OBSERVATIONS ON THE BROMIDE PARTITION TEST IN THE DIAGNOSIS OF NON-PURULENT MENINGITIS

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The Bromide Partition Test

In its earliest stages when treatment will produce the most favourable results, tuberculous meningitis may be difficult to diagnose clinically, since other infective non-bacterial conditions of the central nervous system may present a similar clinical picture at their onset.

Since the bromide partition test and its use in the diagnosis of tuberculous meningitis were described (Taylor, Smith and Hunter, 1954) we have found it a useful aid to diagnosis in six cases of tuberculous meningitis and 20 cases of non-tuberculous meningitis (Fig. 1).

Normally after oral or intravenous administration of sodium bromide, the ratio of serum bromide/cerebrospinal fluid bromide is above 1·65 (usual range 2-3). In cases of tuberculous meningitis the integrity of the blood cerebrospinal fluid barrier is affected and there is an early fall in the ratio below 1·65 towards unity, with a return to normal when the infection is brought under control. In other types of non-purulent meningitis a fall in the ratio does not occur. In cases of purulent meningitis this fall may, or may not, occur. In five cases of purulent meningitis described by Cheek (1956) there was a low ratio in two cases, in the other three the ratio was normal. Owing to the different clinical course of purulent meningitis, this type of test should not be necessary, and no cases of purulent meningitis are included in our series.

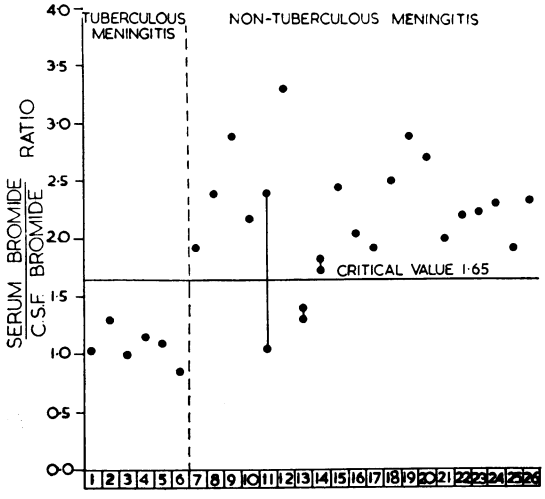

FIG. 1.—Scatter diagram of bromide partition test.

The method used is that described by Taylor, Smith and Hunter (1954). Sodium bromide is given orally, 0·25-1 g. t.d.s., for three days, or as a single intravenous injection of 2-8 g. (the solution contains 8 g. in 30 ml.). Venous blood, 5 ml., and lumbar cerebrospinal fluid, 8 ml., are collected 24 hours after intravenous, and 48 hours after oral administration, for bromide estimation. The authors of the original paper stress the importance of collecting lumbar cerebrospinal fluid as fluid obtained by cisternal or ventricular puncture yields different values.

Analytical Method

Bromide was estimated by the method of Hunter (1953) which is the technique of choice for this test as it enables the relatively small serum and cerebrospinal fluid levels to be estimated with greater accuracy than by other methods (Hunter, Smith and Taylor, 1954). This method is a quantitative application of the Van der Meulen reaction, whereby bromide is oxidized to bromate by hypochlorite. The excess hypochlorite is removed with sodium formate, after which the bromate liberates a corresponding amount of iodine from potassium iodide, which is titrated with N/200 sodium thiosulphate, using a starch indicator. The end point is sharp and satisfactory.

One ml. of serum or cerebrospinal fluid is required for each estimation.

In the majority of cases estimations were carried out in duplicate and the mean value reported. In a few cases, however, shortage of material made this impossible. It is essential to carry out a 'reagent blank' with each test, as there is a somewhat large and variable blank value arising from reagents, which must be deducted

TABLE 1

FIGURES FOR THE FIRST 10 DUPLICATED ANALYSES OF SERUM AND OF CEREBROSPINAL FLUID. SHOWING THE MEAN VALUES REPORTED AND THE DEGREE OF ACCURACY*

