



THE BLOOD-CEREBROSPINAL FLUID BARRIER IN TUBERCULOUS MENINGITIS AND ALLIED CONDITIONS

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The fact that many substances naturally present in blood, or artificially introduced into the bloodstream, either do not penetrate the central nervous system or do so only in small amounts has given rise to the concept of the "blood-brain barrier". Some workers believe that this term is an oversimplification: they maintain that while certain dyes pass freely from blood to nervous tissue without appearing in the cerebrospinal fluid (C.S.F.), others can pass from blood to C.S.F. without penetrating the parenchyma of the brain. The presence of two barriers, a blood-brain and a blood-C.S.F. barrier, has therefore been postulated (Friedman, 1942). But whatever the relationship between the two barriers, if indeed they are distinct, the study in man of the passage of different substances from blood to nervous tissue is a matter of great practical difficulty. On the other hand, study of the partition of substances between blood and C.S.F. is relatively easy, and the chief technical difficulty lies in the choice of a suitable indicator substance. The present study is concerned solely with the passage of substances from blood to C.S.F.; that is to say, with the blood-C.S.F. barrier.

One substance that has proved eminently suitable for studies of this kind is sodium bromide (Walter, 1929). The validity of the bromide test as a measure of the permeability of the blood-C.S.F. barrier has now been demonstrated (Hunter, Smith, and Taylor, 1954). Results of the test are expressed as the "bromide ratio", that is to say, bromide per unit volume serum/bromide per unit volume C.S.F. In subjects without overt disease of the nervous system the bromide ratio at equilibrium varies between 1.95 and 3.39, with a mean of 2.6 and a standard deviation of 0.30 (Taylor, Smith, and Hunter, 1954).

It is commonly held that inflammation of the leptomeninges facilitates the passage of many sub-

stances from blood to C.S.F. Yet in spite of a great deal of work on both man and animals (Katzenelbogen, 1935) the exact effect of leptomeningitis on the permeability of the blood-C.S.F. barrier is still poorly understood: witness the controversy that persists over the necessity or otherwise of intrathecal medication in the treatment of meningitis (Smith, Duthie, and Cairns, 1946; Hoyne and Brown, 1948; Dowling, Sweet, Robinson, Zellers, and Hirsh, 1949; Smith, 1951). As the bromide test is both simple and safe, it provides a highly convenient method for studying the behaviour of the blood-C.S.F. barrier in inflammatory conditions of the nervous system. We have used it now in a large number of cases of tuberculous meningitis and also at different stages of the disease in the same case. We have also made serial estimations of the bromide ratio throughout the course of the intrathecal tuberculin reaction as seen in subjects in whom the meninges were otherwise normal. By the intrathecal tuberculin reaction is meant that wave of sterile meningitis which follows the introduction of tuberculin into the C.S.F. of someone sensitized to tuberculin (Smith and Vollum, 1950). Since in the absence of tuberculous meningitis this reaction is remarkably regular in both occurrence and pattern, it provides an excellent medium for studying the effects of meningeal inflammation on the permeability of the blood-C.S.F. barrier to any given test substance.

Methods

Full details of the bromide test have already been published (Taylor and others, 1954), but may be recapitulated here.

Sodium bromide may be given either by mouth or by intravenous injection. The oral dose for adults is 1 g. of sodium bromide three times a day for three days. Children receive a total dose of 2.25 to 4.5 g., depending on age, also given in divided doses. The intravenous dose for adults is from 6 to 8 g. and for children from 2 to 4 g., made up as a 25% solution in sterile water and given as a single injection. This solution is moderately irritating, and care must be taken to ensure that

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it is all delivered directly into the vein and none allowed to escape into the surrounding tissues.

At least 48 hours must elapse after the last oral dose, and 24 hours after the intravenous injection, in order to ensure that equilibrium is established between blood and C.S.F. Samples are then collected into chemically clean, dry test tubes. Bromide estimations are carried out on the serum and C.S.F. by the method described by Hunter (1953). Five ml. of blood and 1 ml. of C.S.F. is enough to allow the estimation to be done in duplicate. Bromide is excreted so slowly that the doses advised are sufficient to maintain measurable levels in the blood and C.S.F. for several weeks.

When penicillin was used as an indicator substance 500,000 u. was given by intramuscular injection approximately two hours before each lumbar puncture. The penicillin content of the C.S.F. was estimated and the results were expressed as the amount of penicillin present in 1 ml. C.S.F. and not as the blood-C.S.F. ratio.

The Bromide Ratio during the Intrathecal Tuberculin Reaction

When the intrathecal tuberculin reaction is provoked in subjects with normal meninges it follows a reasonably constant and characteristic pattern (Swithinbank, Smith, and Vollum, 1953). As with the intradermal tuberculin reaction, its intensity is the resultant of the quantity of tuberculin given and the sensitivity of the recipient. In its complete form the reaction is diphasic and consists of an initial wave of pleocytosis which is predominantly polymorphonuclear and is accompanied by an abrupt rise in the protein content of the C.S.F. This, the polymorphonuclear phase, is maximal about 24 hours after the injection and is succeeded by a second wave of pleocytosis which is entirely lymphocytic. The second phase is maximal between the fifth and eighth days of the reaction and is usually accompanied by a second peak in the protein curve. When the reaction is incomplete, either the first, polymorphonuclear, or, more commonly, the second, lymphocytic, phase is lacking and the rise in protein content is inconspicuous.

The effect of the reaction on the blood-C.S.F. barrier has been studied, using either penicillin or sodium bromide or both simultaneously, as indicators. The results obtained with penicillin have

already been described. It was shown that whereas the first, polymorphonuclear, phase had little effect on the passage of penicillin from blood to C.S.F., the second, lymphocytic, phase of the reaction was accompanied by a well marked increase in the permeability of the barrier (Swithinbank and others, 1953, Fig. 14 and Table VII).

The results obtained with sodium bromide were rather different.

Effects of the Complete Reaction

The bromide ratio has now been estimated throughout four complete reactions. These reactions were induced by injecting 3.75 μ g. of the purified protein derivative of tuberculin (P.P.D.) at lumbar puncture into the C.S.F. and subsequently collecting samples of blood and lumbar C.S.F. at regular intervals (usually once daily). The findings are summarized in Table I. In every instance the bromide ratio fell to the order of unity within three days of the injection of P.P.D., and in two cases within 24 hours. In other words, the blood-C.S.F. barrier to bromide was abolished during the first, polymorphonuclear, phase of the reaction.

During the second, lymphocytic, phase the bromide ratio either remained low or showed a further fall to values well below unity. As the second phase of the reaction subsided, so the bromide ratio began to climb, but was still well below the limits of normal during the third week of the reaction. In one case (E. M.) observations were continued at frequent intervals for many weeks, and it was not until the eighty-eighth day after the injection of P.P.D. that the bromide ratio reached the lower limit of normal (Table I).

