	+++	+++	90	0000123332

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

15439	38	Tabes dorsalis.....	40	5			170	+	+	4	1122100000
10451-12	60	Tabes dorsalis.....	60	7			190			2	1111100000
46559	52	Tabes dorsalis.....	22	7			165	+		4	1121000000
13963	50	Tabes dorsalis.....	70	10			200	+	+	2	
42695	37	Tabes dorsalis.....	18	7			210			4	0011000000

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

50754	43	Syphilis.....	20	Under 10	+++		150			1	0000000000
48529	8	Congenital syphilis.....	10	Under 10	+++		100			0	0000000000
15319-13	40	Syphilis.....	23	Under 10	+++		160			2	0010000000
48206	35	Syphilis.....	30	Under 10	+++		150			1	1111000000

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

41109	45	Brain tumor.....	55	10			130			1	0100000000
47706	30	Jacksonian epilepsy.....	30	9			150			0	0000000000
17863	40	Jacksonian epilepsy.....	40	6			120			4	
48965	46	Arteriosclerosis.....	51	10			170			0	
47971	35	Delirium tremens.....	40	7			250			1	1111100000
47569	50	Arteriosclerosis.....	60	7			120			1	0000000000
8050	70	Arteriosclerosis.....	40	9			150			4	0000000000

—GROUPS OF NORMAL PERSONS AND PERSONS WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM—(Continued)

Group II.—Individuals Having Both Physical and Laboratory Evidence of Organic Central Nervous System Disease.—(Continued)

Urine	Subjective Symptoms	Physical Signs					
		Eyes	Knee Jerk	Ankle Jerk	Bladder	Dysarthria	Ataxia
Normal	Herpes zoster; headache.....	Pupils unequal	Normal	Normal	Normal	None	None
Normal	Pains in legs.....	Pupils fixed	Increased	Increased	Normal	None	None
Few casts	Headaches; excitement	Pupils sluggish	Increased	Increased	Normal	Present	Present
Few casts	Paresis left hand; headache.....	Optic neuritis	Normal	Normal	Normal	None	None
Normal	Pains in legs; depressed.....	Pupils sluggish	Absent	Sluggish	Normal	None	Slight
Trace alb.	Dizziness; headache; nausea; visual disturbances	Pupils sluggish; optic neuritis	Unequal	Sluggish	Normal	None	Present
Normal	Pain in neck and arms, with weakness and wasting	Pupils unequal	Normal	Normal	Normal	None	None
Normal	Paralysis of legs.....	Pupils irregular	Exaggerated	Increased	Dribbling	None	Spastic
Few casts	Paralysis of legs; pain in legs....	Pupils irregular	Increased	Increased	Normal	Present	Marked
Normal	Stupor; headache	Pupils unequal and dilated	Sluggish	Sluggish	Normal	None	None
Pus cells	Headache; delirium	Pupils unequal	Increased	Increased	Normal	None	None

Group III.—Individuals Having Positive Physical Evidence of Organic Nervous Disease but Practically Negative Laboratory Findings

Normal	Pains in legs; difficult urination...	Pupils sluggish	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; dizziness (Charcot joint)	Pupils sluggish; irregular	Absent	Absent	Dribbling	None	Marked
Normal	Pains in legs; dizziness.....	Pupils irregular	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; headache, dizziness..	Pupils fixed	Absent	Absent	Normal	None	Marked
Normal	Pains in legs; crises.....	Pupils fixed	Absent	Absent	Normal	None	Marked

Group IV.—Individuals Having Syphilis but No Physical or Laboratory Evidence of Central Nervous System Involvement

Normal	Impotence.....	Pupils normal	Normal	Normal	Normal	None	None
Normal	Necrosis of nose.....	Pupils normal	Normal	Normal	Normal	None	None
Normal	Headache and nervousness.....	Pupils normal	Normal	Normal	Normal	None	None
Normal	Headaches; depression; pares-thesias	Pupils normal	Increased	Normal	Normal	None	None

Group V.—Individuals Having Physical or Symptomatic Evidence of Central Nervous Disease but Negative Laboratory Findings