Specimen No.	Serum				Cerebrospinal Fluid			
	I	II	Mean	Accuracy (%)	I	II	Mean	Accuracy (%)
1	35·6	36·2	35·9	±0·84	13·0	13·4	13·2	±1·52
2	61·0	61·2	61·1	±0·16	65·0	63·0	64·0	±1·56
3	35·6	34·1	34·8	±2·21	32·0	29·6	30·8	±3·90
4	131·0	129·0	130·0	±0·77	5·8	5·8	5·8	±0·00
5	92·8	91·2	92·0	±0·87	26·4	27·4	26·9	±1·86
6	17·6	19·2	18·4	±4·30	18·5	19·5	19·0	±2·63
7	14·2	13·4	13·8	±2·90	24·7	24·7	24·7	±0·00
8	56·0	57·0	56·5	±0·89	27·7	25·7	26·7	±3·72
9	24·5	24·5	24·5	±0·00	5·7	3·8	4·75	†±20·0
10	19·7	19·5	19·6	±0·51	27·0	27·0	27·0	±0·00
	Accuracy: average ±1·35% (Range: 0·00–4·30%)				Accuracy: average ±1·69% (Range: 0·00–3·90%)			

* Results are expressed as bromine mg. %.

† Not included in calculating the average and range for this series. This much larger error is due to the difficulty in estimating the very small amount of bromine present.

from the serum and cerebrospinal values. Initially, the method involves ashing protein-free alcoholic extracts of serum and cerebrospinal fluid in nickel crucibles, but apart from these no special apparatus is required other than what is normally available in a clinical laboratory. The original method suggests that 4 ml. of alcoholic supernatant fluid be used for the estimation after protein precipitation. This is satisfactory for cerebrospinal fluid but in the case of sera we frequently found it difficult to realize this volume. As a routine, we therefore employed 3·5 ml. and corrected the calculation accordingly. The accuracy of the method appears satisfactory. From the point of view of a busy clinical laboratory, one might perhaps make the criticism that it is somewhat time-consuming.

Results are expressed as mg. % of bromine, and Table 1 gives the figures for the first 10 duplicated analyses, for serum and cerebrospinal fluid respectively. Some of these figures refer to adult cases of meningitis and are not dealt with in this paper. The accuracy is expressed as the percentage difference between the individual analyses and the mean value reported. Hunter (1953) claims an accuracy of approximately ± 1% for the method, and the majority of our own analyses agree with this. At the outset of this work, recovery tests were carried out with sodium bromide added to serum at a concentration of 10 mg. %, expressed as bromine. The recovery range was 97% to 104%, but it was possible to improve on this standard of accuracy with the higher concentrations encountered in the test specimens.

TABLE 2

Case No.	Serum Bromide (mg. %)	C.S.F. Bromide (mg. %)	Serum CSF Ratio	Mantoux 1·1000	Culture C. Guinea Pig G.	Cerebrospinal Fluid Findings: Cells (per c.mm.)	Protein (mg. %)	Glucose (mg. %)	T.B. Family History	Diagnosis
1	19·2	18·4	1·04	–	CG+	424	240	21	–	
2	38·2	27·6	1·38	+	G+	62	120	43	– (milk)	Tuberculous meningitis
3	27·0	27·0	1·00	+	C–	350	260	15	–	Tuberculous meningitis
4	30·8	25·9	1·19	+	C–G–	244	180	20	+	Tuberculous meningitis
5	20·2	18·4	1·10	+	C–	230			+	Tuberculous meningitis
6	24·2	28·1	0·86	+	C–G+	128	128	40	–	
7	33·0	17·2	1·92	–	C–G–	1,340	80	45	–	Non-specific meningitis
8	13·9	5·8	2·40	–	G–	176	30	49	–	Non-specific meningitis
9	13·8	4·75	2·90	–	C–	266	55	60	+	Poliomyelitis
10	28·3	13·2	2·18	+	C–	3	80	62	–	Tuberculoma of cerebellum
11	27·3 / 38·0	25·0 / 15·6	1·09 / 2·40	–	G–	260	150	55		Non-specific meningitis
12	45·0	13·5	3·35	–	C–	454	30	46	–	Non-specific meningitis
13	33·4 / 47·5	24·0 / 35·0	1·40 / 1·36	–	C–	828	30	40	–	Non-specific meningitis
14	42·0 / 48·0	24·5 / 26·3	1·72 / 1·82	–	C–	324	58	52	+	Mumps. Encephalitis
15	13·8	5·6	2·45	–	C–	62	40	90	+	Non-specific meningitis
16	14·9	7·2	2·05	–		800	48	55	–	Non-specific meningitis
17	37·3 / 59·4	19·4 / 30·6	1·93 / 1·93	+	C+ (from foot)	94	35	43	–	Miliary tuberculosis
18	14·2	5·7	2·50	–	C–	20	54	40	–	Mumps. Encephalitis
19	38·4	13·4	2·90	–	C–G–	432	30	37	–	Mumps. Encephalitis
20	23·8	8·6	2·76	–		90	70	70	+	Non-specific meningitis
21	30·4	15·2	2·00	–		3	32	78	–	Non-specific meningitis
22	25·0	11·4	2·20	+ (BCG)	C–	140	60	59	+	Poliomyelitis
23	27·5	12·3	2·24	–	C–G–	216	70	46	+	Non-specific meningitis
24	51·5	22·8	2·25	—	C–	202	40	67		Poliomyelitis
25	18·1	9·5	1·92	–		90	20	80	–	Mumps. Encephalitis
26	51·5	21·9	2·36	–	C–	48	35	54	+	Poliomyelitis