The typical behaviour of the bromide ratio in relation to the disturbances in cell and protein contents of the C.S.F. is shown in Fig. 1 (Case E. M.). In this case penicillin was also used as an indicator. Whereas most penicillin appears in the C.S.F. at the peak of the second phase, the maximal rate of fall in the bromide ratio coincides with the onset of the first wave of pleocytosis and rise in protein content. There is, however, no indication of a rise in the bromide ratio corresponding with the rapid

TABLE I
BROMIDE RATIOS IN FOUR COMPLETE INTRATHECAL TUBERCULIN REACTIONS IN SUBJECTS WITH NORMAL MENINGES

Case	Bromide Ratio when P.P.D. Given	Lowest Value during 1st Phase	Days after Injection	Lowest Value during 2nd Phase	Days after Injection	Value during 3rd Week	First Value in Normal Range	Day of Occurrence
E.M.	2.65	0.99	2nd	0.85	8th	1.05	2.17	88
W.S. (i)	2.48	0.95	1st	1.35	7th	1.8	Not recorded	
W.S. (ii)	2.75	1.09	1st	0.77	6th	1.89	Not recorded	
P.P.	2.81	1.01	3rd	1.02	5th	1.48	Not recorded	

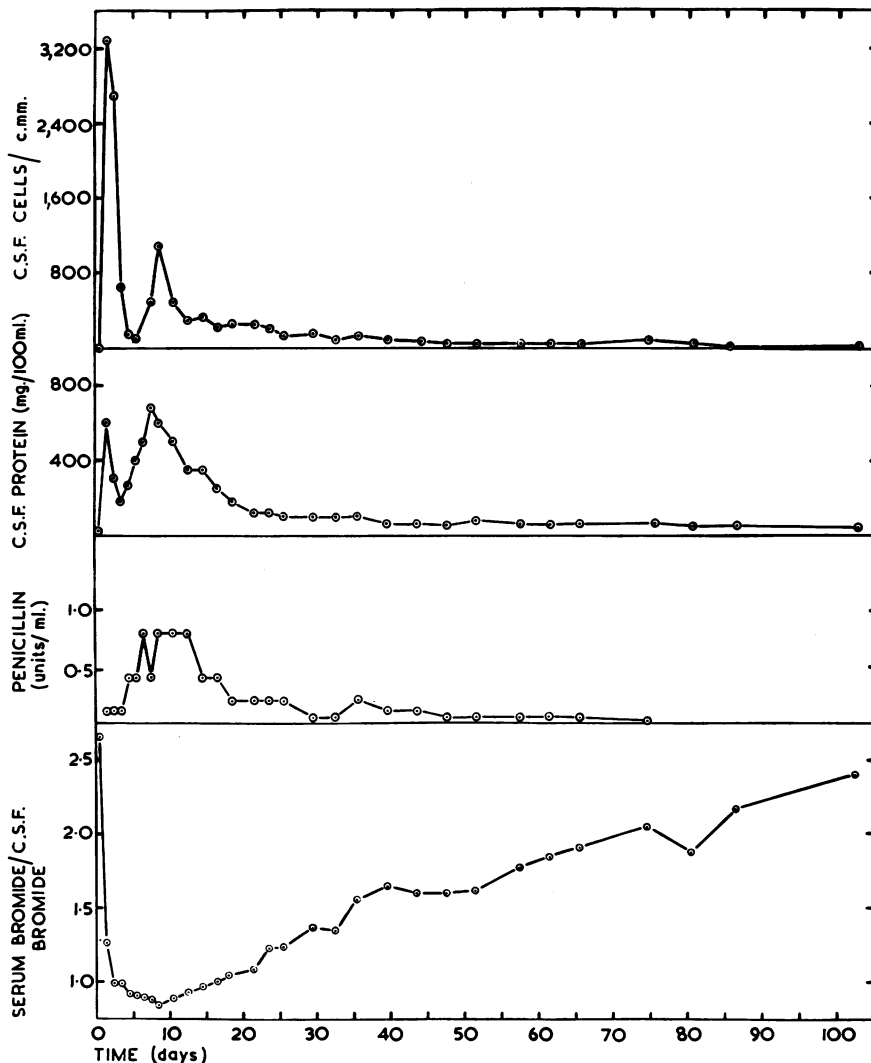


FIG. 1.—Effect of intrathecal P.P.D. on C.S.F. cells and protein, and on the penetration of penicillin and bromide from blood to C.S.F. in subject with normal meninges (Case E. M.). 3.75 μ g P.P.D. by lumbar injection on Day 1. Last dose of oral sodium bromide 72 hours before Day 1.

fall in cell count and protein content that marks the end of the first phase of the reaction. The second phase of the reaction is accompanied by a further small fall in the bromide ratio. As this second phase subsides, the bromide ratio slowly begins to climb, but its return to within normal limits is delayed well beyond that of the protein content.

The dissociation that appears as the reaction evolves between the increase in the permeability of the barrier to bromide and the intensity of the meningeal inflammation is further illustrated by Table II. This shows the daily values obtained for the bromide ratio compared with the total cell counts

and protein estimations during the first phase of the reaction in Case P. P. During the first 24 hours

TABLE II
TOTAL CELL COUNT AND PROTEIN CONTENT OF THE C.S.F., TOGETHER WITH THE BROMIDE RATIOS THROUGHOUT THE FIRST FIVE DAYS OF A COMPLETE INTRATHECAL TUBERCULIN REACTION

	Time in Days				
	1	2	3	4	5
Bromide ratio	2.81	1.33	1.19	1.01	0.99
Cells/c.mm.	12	4,560	2,510	350	254
Protein (mg./100 ml.) .. .	30	300	170	160	180

P.P.D. given on Day 1.

