THE ENTRY OF RADIOSODIUM AND OF BROMIDE INTO HUMAN CEREBROSPINAL FLUID

BY

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The work described in this paper evolved during the course of some studies on the pathogenesis of disseminated sclerosis. In 1949 one of us (R. B. B.), impressed by the possibility that the plaques of disseminated sclerosis are the expression of an allergic response to substances of high molecular weight, advanced the following hypothesis. In most of the tissues of the body the lymphatics remove from the tissue fluid any large molecules, such as proteins and lipoids, that escape from the blood at the arterial end of the capillaries and fail to re-enter at the venous end. In the central nervous system, however, there is no true lymphatic system, and the only means of disposing of such molecules from the tissue fluid appears to be by way of the perineural or perivascular spaces into the main subarachnoid pathways, and thence through the arachnoid villi into the venous blood. But in order that fluid may flow in this direction the pressure in the capillaries of the central nervous system must exceed that of the cerebrospinal fluid (C.S.F.); and if, for any reason, this pressure relationship were reversed, then, presumably, the direction of flow would also be reversed, and fluid would pass from the main subarachnoid pathways back along the perivascular spaces towards the venous end of the capillaries. Here water and the smaller ions and molecules could pass freely back into the venous blood. Proteins, lipoids, or other large molecules that had been liberated from the neurons would, however, be unable to do so and might then accumulate around the venules in sufficient amounts to sensitize the tissues in their vicinity and so cause localized allergic reactions. This theory accords well with the finding that small and early plaques of disseminated sclerosis are frequently distributed round minute veins (McAlpine, Compston, and Lumsden, 1955), and also with the fact that perivascular demyelination can be produced experimentally by what is, in all probability, an allergic mechanism.

We have termed this hypothesis "the reverse

flow theory"; and it may be said at once that, although in the course of our studies we have found nothing incompatible with this theory, we have not yet been able to establish it as fact. It has, however, already shown its value by provoking an intensive study into the formation and composition of the C.S.F. in different neurological disorders.

1. The Choroidal Barrier Theory

With the reverse flow theory we coupled the suggestion that the well-known "bromide barrier", which causes the bromide content of human C.S.F. to be less than half of that found in the serum, exists in the epithelial cells of the choroid plexus and does not occur in the meninges. On this view, which we refer to as the "choroidal barrier" theory, normal C.S.F. would consist of a relatively bromide-free fluid from the choroid plexus mixed with bromide-containing fluid from the meninges, ependyma, and capillaries of the central nervous system.

It was suggested by Weed (1914) and recently confirmed by work with isotopes that the choroid plexus is not the only route by which substances enter the C.S.F. (Sweet, Selverstone, Soloway, and Stetten, 1950; Sweet and Locksley, 1953; Tubiana, Benda, and Constans, 1951).

We think the results shown below give considerable support to the choroidal barrier theory, although we have not been able to distinguish with certainty between fluid from the choroid plexus and that from the ependyma.

For this study accurate methods of estimating bromide in body fluids were essential. Improved methods were devised (Hunter, 1952; Hunter and Goldspink, 1954), and with them the partition of bromide between blood and C.S.F. in tuberculous meningitis and allied conditions was studied extensively (Hunter, Smith, and Taylor, 1954). It was shown that after equilibrium was established the lumbar C.S.F. invariably contained more bromide than the ventricular, while the bromide

content of cisternal fluid was intermediate between the two (Smith, Taylor, and Hunter, 1955). This finding confirmed those of Masserman (1934) and Schönfeld and Leipold (1925) and lent support to the hypothesis that the bromide in the C.S.F. came from sources other than the choroid plexus. To obtain further evidence on this point our later studies included the use of Na^{24} , and estimations of the concentrations of both Na^{24} and bromide in the C.S.F. at various periods after intravenous injection. This paper reports the results of these rate-of-entry studies, their bearing on the above theory of C.S.F. production, and their modification in certain diseases.