Material and Results

In the six cases of tuberculous meningitis (Table 2) the bromide ratio was depressed in all cases. In Cases 3 and 5 the test was useful in confirming the clinical diagnosis. Case 1 presented the typical features of tuberculous meningitis but the Mantoux reaction was negative on admission. A bromide ratio of 1·04 was useful additional evidence in favour of the diagnosis. Cases 2, 4 and 6 presented diagnostic problems as the clinical picture was not typical, and, as they illustrate the practical value of the test, they are presented more fully.

Case 2. A girl, aged 5 years, was well until the day of admission when she was suddenly unable to speak, did not recognize her mother and looked vacant for a few minutes. She vomited at the end of the attack. There was nothing relevant in her previous or family history, but the milk supply was from a doubtful source. The child was well on admission and physical examination was negative. Investigations included: haemoglobin 81%, white blood cells 8,000 per c.mm., 62% polymorphs. The urine was normal and there were no pathogens in the stool. A Mantoux test was 1:1,000 positive. Radiographs of the skull and chest were normal, while that of the abdomen showed calcified mesenteric glands. She was well for 10 days when she had a further minor convulsion lasting a few seconds. Three days later she was less well and vomited several times. Physical examination remained negative. Lumbar puncture showed 62 cells per c.mm., protein 120 mg. %, glucose 43 mg. %. She was thought possibly to be suffering from early tuberculous meningitis and was started on streptomycin, isoniazid and P.A.S. while a bromide partition test was done, the ratio being 1·38 which was in favour of the diagnosis. A guinea pig inoculated with the original cerebrospinal fluid showed evidence of tuberculosis. She made an excellent recovery.

Case 4. A boy, aged 2 years, whose father had recently been admitted to a sanatorium with pulmonary tuberculosis, was found to have an early primary complex just discernible on his contact film. Unfortunately, the family did not attend for their Chest Clinic appointment and shortly afterwards this child was admitted following a convulsion with a history of vomiting and irritability of one week's duration. On examination he was unconscious and twitching. There was no meningism, or localizing signs in the central nervous system. He had an acute right otitis media requiring paracentesis, otherwise physical examination was negative. Investigations included haemoglobin 68%, white blood cells 11,000 per c.mm., 50% polymorphs. A radiograph of the skull was normal, that of the chest showed a right primary complex. Pus from the right ear was sterile and *M. tuberculosis* was not isolated. Cerebrospinal fluid cells were 244 per c.mm., 91% lymphocytes, protein 180 mg. %, glucose 20 mg. %. A Mantoux test was 1:1,000 positive. The child was thought to be suffering from tuberculous meningitis and was started on treatment with streptomycin, isoniazid and P.A.S. A bromide ratio of 1·19 confirmed this diagnosis and was useful in ruling out the possibility that he was suffering from an intracranial complication of his ear disease.

Case 6. A girl, aged 6 years, was admitted as a 'pyrexia of unknown origin' with a five days' history of headache, abdominal pain and vomiting. Physical examination was negative. Routine investigations included haemoglobin 72%, white blood cells 14,000 per c.mm. A radiograph of the chest was normal. The urine contained a trace of albumen. Agglutinations to *Salmonella* and *Brucella* groups were negative. A blood culture was sterile and there were no pathogens in the stool. A Mantoux test was 1:1,000 positive. Cerebrospinal fluid cells were 128 per c.mm., protein 128 mg. %, glucose 40 mg. %. Bromide ratio 0·86.

During the investigations apart from a pyrexia she remained relatively well and there were no clinical signs of tuberculous meningitis until the diagnosis had been made and she was on treatment with streptomycin, isoniazid and P.A.S.