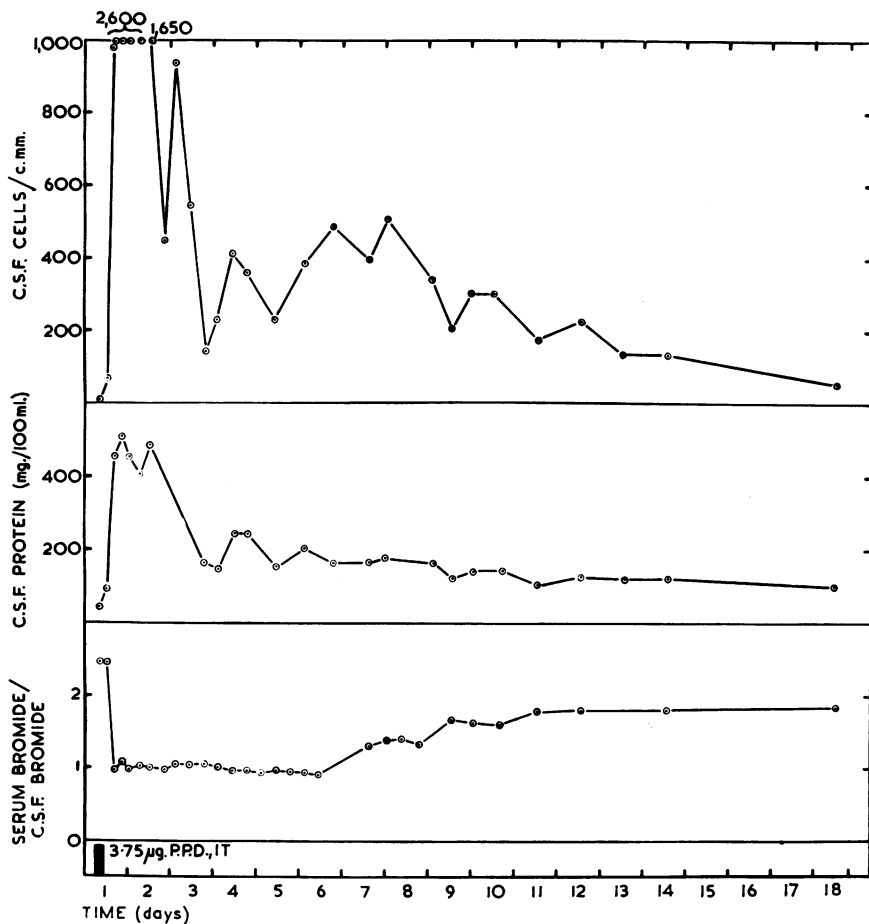


FIG. 2.—Effect of intrathecal P.P.D. on C.S.F. cells and protein and on the bromide ratio in subject with normal meninges (Case W. S.).

The lumbar C.S.F. was examined every four hours during the first five days of the reaction.

Last dose of oral sodium bromide 57 hours before Day 1. 3.75 µg P.P.D. by lumbar injection at first tap on Day 1.

the bromide ratio falls as the meningeal reaction develops, but thereafter the ratio continues to fall, even though the inflammation, as judged by the cell counts and protein estimations, is steadily waning.

In one case the early stages of the reaction were studied in more detail by means of lumbar puncture done every four hours (Swithinbank and others, 1953, Fig. 3). Fig. 2 shows the astonishing rapidity with which the barrier was abolished. Four hours after the injection the bromide ratio had not altered significantly, but by the eighth hour it had fallen to unity.

Effect of the Incomplete Reaction

When the tuberculin sensitivity of the recipient is low, or is artificially induced by vaccination, the intrathecal reaction is usually incomplete, the commonest anomaly being absence of the second, or lymphocytic, phase (Swithinbank and others, 1953,

Table V and Fig. 11). The bromide ratio has now been followed throughout four such abortive reactions (Table III). As in the complete reaction, the bromide ratio fell steeply during the first 24 hours, though it never reached unity. This depression was, however, quite short lived, and by the end of the second week the barrier was fairly well re-established.

Effect of Benadryl

As there is some evidence suggesting that antihistaminic drugs can modify both the intradermal (Sarber, 1948; Graub and Barrist, 1950) and intrathecal tuberculin reaction (Swithinbank and others, 1953), the following observations were made.

The subject, P. P., who had already shown a complete intrathecal reaction accompanied by typical changes in the blood-C.S.F. barrier to both bromide and penicillin (see Tables I and II), received a second lumbar injection of P.P.D. some months later. On this second occasion, however, 75 mg.

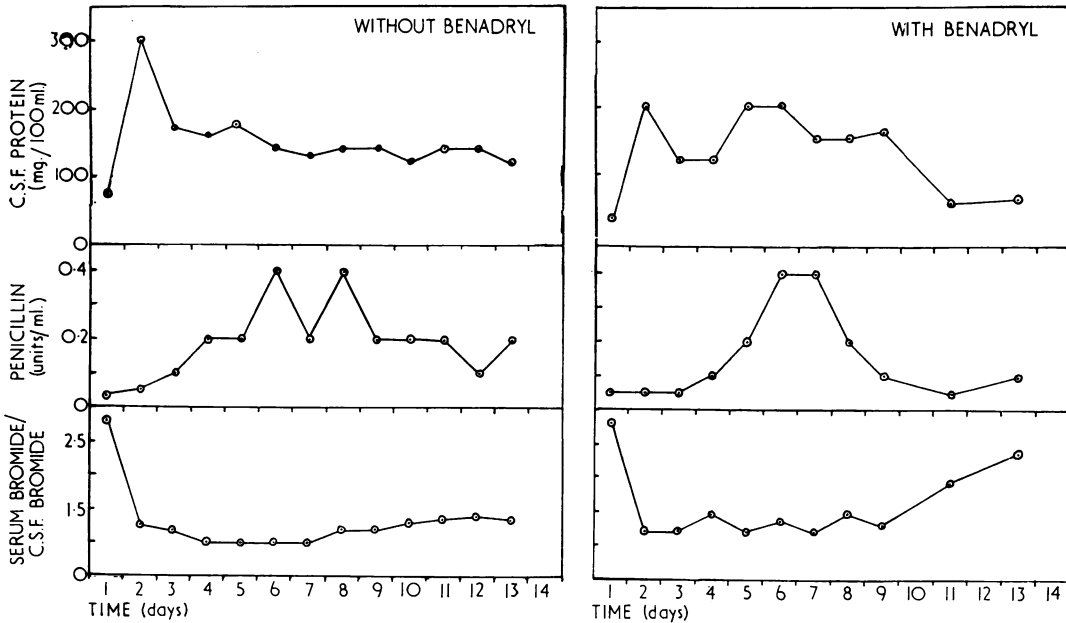


FIG. 3.—Behaviour of penicillin, C.S.F. protein, and bromide ratio following intralumbar P.P.D. without and with "benadryl"; 3.75 µg P.P.D. by lumbar injection on Day 1 in both régimes. Benadryl, 75 mg., given by mouth every four hours throughout second reaction.

"benadryl" was given by mouth every four hours throughout the period of observation and the injection of P.P.D. given only after the first three doses.

When no "benadryl" was given the cell count 24 hours after the injection of P.P.D. was 4,560 per c.mm., with 94% polymorphonuclears, and there was a well marked second rise in the cell count which reached a maximum on the sixth day. In the second reaction, however, the total cell count 24 hours after injection was only 900 per c.mm. (80% polymorphonuclears), while there was no significant second rise.

The protein and penicillin contents of the C.S.F. throughout both reactions are shown in Figs. 3a and 3b, together with the bromide ratios. When

"benadryl" was given the rise in protein content was both smaller and less persistent than in the first reaction. The initial fall in the bromide ratio was identical in the two reactions; but whereas, when no "benadryl" was given, the fall continued for another two days and the rise was so delayed that on the thirteenth day the ratio was still only 1.34, in the second reaction there was no further fall after the first day and by the thirteenth day the ratio had risen to 2.1, i.e., to within the lower limit of the normal range. Similarly with the penicillin: its passage from blood to C.S.F. was facilitated in both reactions but the return to normal was accelerated when "benadryl" was given. It appears, therefore, that in this case at least the administration

TABLE III
BROMIDE RATIOS IN FOUR INCOMPLETE INTRATHECAL TUBERCULIN REACTIONS

Case	Bromide Ratio when P.P.D. Given	Lowest Value during 1st Phase	Days after Injection	Lowest Value during 2nd Phase	Days after Injection	First Normal Value	Day of Occurrence	Remarks
C.F.	3.39	1.32	1st	1.52	5th	2.2	10th	Low sensitization
A.W.	2.66	1.5	1st	No second phase		2.21	15th	Low sensitization
J.D.	Samples lost	1.18	1st	1.5	5th	2.34	13th	Artificial sensitization
M.W.	2.22	1.23	1st	No second phase		2.30	14th	Artificial sensitization

of "benadryl" hastened the restoration of the blood-C.S.F. barrier to protein, bromide, and penicillin.