Normal	Headache.....	Disks pale	Normal	Normal	Normal	None	None
Normal	Convulsions.....	Normal	Normal	Normal	Normal	None	None
Normal	Convulsions; headache	Normal	Unequal	Unequal	Normal	None	None
Trace alb.	Weakness; headache; blood pressure 240 mm.	Normal	Normal	Normal	Normal	None	None
Normal	Hallucinations.....	Normal	Normal	Normal	Normal	None	None
Few casts	Nervousness; dizziness; pares-thesias	Normal	Normal	Normal	Normal	None	None
Few casts	Aphasia; dizziness; weakness; blood pressure 190 mm.	Normal	Normal	Normal	Normal	None	None

The pressures against were increased. The eleven cases of cerebro-spinal syphilis ranged from fifteen to seventy-four minutes, with one exception running twenty-five minutes or over, averaging forty-three minutes. The average age was lower in this group than in the two preceding. The remaining observations ran forty, five, fourteen, thirty and fifty-five minutes, respectively.

It will be observed that all of these persons, with one exception, the patient with Erb's syphilitic spastic paralysis, showed evidence of more or less meningeal inflammation as indicated by pleocytosis, increased globulins, etc. Histologically, also, all of these types of disease are known to exhibit meningeal changes.

In tabes "thickening or cellular infiltration of the spinal meninges, most marked in the posterior portion of the cord," was found present in all of fourteen cases recently studied by Dr. W. F. Schaller,⁵ who is of the opinion that "the tabetic degeneration is a radiculitis subsequent to a primary syphilitic meningitis." This accords with the findings of Spiller,⁶ Bresowsky⁶ and Schröder.⁷ Nageotte believes that the posterior column degeneration is due to an inflammatory process of the radicular nerves involving the perineurium and endoneurium and taking the form of a transverse neuritis, that is just mesial to the spinal ganglia. Here the inflammatory process starts along the posterior columns producing at the same time the characteristic thickenings and round cell infiltration of the meninges throughout the posterior spinal region. This author, with Mott, believes that a considerable absorption of spinal fluid takes place normally by way of the perineural lymphatics which, under the conditions mentioned above, would be greatly impeded.

In paresis Kraepelin⁸ says:

It is not uncommon to find pachymeningitis interna and hematoma of the dura, usually a mere delicate film, but sometimes in the form of a thick coat made up of several layers or of an extensive fresh extravasation of blood, generally on the vertex. One also frequently sees more or less widespread superficial hemorrhages. The pia is always more or less cloudy and thickened, sometimes excessively, especially along the vessels. Microscopic examination shows an increase in the connective tissue and localized infiltrations with lymphocytes and plasma cells. . . . These alterations are generally most apparent over the anterior and middle portions of the hemisphere convexities, also on the inner surface, but less prominent on the basal surface and entirely lacking over the occipital lobes. . . . The veins are greatly distended and

5. Schaller: Early Diagnosis of Tabes Dorsalis, *Jour. Am. Med. Assn.*, 1917, **68**, 190.

6. Spiller: Pathology of Tabetic Ocular Palsy, *Jour. Nerv. and Men. Dis.*, 1915, **42**, 15.

7. Schröder: Ein Beitrag zur Histopathologie der Tabes Dorsalis. *Zentralbl. f. Nerven- u. Psychiat.*, New Series, 1906, **17**, 585.

8. Kraepelin: General Paresis. *Nervous and Mental Disease Monographs*, No. 4.

often show thickened walls. The Pacchionian granulations are frequently overdeveloped. In the spinal cord one observes occasional pachymeningitis and frequent leptomeningitis more marked over the dorsal columns. . . . Fürstner is inclined to believe that the spinal cord is affected without exception in paresis. The alterations were most severe in the lumbar and dorsal cord and gradually diminished as they were followed upward. Alzheimer and others have demonstrated infiltration of the vessels with lymphocytes and plasma cells, both in the pia and in the cord itself.

Barker⁹ says: "The pathologic basis of cerebrospinal syphilis consists of a syphilitic infiltration and gumma formation that affects the vascular system and the meninges and the white and gray matter of the brain and cord." Spiller thinks that in all these forms of syphilitic disease the process is not limited, but is an involvement of the whole cerebrospinal tract, being only more pronounced in certain areas in the different clinical types.

The widespread vascular and meningeal involvement in these three clinical forms of disease may account for the small degree of difference in their average appearance time. As before noted, these averages were forty-two, thirty-six, and forty-three minutes, respectively. The widest range was in cerebrospinal syphilis, fifteen to seventy-four minutes.