In the above six cases presenting as tuberculous meningitis, proof of the diagnosis was obtained in five. Three were confirmed by guinea pig inoculation (Cases 1, 2, 6) and two others developed choroidal tubercles (Cases 4, 5). In the remaining case the subsequent course of the disease was typical of tuberculous meningitis, and there is little doubt about the final diagnosis. Treatment with antituberculous drugs does not affect the bromide ratio in the early stages. Cases 1, 2, 4, 5 and 6 were started on treatment a few days before or during the bromide partition test. Case 3 had been on treatment for 17 days when the test was done. This is particularly useful as treatment may be started at once in uncertain cases without affecting the result, and, conversely, the patient need not be committed to a full course of treatment in the event of a negative result.

Case 14 illustrates the latter point. A child, aged 15 months, whose father had had a recent pulmonary tuberculosis, was admitted following a convulsion. Ten days previously his brother had developed mumps and he had had transient facial swelling. Physical examination was normal. Relevant investigations included a Mantoux test 1:1,000, and 100 negative. Radiographs of the chest and abdomen were normal. Cerebrospinal fluid cells were 324 per c.mm., 89% lymphocytes, protein 58 mg. %, glucose 52 mg. %. The fluid was taken on admission at night and a technician reported acid-fast bacilli in the smear. In view of this he was started on treatment with streptomycin, I.N.A.H. and P.A.S. The bromide ratio was 1·72 and a repeat ratio 1·82. In view of the history, clinical course and high bromide ratio he was thought to be probably suffering

from mumps encephalitis and he did not have a full course of anti-tuberculous drugs.

The bromide ratio is said to rise when infection is brought under control (Taylor, Smith and Hunter, 1954). In three of our cases repeat bromide partition tests were done during treatment (Fig. 2). Clinical improvement was accompanied by a rising ratio in each case. In Case 6 when the response to treatment was initially poor, the bromide ratio remained low, rising later when the clinical condition was also improving.

In the 20 cases of non-tuberculous meningitis the bromide ratio was normal in 18 of the cases. It was particularly helpful in six of these children (Cases 9, 15, 20, 22, 23, 26) who presented with early non-purulent meningitis and in whose case there was a family history of tuberculosis. Further, when poliomyelitis has been prevalent, or when there has been a history of contact with a disease such as mumps when encephalitis may occur, the bromide partition test has been a useful aid in eliminating tuberculous meningitis which must always come into the differential diagnosis.

Three of the cases with normal bromide ratios had positive Mantoux reactions. One had had B.C.G. The other two, one of interest, are presented more fully.

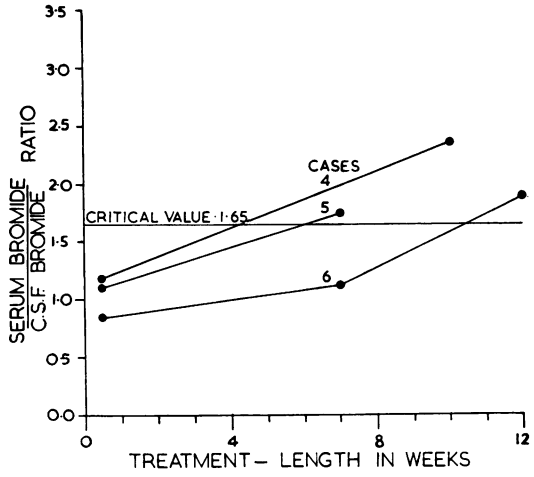

FIG. 2.—Alterations in the $\frac{\text{serum bromide}}{\text{C.S.F. bromide}}$ in tuberculous meningitis cases treated with P.A.S., I.N.A.H. and I.M. streptomycin.

Case 10. A girl, aged 9 years, was admitted with a history of general ill health, poor appetite, loss of weight and a noticeable falling off in her school work, of one year's duration. In the five days before admission she had had six attacks of headache, nausea and vomiting followed by unconsciousness for one minute. Physical examination was normal apart from a systolic murmur in her heart (pulse 86 per minute, blood pressure 95/50) and early papilloedema. Investigations included haemoglobin 78%, white blood cells 7,000 per c.mm., 74% polymorphs. The E.S.R. was 60 mm. in one hour. Blood urea was 38 mg. %. Blood chemistry was normal. There was a trace of albumen in the urine. Radiographs of the chest and abdomen were normal. A radiograph of the skull showed increased digital markings. Lumbar puncture showed fluid at increased pressure, cells 3 per c.mm. mononuclear, protein 80 mg. %, sugar 62 mg. %, Lange 5,554,310,000. The Wassermann reaction was negative, a Mantoux test positive. In view of her positive Mantoux, raised E.S.R. and changes in the cerebrospinal fluid, a bromide ratio was done, which at 2·18 was against a diagnosis of tuberculous meningitis.