Effect of Cortisone

It has been amply shown that cortisone and A.C.T.H. can modify tuberculin sensitivity as judged by their effect on the intradermal tuberculin reaction (Long and Favour, 1950). Their mode of action is obscure (Long, Miles and Perry, 1951), but that cortisone, at least, is active on local as well as on systemic administration has been demonstrated both in the skin (personal observation) and in the anterior chamber of the eye. As there is also evidence that A.C.T.H. is able to bring about a rapid decrease in the abnormalities of the C.S.F. seen in tuberculous meningitis (Bulkeley, 1953), it seemed desirable to study the effect of cortisone on the intrathecal tuberculin reaction. The following two experiments were therefore performed.

Two subjects (A. G. and W. S.), in whom the Mantoux test was strongly positive to O.T. 1/1,000 and each of whom had previously shown a complete intrathecal tuberculin reaction to 3.75 µg P.P.D., received an intravenous injection of sodium bromide. Forty-eight hours later both received an intrathecal injection of 3.75 µg P.P.D. by lumbar puncture. At the same time one (W. S.) was given 50 mg. cortisone by mouth, and the other (A. G.) 5 mg. cortisone intrathecally. The subsequent reactions and their effect on the blood-C.S.F. barrier to bromide and, in Case W. S., to penicillin, were followed in the usual way. The results are shown in Table IV.

When 50 mg. cortisone was given by mouth there was an almost complete suppression of the poly-

morphonuclear component of the reaction: the total cell count 24 hours after injection was 540 per c.mm., but only 4.4% of these were polymorphonuclears. The protein component, the second phase of the reaction, and the facilitation of the passage of penicillin were not significantly altered. In spite of the considerable modification of the first phase, the bromide ratio still fell sharply during the first 24 hours of the reaction, though the level it reached, i.e., 1.24, was well short of unity. By the next day the ratio had already risen appreciably, and by the eleventh day was within normal limits. A similar though less well marked effect was seen when 5 mg. cortisone was given by intrathecal injection.

From these very limited observations it appears that both "benadryl" and, to a greater extent, cortisone are capable of modifying the intrathecal tuberculin reaction, the one by damping down the second phase and the other the first phase of the reaction. Both these anomalies can occur naturally, either when a very small dose of P.P.D. is given or when the sensitivity of the recipient is low (Switbank and others, 1953, Figs. 1 (a) and 11). It is of interest that both when the reaction was naturally anomalous and when it was artificially modified the return of the bromide ratio to normal was accelerated. It appears, therefore, that cortisone and, to a lesser extent, "benadryl" are antagonistic to tuberculin in their effect on the blood-C.S.F. barrier.

Effect of Intramuscular Tuberculin

It has already been shown that the intramuscular injection of tuberculin has no effect either on the

TABLE IV
EFFECT OF CORTISONE ON THE BEHAVIOUR OF THE CELL AND PROTEIN CONTENTS OF THE C.S.F. AND THE BROMIDE RATIOS THROUGHOUT THE INTRATHECAL TUBERCULIN REACTION

Days	1	2	3	4	5	6	7	8	9	10	11	14-16
CASE W.S. Reaction I												
Cells/c.mm.	14	2920	538	410	236	483	393	507	205	300	300	134
% Polymorphs	0	90	31	5	14	1	0.5	0.5	0	0.5	0.5	1
Protein (mg./100 ml.)	40	400	160	240	148	160	160	180	120	140	100	120
Bromide ratio	2.48	1.04	1.06	0.96	0.96	0.91	1.31	1.36	1.65	1.63	0.79	1.8
Reaction II (bovine P.P.D.)												
Cells/c.mm.	1	2450	—	720	—	536	—	1728	—	1000	—	378
% Polymorphs	0	70	—	?	—	0.05	—	0.05	—	0.05	—	3
Protein (mg./100 ml.)	30	360	—	360	—	360	—	240	—	200	—	180
Bromide ratio	2.75	1.09	—	0.93	—	0.77	—	0.83	—	0.87	—	1.24
Reaction III (cortisone 50 mg. p.o.)												
Cells/c.mm.	3	540	310	450	542	500	390	536	332	—	159	170
% Polymorphs	0	4.4	6	2	0	0	0	1	1	—	0	0
Penicillin	0	<0.05	0.05	?	0.1	0.05	0.1	>0.05	0.05	—	0.05	—
Protein (mg./100 ml.)	40	300	120	180	180	160	120	140	140	—	100	60
Bromide ratio	3.44	1.24	1.46	1.32	1.42	1.19	1.71	1.39	1.61	—	2.5	2.7
CASE A.G. (cortisone 50 mg. I.T.)												
Cells/c.mm.	0	252	154	228	148	208	233	264	270	—	163	139
% Polymorphs	0	47	16	10	1.5	0	0.5	1.6	2.5	—	0	0
Penicillin	0	<0.05	0.05	<0.05	0.1	0.05	0.1	0.05	—	—	—	—
Protein (mg./100 ml.)	35	120	120	120	120	100	120	120	120	—	110	60
Bromide ratio	2.75	1.41	1.41	1.4	1.31	1.5	1.54	1.54	1.49	—	1.74	2.03

P.P.D. given on Day I.

TABLE V

DISTRIBUTION OF THE BROMIDE RATIOS AT THE OUTSET OF TREATMENT IN 45 CASES OF TUBERCULOUS MENINGITIS TOGETHER WITH THE STAGE OF THE DISEASE AND ULTIMATE OUTCOME

Bromide Ratio		<0.7	0.7-0.99	1.0-1.29	1.3-1.59	1.6-1.89	2.0-2.19	>2.19	Total
No. of Cases	0	18	19	5	2	1	0	45
Cases : Stage of Disease	"Early" ..	—	4	4	1	1	1	—	11
	"Intermediate" ..	—	12	12	3	—	—	—	27
	"Late" ..	—	2	3	1	1	—	—	7
Died	—	5	4	1	0	0	—	10

cell and protein contents of the C.S.F. or on the blood-C.S.F. barrier to penicillin (Swithinbank and others, 1953, Fig. 13). The bromide ratio has also been estimated daily for six days following the intramuscular administration of tuberculin in a dose sufficient to cause a clinical reaction. No significant change in the ratio was seen.

The Bromide Ratio in Tuberculous Meningitis

The effect of tuberculous meningitis on the blood-C.S.F. barrier to bromide is identical with that of the experimental intrathecal tuberculin reaction. During the active stage of the disease a profound fall in the bromide ratio is the rule, with a return towards normal as convalescence advances. This depression of the bromide ratio has proved so characteristic of tuberculous meningitis, as opposed to other varieties of "lymphocytic" meningitis with comparable changes in the C.S.F., that it has provided the basis for a diagnostic test (Taylor and others, 1954).