Pachymeningitis cervicalis hypertrophica syphilitica is by definition a meningeal disease. Whether the delay in this instance was due to changes in the absorbing power of the meninges of the cord, or whether it was due to blocking of the circulation to cerebral absorbing areas, is not certain.

As indicated in the table the case of amyotrophic lateral sclerosis showed definite evidence of syphilis of the central nervous system with meningeal involvement. Spiller¹⁰ cites two cases which were "typical clinically and pathologically of amyotrophic lateral sclerosis," and which showed round cell infiltration in the pia typical of syphilitic disease in addition to the usual systemic degeneration. This meningeal infiltration, though probably not extensive, would perhaps account for the very slight delay in the phenolsulphonephthalein excretion. On the other hand, the patient with Erb's paraplegia, with no signs of meningeal inflammation in the fluid, gave a normal excretion time.

The patient with gumma of the parietal bone, while listed separately, might have been included among those with cerebrospinal syphilis, having evidence of meningeal inflammation in the pleocytosis and increased globulin and albumin.

The case of tuberculous meningitis, the only nonsyphilitic disease in this group, came to necropsy and showed very extensive thickening and edema of the meninges of both the brain and cord.

9. Barker: *Monographic Medicine*, 1916, **4**, 549.

10. Spiller: Syphilis as a Cause of Systemic Degeneration of the Motor Tract. *Jour. Nerv. and Ment. Dis.*, 1912, **39**, 584.

Group III.—This group consists of five clinical tabetics who differ from the foregoing only in the meager pathologic findings in the spinal fluid, all having negative Wassermann, Nonne and Noguchi reactions, cell counts (four or less), and practically negative colloidal gold reactions. Three of these were negative when first observed; two had been thoroughly treated and were negative at the time of these observations. It will be noted, however, that the average excretion time was forty minutes, only two minutes less than that of the tabetics in the foregoing group. This suggests one possibility of a diagnostic significance for this method.

Group IV.—This group represents four syphilitics with no laboratory or physical evidence of central nervous system disease. Their average was twenty-one minutes, or somewhat more than twice that found in the normal controls. The value of this procedure in detecting early involvement of the central nervous system will be further considered in a subsequent communication.

Group V.—This is a mixed series of seven persons having definite physical or symptomatic evidence of organic disease of the central nervous system, but with negative spinal fluids. None of these were syphilitics. The average appearance time was forty-five minutes. There was no definite correspondence to age, nor were the spinal fluid pressures definitely increased. The group represents one brain tumor, two cases of jacksonian epilepsy, three of advanced arteriosclerosis and one of delirium tremens. It is conceivable that in these individuals more or less extensive involvement of the vascular or lymphatic apparatus might exist. This, though not actively inflammatory giving rise to pleocytosis and increase in globulins, might account for the delayed excretion.

In attempting to explain these delays in more than a general way one is met by several difficulties. If one presupposes a limited area of absorbing tissue, the cerebral arachnoid villi for example, a uniform damage to this area would have to be assumed, or that some obstruction to the free flow of the phenolsulphonephthalein to this area must exist. In some such way the wide range of results in persons having the same type of disease, cerebrospinal syphilis, for example, might be explained. Until more necropsies are secured no more definite information as to the method of excretion of the phenolsulphonephthalein can be given by this procedure. It would seem, however, that inflammations involving the meninges with consequent vascular and lymphatic changes cause a delayed excretion of the dye. Even in those instances in which the symptomatology would suggest a localized lesion, the delay in the appearance time would raise the question of a generalized involvement of the meninges.

SUMMARY

1. Phenolsulphonephthalein when injected into the subarachnoid space in normal persons appears in the urine in ten minutes or less.
2. Diseases of the central nervous system, especially when involving the meninges, produce a lengthening of the appearance time to as much as seventy minutes in some cases.
3. This delay cannot be accounted for by disease of the kidneys, or by the reduction of the phenolsulphonephthalein in the spinal fluid.
4. Advanced general arteriosclerosis may be a factor in causing the delay in some instances.
5. In syphilis a lengthening of the appearance time may be produced before any other evidence of central nervous system involvement has appeared.
6. The method may prove of value in detecting instances of organic central nervous system disease in which the ordinary spinal fluid findings are negative or incomplete.
7. At this time no definite conclusion can be drawn as to the exact location of the absorbing tissues.

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