She developed increasing papilloedema and ataxia and was transferred to a neuro-surgical unit where craniotomy was performed. A tuberculoma of the cerebellum was found and successfully removed. The normal bromide ratio in this case was both helpful and interesting.

Case 17. A girl, aged 2½ years, was admitted with a history of a minor injury to her right foot a few days previously: an indurated swelling had developed at the site of the injury. On the day of admission she vomited and had a series of generalized convulsions. On examination she was convulsed and neck stiffness was present. There was a fluctuant swelling on the dorsum of her right foot and her right knee was swollen. There were no other abnormal signs. Investigations included haemoglobin 71%, white blood count 11,300 per c.mm.. 80% polymorphs. There were no pathogens in the stool, A radiograph of the skull was normal, that of the chest showed increased shadowing at the right hilum. A Mantoux test was 1:1,000 positive. Urine protein was 700 mg. %, with two pus cells per high power field in uncentrifuged urine. Blood urea was 34 mg. %. An E.S.R. was 21 mm. in one hour. Cerebrospinal fluid cells were 94 per c.mm., 19% polymorphs, 81% lymphocytes, protein 35 mg. %, glucose 43 mg. %. Pus from the swelling of the foot contained tubercle bacilli. The bromide ratio was 1·93.

She was thought to be suffering from miliary tuberculosis and was started on treatment with streptomycin, isoniazid and P.A.S.

The normal bromide ratio, which was confirmed on a repeat test, is interesting. Cheek (1956) quotes Taylor, Smith and Hunter as saying that in miliary tuberculosis not involving the central nervous system the bromide ratio remains normal. In this case the meningeal signs and cerebrospinal fluid changes occurred during the period of invasion and she did not develop a true tuberculous meningitis.

In two of the cases the bromide ratio was low, giving false positive results.

Case 11. A girl, aged 11 years, was admitted as a surgical emergency with abdominal pain which rapidly improved, but she developed a pyrexia and persistent

headache. Relevant investigations included a Mantoux test, 1:1,000 negative. Cerebrospinal fluid cells were 260 per c.mm., 94% lymphocytes, protein 150 mg. %, glucose 55 mg. %. She was kept under observation and put on no treatment while a bromide ratio was done, the ratio being 1·09. By then she was quite well and the cerebrospinal fluid was returning to normal. A repeat ratio was 2·40.

Case 13. A boy, aged 4 months, who had had signs of a cerebral injury in the neonatal period was admitted following a convulsion. Physical examination was normal. Relevant investigations included a Mantoux test, 1:1,000 negative. Cerebrospinal fluid cells were 828 per c.mm., 94% lymphocytes, protein 30 mg. %, glucose 40 mg. %. The bromide ratio was 1·40. The child remained well and, as the cerebrospinal fluid was also improving, he was given no treatment and continued to improve. A repeat ratio was 1·36. He made an uneventful recovery.

These results agree with those of Taylor, Smith and Hunter (1954) who reported 7% false positive results in their series.

Summary

The serum/cerebrospinal fluid bromide ratio ('bromide partition test') of Taylor, Smith and Hunter (1954) has been applied in 26 cases of non-purulent meningitis of which six were tuberculous and 20 non-tuberculous.

In the tuberculous cases the accuracy was 100%, no false negatives being obtained. In three of the tuberculous cases, the ratio was determined at intervals during treatment and clinical improvement was accompanied by a rising ratio.

In the non-tuberculous cases, the accuracy was 90%, two out of 20 cases giving false positive results (Cases 11 and 13). Similar findings have been reported by Taylor, Smith and Hunter who found a low ratio in 7% of 66 cases of non-tuberculous meningitis.

Taken in conjunction with the clinical findings, the bromide partition test appears to be a valuable adjunct in the early diagnosis of tuberculous meningitis and may prove also to be a useful criterion for following the course of clinical improvement.

We are grateful to Dr. P. Kidd for first drawing our attention to this diagnostic technique and to Dr. A. G. V. Aldridge for his interest in the work and for permission to publish material relating to his cases. Mr. F. Hughes kindly prepared Figs. 1 and 2 for us.

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