The bromide ratio has now been estimated in 45 cases of tuberculous meningitis during the first month, and usually during the first week, of admission to hospital. The diagnosis was confirmed bacteriologically in every case but one; no patient had received any tuberculin at the time of the tests, and none showed any evidence of spinal block. The results are shown in Table V. Of the 45 cases, in 37 the ratio was less than 1.3 and in 18 it was less than unity, while in only three did it exceed 1.6.

Table V shows the distribution of these cases in regard both to the stage of the disease at the outset of treatment and to the ultimate mortality. The stage of the disease is defined as "early", "intermediate", and "late" in terms of a simple classification based, not on duration of symptoms, but on the patient's clinical condition (Medical Research Council, 1948), and it is now established that, given adequate treatment, it is the stage reached by the disease when treatment is begun that is the overriding factor in prognosis (Lorber, 1954). In this series of cases the time when treatment was begun corresponds with fair accuracy to the time the bromide test was performed.

It is clear from Table V that the characteristic and profound depression of the bromide ratio is independent of the stage of the disease and therefore of the ultimate prognosis. For example, of the 11 cases in which the disease was still at the "early" stage, in eight the bromide ratio was already lower than 1.3 and in four it was below unity. At the other end of the scale, of those three exceptional cases in which the bromide ratio exceeded 1.6 the disease was in the "early" stage in two, but in the third was very advanced.

It appears, therefore, that the depression of the blood-C.S.F. barrier is something more than an expression of the extent and intensity of the inflammatory changes in the leptomeninges. This conclusion is supported by the finding that, in tuberculous meningitis, there is no quantitative relationship between the depression of the bromide ratio and either the cell count or protein content of the C.S.F. Thus, while it is true that a high protein content of, for example, 400 mg. per 100 ml. or over, has always been accompanied by a low bromide ratio, the converse does not hold, and ratios of unity or below have not infrequently been found in fluids that contained less than 100 mg. protein per 100 ml. (Taylor and others, 1954, Fig. 3).

As the active meningeal infection is controlled, so the blood-C.S.F. barrier to bromide is gradually restored. Table VI shows the distribution of cases according to the ratios found during the period of intrathecal medication*, which corresponds with the period of active infection as judged by certain well defined clinical and pathological criteria (Cairns and Smith, 1952; Smith, 1952), compared with the ratios found at the first estimation and during convalescence. As already stated, all the first estimations were done during the first month in hospital, and the great majority during the first week. The estimations tabulated as "during treatment" were done later than the first month, and where several had been done the earliest was chosen. When P.P.D. was used in treatment the values obtained just before the injection were

* It has already been shown that intrathecal medication alone, in the absence of active tuberculous meningitis, has no significant effect on the blood-C.S.F. barrier to bromide (Taylor and others, 1954).

TABLE VI
DISTRIBUTION OF THE BROMIDE RATIOS THROUGHOUT THE COURSE OF THE ILLNESS IN TUBERCULOUS MENINGITIS

	No. of Cases	<0.7	0.7-0.99	1.0-1.29	1.3-1.59	1.6-1.89	1.9-2.19	>2.19	Mean
1st Estimation	45	0	18	19	5	2	1	0	1.13
During I.T. treatment without P.P.D.	14	0	5	4	3	0	2	0	1.2
During I.T. treatment with P.P.D.	22	1	9	6	6	0	0	0	1.07
Early convalescence	29	0	0	3	11	7	5	3	1.71
Late convalescence	22	0	0	0	3	6	6	7	2.02

chosen rather than those at the height of the reaction. "Early convalescence" is defined as any time between the conclusion of the intrathecal medication and the end of the sixth month in hospital, and "late convalescence" as between the conclusion of intrathecal medication and the end of the first year. Where several such estimations were done the latest were chosen.

Table VI shows that, whether or not P.P.D. is used in treatment, the peak incidence during the stage of active infection remains the same as at the time of the first estimation and lies between 0.7 and 1.29. During early convalescence the peak shifts to the right, to lie between 1.3 and 1.89. This shift becomes still more marked during late convalescence, when the mean value for a total of 22 cases is 2.02, that is to say, at the lower limit of normal (Fig. 4).

The behaviour of the blood-C.S.F. barrier to bromide throughout the course of the illness is exemplified by the following case, in which serial estimations of the bromide ratio were done for both lumbar and cisternal fluid and in which intrathecal P.P.D. was not used in treatment.

Case No. 182.—A regular soldier aged 26 years was admitted to the Military Hospital for Head Injuries, Wheatley, on March 3, 1953, suffering from Pott's disease with incipient paraplegia, chronic phthisis, and renal tuberculosis. During the first three weeks in hospital he developed obvious signs of meningitis, and lumbar puncture on March 24 yielded a fluid which showed the characteristic changes of tuberculous meningitis and in which *M. tuberculosis* was identified by direct examination and culture. Treatment was begun immediately with daily intrathecal and systemic administration of both streptomycin and isonicotinic acid hydrazide (I.N.A.H.). Because of the extent and severity of the systemic disease, tuberculin was given by intramuscular injection, but no intrathecal P.P.D. was injected for fear of exacerbating the paraparesis.

The daily intrathecal medication was continued for a total of 190 days and the intramuscular streptomycin for 200 days. The streptomycin was then stopped because of incipient deafness, but the oral I.N.A.H. and *para*-amino-salicylic acid (P.A.S.) were continued for a total of 400 days.

For the first month the patient remained critically ill. He then slowly but steadily improved, and 15 months after the beginning of treatment he was free from all signs and symptoms and on full activity, though still wearing a spinal brace. Radiographs of the chest and spine showed satisfactory healing, and the urine was normal in all respects. The C.S.F. then contained 70 mg. protein per 100 ml. as its only abnormality, while repeated cultures of C.S.F., urine, and laryngeal swabs had all been negative for many months.

Serial estimations of the bromide ratio were made

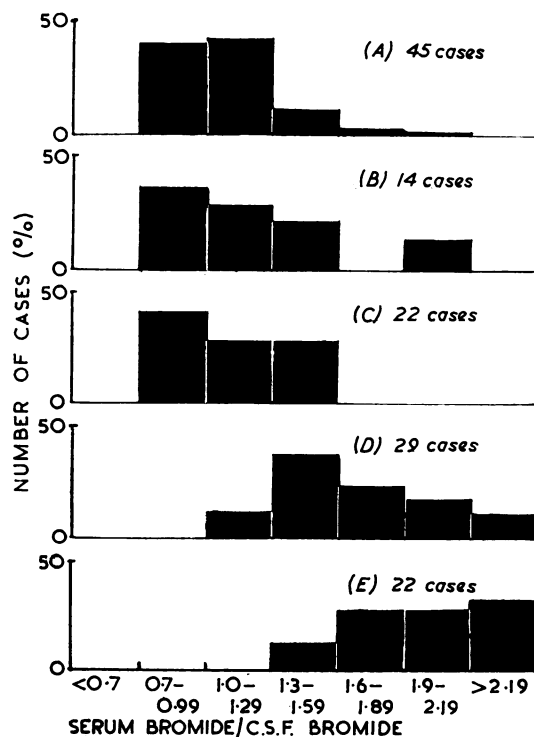
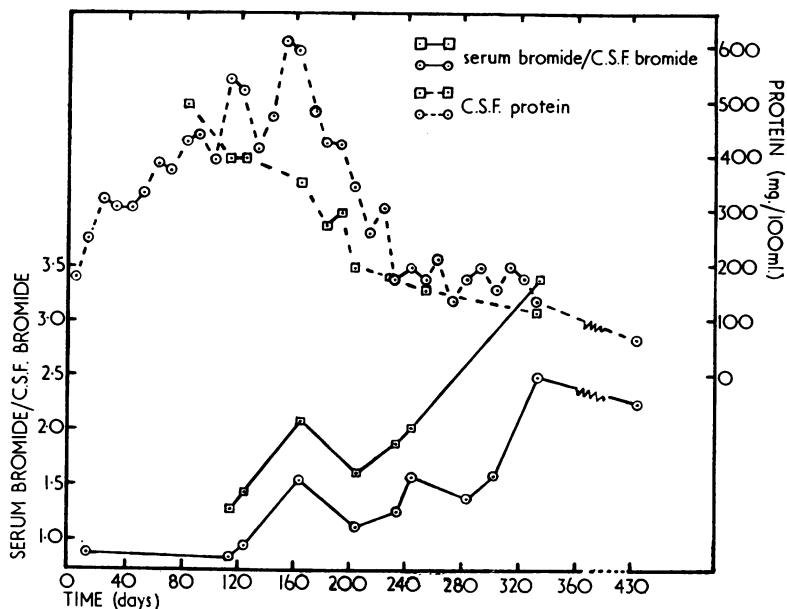


FIG. 4.—Bromide ratios during the course of the illness in tuberculous meningitis. A, at outset of treatment. B, during period of intrathecal medication. No P.P.D. given. C, during period of intrathecal medication. P.P.D. used in treatment. D, during early convalescence. E, during late convalescence.

FIG. 5.—Protein content (mean for each 10-day period) and bromide ratio for both cisternal and lumbar C.S.F. throughout the course of the illness in Case 182. No intrathecal P.P.D. given. Meningeal infection considered obsolete after 190 days.



throughout the illness. The results are shown in Fig. 5, together with the average value of the protein content of the lumbar C.S.F. for each 10-day period of treatment.

It has been found that the behaviour of the protein content of the C.S.F. reflects the activity of the meningeal infection fairly accurately (Cairns and Smith, 1952). In this case repeated cisternal punctures were done in order to make sure that the high protein levels in the lumbar C.S.F. were not due simply to the local effect of the spinal lesion. As the protein values for lumbar C.S.F. were closely paralleled by those for cisternal, they were in all probability an accurate index of the progress of the meningitis. When the infection was obsolescent, as indicated by a sustained fall in the protein curve, so the bromide ratio for lumbar fluid steadily rose and was paralleled by a rise in the ratio for cisternal fluid, though at a higher level.

Other evidence that a return of the bromide ratio to within the limits of normal is an indication that the meningeal infection is obsolete was provided by three fatal cases in which the patients died from causes other than the meningitis. Estimation of the bromide ratios during late convalescence gave values of 2.0, 2.25, and 2.48 respectively, and careful post-mortem studies confirmed that in all three cases the meningitis was well healed. By contrast, in a fourth case in which the patient died from a recrudescence of the meningitis after withdrawal of the intrathecal medication, the bromide

ratio at the end of the previous course of treatment never rose above 1.08.

A bromide ratio of 2.0 or higher has now been found in 25 cases at a time when, on clinical grounds, the infection was thought to be obsolete. None of these patients has yet shown any evidence of relapse, but the follow-up period is still too short for the restoration of the blood-C.S.F. barrier to bromide to be accepted as a criterion of cure.

The Bromide Ratio at Different Levels of the Neuraxis

It has already been shown that, in the absence of meningitis, fluid withdrawn from the lateral ventricles contains only about one half the amount of bromide of the lumbar C.S.F. The bromide ratio (S/V) is correspondingly higher and normal values probably range between 3.28 and 4.9. Such few observations as have been made on fluid withdrawn from the cisterna magna indicate that the ratio serum bromide/cisternal C.S.F. bromide (S/C) lies between that for lumbar (S/L) and for ventricular (S/V) C.S.F. (Hunter and others, 1954).

The bromide ratio for either ventricular or for cisternal fluids, or for both, has now been estimated simultaneously with that for lumbar C.S.F. in several cases of tuberculous meningitis and also at different stages of the illness in the same case. The results are shown in Table VII, together with the protein content of the C.S.F. The bromide ratio for ventricular fluid (S/V) has invariably been higher than that for lumbar (S/L), while the cisternal ratio

TABLE VII

SIMULTANEOUS ESTIMATIONS OF THE BROMIDE RATIO FOR LUMBAR C.S.F. AND FOR EITHER CISTERNAL OR VENTRICULAR FLUID OR BOTH AT DIFFERENT PERIODS IN THE ILLNESS AND WITH AND WITHOUT MANOMETRIC SPINAL BLOCK

Stage of Illness	Serial No.	Spinal Block	Lumbar (L)		Cisternal (C)		Ventricular (V)	
			S/L	Protein (mg./100 ml.)	S/C	Protein (mg./100 ml.)	S/V	Protein (mg./100 ml.)
On admission	166	No	1.07	210		Not recorded	1.38	10
	173	No	0.93	150		Not recorded	2.27	45
	202	No	1.29	160	2.94	68	Not recorded	85
	54X	No	1.08	174	—	—	1.9	85
	207	Yes	0.79	750	—	—	2.78	27
During intrathecal treatment	140	No	0.89	295	1.26	76		Not recorded
	145	No	1.05	125	2.42	40		Not recorded
	154	No	0.97	143	—	—	3.04	7
	182 (i)	No	0.88	520	1.31	325	—	—
	20X	No	0.94	—	1.05	—	1.39	—
	46X	No	1.12	105		Not recorded	3.08	35
	112	Yes	0.96	—	1.49	—	1.58	—
	125 (i)	Yes	1.01	4400	1.48	87	—	—
	23X	Yes	0.89	1332		Not recorded	2.14	23
	52X	Yes	0.87	1600	1.98	32	3.10	20
	39X (i)	Yes	0.87	530	1.28	100		Not recorded
	55X	Yes	0.81	95	1.74	15		Not recorded
Early convalescence	106 (i)	No	1.02	51	1.65	9	1.99	7
	182 (iii)	No	1.14	260	1.62	160		Not recorded
	193 (i)	No	1.0	275	1.52	110		Not recorded
	193 (iii)	No	1.14	190	1.55	102		Not recorded
	125 (iii)	Yes	1.06	3950	2.57	56		Not recorded
	39X	Yes	1.67	365	2.65	16		Not recorded
Mid-convalescence	106 (ii)	No	2.0	45		Not recorded	3.28	23
	163	No	1.35	60		Not recorded	2.85	38
	182 (iii)	No	1.60	174	2.04	102		Not recorded
	193 (iii)	No	1.30	173	1.79	123		Not recorded
	19X	No	1.51	—	2.43	—	3.37	—
	125 (iii)	Yes	1.29	1200	3.45	20		Not recorded

(S/C) has been intermediate between the two. But although the relationship $S/V > S/C > S/L$ has so far proved invariable, it is clear from Table VII that all three ratios are depressed during the active stage of the illness and rise as convalescence advances. The characteristic relationship between S/L and S/C, and the behaviour of both during the course of the illness, are well shown by Case 182 (Fig. 6).

The gradient for the bromide content of the C.S.F. at different levels of the neuraxis is thus in the same direction as for the protein content. But whereas the disparity between the protein contents of lumbar C.S.F. and of either cisternal or ventricular fluid is greatly enhanced by the presence of manometric spinal block, the relationship between the S/L and either S/C or S/V does not appear to be proportionately affected. Nor, although the bromide and protein contents vary in the same direction, is there any quantitative relationship between them. For example, in Case 106 (i) the ratios S/C and S/V are depressed, although the protein contents are normal. Again, in Case 140, the ratio $S/C = 1.26$, that is to say it was greatly depressed even though the protein content was only 76 mg. per 100 ml. By comparison, in Case 182 (i) $S/C = 1.31$; that is to say it was actually a little

higher than in Case 140, even though the protein content was as high as 325 mg. per 100 ml.

The Effect of the Intrathecal Tuberculin Reaction in Cases of Tuberculous Meningitis

When intrathecal P.P.D. is used in the treatment of tuberculous meningitis its effect on the bromide ratio for lumbar fluid may not be apparent because the ratio S/L is already depressed by the meningitis. Even so, the lowest values yet recorded for S/L have been found in cases of tuberculous meningitis under treatment with P.P.D., when S/L has on occasions been as low as 0.71, 0.72, and 0.68.

When treatment with P.P.D. is continued into convalescence each reaction will cause a new, though temporary depression of the ratio, just as it brings about a recurrence of the physical and mental signs of the meningitis (Williams and Smith, 1954). For this reason a low bromide ratio cannot be interpreted as evidence of continued infection until at least two weeks and probably longer have elapsed since the last intrathecal injection of P.P.D.

The effect of the intrathecal tuberculin reaction is seen better in cisternal than in lumbar fluid because the ratio S/C is usually well above unity even at the height of the infection. When, however, P.P.D. is injected directly into the cisterna

FIG. 6a.—Behaviour of bromide ratio and lumbar and ventricular C.S.F. protein following lumbar injection of 7.5 µg P.P.D. on Day 1. Last oral dose of sodium bromide six days before Day 0.

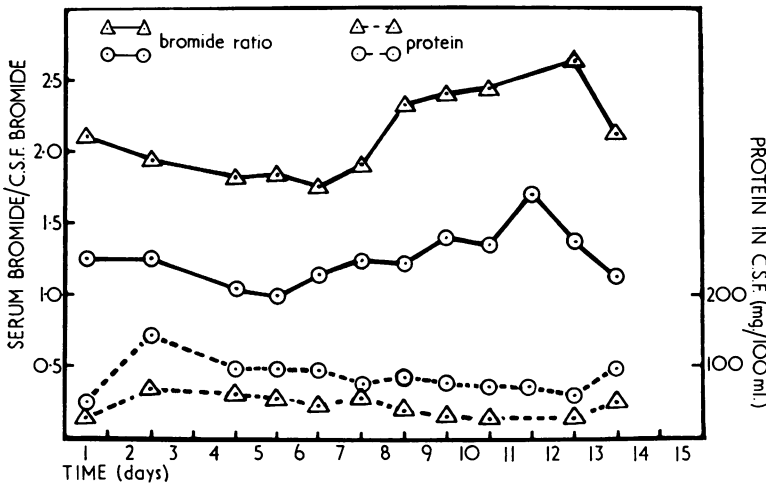
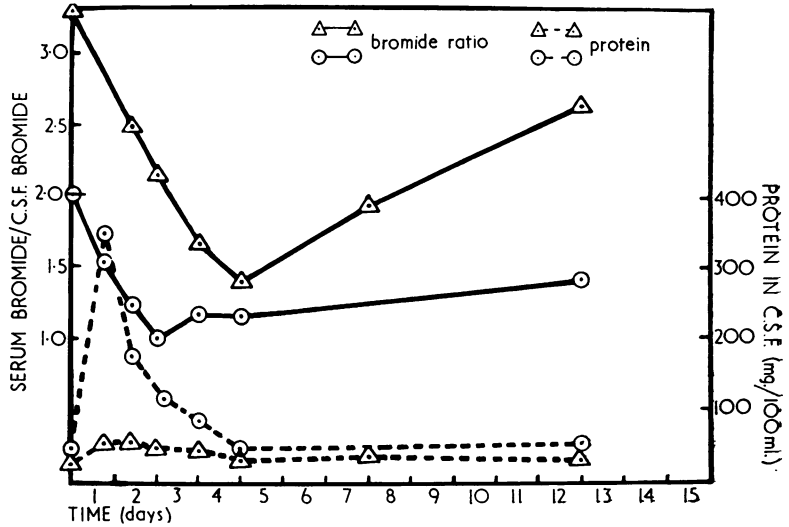


FIG. 6b.—Behaviour of bromide ratio and lumbar and ventricular C.S.F. protein following intraventricular injection of 7.5 µg P.P.D. on Day 1. Last oral sodium bromide 48 hours before Day 1.

magna the ratio S/C falls towards unity as the reaction develops and then re-establishes itself as the reaction subsides.

The effect of the reaction on the ratio for ventricular fluid was studied in Case 106, in which two reactions were provoked during late convalescence. In the first the P.P.D. was injected by lumbar puncture and in the second by ventricular puncture. The behaviour of the protein contents and of the ratios S/L and S/V throughout both reactions is shown in Figs. 6a and 6b. When the P.P.D. was given by lumbar puncture there was a brisk rise in the protein content of lumbar C.S.F., accompanied by the expected fall in S/L. The protein content of the ventricular fluid was, however, little disturbed, and although the ratio S/V was depressed the fall

was not only delayed well beyond that of S/L (Fig. 6a) but was never so marked. This relationship was preserved even when the P.P.D. was injected directly into the ventricle. The resulting rise in protein, though small, was greater in the lumbar than in the ventricular fluid, while the fall in S/V was not only considerably smaller than that of S/L but did not reach its maximum until S/L had begun to increase (Fig. 6b).

It appears, therefore, that while the effect of the intrathecal tuberculin reaction on the blood-C.S.F. barrier to bromide is similar for both lumbar and cisternal fluid, it is different for ventricular fluid in that the rise in the bromide content of the ventricular fluid is both smaller and slower than in lumbar C.S.F.

Discussion and Conclusions

Many attempts have been made in the past to increase the permeability of the blood-C.S.F. barrier and so render the central nervous system more accessible to therapy. For example, there is a considerable body of literature on the use of theophylline, urotropine, salicylates, and other substances as adjuvants to arsenic, quinine, and therapeutic sera. Most of such work, however, is either frankly disappointing or lacks quantitative criteria and is therefore inconclusive. Nor is it easy to find definite evidence of any agent that changes barrier permeability from among the extensive observations that have been made with dyes. There are, of course, a great many accounts of the increase in permeability of the barrier in certain diseases, and particularly in meningitis; but once again quantitative data are largely wanting, hence the diversity of opinion that persists as to the efficacy or otherwise of systemic chemotherapy in the treatment of meningitis.

Perhaps the first really promising approach towards a quantitative method for assessing changes in the blood-C.S.F. barrier was made when Walter described his bromide distribution test (Walter, 1929). The full value of this test has, however, only become apparent since precise methods for bromide determination have been developed (Hunter, 1953; Hunter and Goldspink, 1954). The bromide test possesses certain unique advantages and should provide a useful method for assessing the efficacy of agents that are claimed to alter the permeability of the barrier. The test has proved useful in both the diagnosis and management of tuberculous meningitis, but what is more important is that it has made it possible to demonstrate the profound and dramatic effect on the blood-C.S.F. barrier exerted by tuberculin when this is introduced into the C.S.F. of the sensitized subject. We can find no record of a comparable effect produced by any specific factor; still less by a factor that occurs in nature and in amounts that are probably of the same order as those used experimentally.

The results of the bromide test in tuberculous meningitis, in other varieties of "lymphocytic" meningitis, and in the intrathecal tuberculin reaction, together with observations made on the passage of penicillin from blood to C.S.F., go some way towards resolving the confusion that exists concerning the effect of leptomeningitis on the permeability of the blood-C.S.F. barrier. In the first place, study of the intrathecal tuberculin reaction shows that the effect of a given inflammatory process on the blood-C.S.F. barrier is not necessarily uniform in respect of different substances. Thus, in the

complete reaction the permeability of the barrier is increased for both bromide and penicillin, though to a different degree; but the maximal effect for the two substances is seen at different stages of the reaction. Further, in those anomalous reactions in which the second phase is lacking the passage of bromide is still greatly facilitated (Table III), although the barrier to penicillin is not detectably affected (Swithinbank and others, 1953, Table VII).

Again, the contrast between the low bromide ratio so characteristic of the intrathecal tuberculin reaction and of tuberculous meningitis, and the much higher ratios found in other varieties of "lymphocytic" meningitis shows that the effect on the barrier varies with the aetiological agent. We have not as yet had many opportunities for studying the bromide ratio in acute purulent meningitis, but such observations as have been made support this conclusion, since it is apparent that the barrier is neither so regularly nor so profoundly affected as in tuberculous meningitis. For example, in one case of pneumococcal meningitis the bromide ratio never fell below 1.84, and early in the illness, at a time when pneumococci could still be isolated from the C.S.F., it was as high as 2.16.

Since, therefore, the effect of meningeal inflammation on the blood-C.S.F. barrier varies with the aetiology of the inflammation and with respect to different substances, it follows that no valid generalization can yet be made concerning the effect of leptomeningitis on the passage of medicaments from blood to C.S.F. It follows, too, that the great increase in barrier permeability seen in the intrathecal tuberculin reaction and in tuberculous meningitis must depend on something other than straightforward, non-specific meningeal inflammation. This conclusion is supported by the detailed observations made during the experimental reaction. Judging by the height of the pleocytosis and protein content of the C.S.F., the intensity of the inflammation is greatest during the first, or polymorphonuclear, phase. Yet the greatest penetration of penicillin and the maximal depression of the bromide ratio, though not its rate of fall, coincided with the second, or lymphocytic, phase of the reaction. Moreover, during the interval between the two phases facilitation of the passage of both bromide and penicillin may still increase, even though the pleocytosis and elevation in protein content are subsiding rapidly (Fig. 1 and Table II).

It has already been shown that the meningeal disturbances that follow the introduction of tuberculin into the C.S.F. of a sensitized subject is the direct result of an antibody-antigen reaction (Swithinbank and others, 1953). There is, moreover,

good reason to believe that the C.S.F. changes of tuberculous meningitis are also the expression of similar, though spontaneous, intrathecal tuberculin reactions (Taylor, Smith, and Vollum, 1955). It is suggested, therefore, that the marked depression of the barrier is in some way a function of the hyper-sensitive response as such; and that in those varieties of meningitis in which the barrier is little affected some mechanism other than an antibody-antigen reaction is responsible for the inflammation.

The choroid plexus is commonly credited with playing a predominant, if not exclusive, part in elaboration of the C.S.F. This is not the place to discuss the vexed question of where the so-called blood-C.S.F. barrier is situated nor to speculate on its nature. It should, however, be noted that the bromide test promises to provide a useful tool not only for studying the effect produced on the barrier by different pathological processes but also for elucidating certain problems connected with the physiology of C.S.F. formation. Thus, the finding that lumbar fluid has invariably contained more bromide than fluid from the lateral ventricle, and that the relationship $S/V > S/L$ cannot be reversed, even by injecting tuberculin directly into the ventricle, is hardly compatible with the view that the choroid plexus is the sole, or even the chief, route by which bromide enters the C.S.F.

Summary

The bromide test has proved a valid means of measuring the permeability of the blood-C.S.F. barrier. Results are expressed as the "bromide ratio". The test has been used extensively in cases of tuberculous meningitis and also in the experimental intrathecal tuberculin reaction.

When the experimental intrathecal tuberculin reaction is fully developed the blood-C.S.F. barrier is abolished to bromide and impaired to penicillin. In abortive reactions the barrier to bromide is still seriously impaired but is restored more rapidly than after the complete reaction.

There is no quantitative relationship between the intensity of the inflammation of the meninges, as judged by the height of the pleocytosis and protein content of the C.S.F., and the depression of the barrier.

Cortisone and, to a lesser extent, "benadryl" appear to be antagonistic to tuberculin in their effect on the blood-C.S.F. barrier.

The effect of tuberculous meningitis on the blood-C.S.F. barrier to bromide is identical with that of

the experimental intrathecal tuberculin reaction. The ratio remains low as long as the infection is active and returns to normal during convalescence.

Studies of the bromide ratio for ventricular (S/V), cisternal (S/C), and lumbar C.S.F. (S/L) show that the relationship $S/V > S/C > S/L$ is invariable. In active tuberculous meningitis all three ratios are depressed but their relationship is never reversed.

The effect of the intrathecal tuberculin reaction in the presence of tuberculous meningitis is to lower all three ratios still further. The depression of S/V is delayed and smaller than that of S/L, even when the tuberculin is injected directly into the ventricle.

The significance of these findings is discussed, and it is concluded that the depression of the blood-C.S.F. barrier is a direct expression of an intrathecal antibody-antigen reaction.

It is highly unlikely that the choroid plexus is the sole, or even the chief, route by which bromide enters the C.S.F.

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