2. Technique, Material, and Methods

The clinical material for this study was drawn from cases of various neurological disease, both non-inflammatory and inflammatory. The non-inflammatory diseases included many cases of disseminated sclerosis and Parkinson's disease, and a few cases of other diseases of the basal nuclei and of motor neurone disease. These were drawn largely from the neurological wards of Stoke Mandeville Hospital, supplemented by certain cases from the Neurosurgical Department of the United Oxford Hospitals and by a special group of elderly patients with mental changes from the Cowley Road Hospital, Oxford. Among the inflammatory diseases are included a large number of cases of tuberculous and other varieties of meningitis which were drawn chiefly from the Tuberculous Meningitis Unit of the United Oxford Hospitals and from the Military Hospital for Head Injuries, Wheatley.

All these patients required lumbar punctures either in diagnosis or treatment. If for these same reasons ventricular or cisternal puncture was indicated, we were able to take advantage of this as well; such opportunities were, however, mainly confined to the inflammatory group.

Most of the lumbar punctures were done with the patient in the lateral position, and cisternal punctures in the sitting position. During the test the patients' activities were usually unrestricted, and although a few patients were ambulant the great majority were in bed.

At the beginning of the test a small quantity of blood was withdrawn from the basilar vein for estimation of the bromide already present. This was immediately followed by the intravenous injection of about 220 microcuries of isotonic radio-sodium chloride (0.5—1 ml.), together with 2 g.—6 g. non-radioactive sodium bromide (8—24 ml. 25% solution) given with the usual precautions (Taylor, Smith, and Hunter, 1954).

Approximately four hours later a few millilitres of C.S.F. were withdrawn and analysed for radiosodium, for bromide and protein, and occasionally for chloride. Two to 5 ml. of venous blood were taken at the same time, and the bromide and radiosodium content determined.

The radio counting was done, usually with immersion counters and sometimes with end window counters, as described elsewhere (Stott and Cullis, in preparation). The standard deviation of pairs of estimations, of

Na^{24} in samples of C.S.F. was 2.42% (on 57 pairs). This included some tests on very weak samples in which only 2,000 to 3,000 impulses were counted, and therefore the random error was considerable. A representative set of tests from which this random error was subtracted gave pairs with a standard deviation appreciably lower at 1.84%.

The analyses of bromide and other non-radioactive substances were made by Dr. G. Hunter and his staff as described elsewhere (Hunter, *loc. cit.*).

Except where otherwise stated, all the figures and calculations in this paper refer only to lumbar C.S.F.

Correction for Timing.—For comparison of results taken at times fairly close to four hours the observed concentrations were adjusted to four-hour values by multiplying by 240 and dividing by the actual number of minutes between injection and sampling.

Table I includes five cases in which samples were taken at times varying between five hours and five hours 10 minutes after intravenous injection. As shown in Section 10 an exponential or simple proportional correction would be inaccurate if applied over any large fraction of the fifth hour after injection. Since the rate of entry during the fifth hour in any patient shows some correlation with the rate during the previous four hours, the data shown in Table II, Group I, were used to calculate the regression line of the rate of entry during the period four to four and a half hours upon the rate of entry during the previous four hours. From this line separate correction factors were calculated for each of the five cases mentioned above.

Correction for Bromide Present before a Test.—When the bromide content of the initial specimen of serum was less than 3—4 mg./100 ml., as was usual, the small correction involved could be applied to the observed serum concentrations by deducting the initial value from the four-hour value. If the initial value for the C.S.F. was known it was similarly deducted; if not, the initial value for the serum was divided by the bromide ratio at equilibrium, and the quotient deducted from the four-hour value found for the C.S.F. Most of the tests in which the initial serum bromide exceeded 5 mg./100 ml. were discarded, since the resulting correction of 2 mg./100 ml. or more amounted to a serious fraction of the four hour value and its accuracy was doubtful.

3. Definitions

To save words we use certain terms with the following specialized meanings:—

The Bromide Ratio.—The bromide ratio, as with previous workers, means the ratio "serum bromide concentration/C.S.F. bromide concentration", at any time long enough after the administration of bromide for approximate equilibrium between plasma and C.S.F. to have become established. Owing to the slow excretion of bromide from the body, tests of this equilibrium ratio can be made for several weeks after the last administration of bromide without the need for fresh doses. It has been shown (Hunter *et al.*, 1954) that in the concentration used in these tests (less than 60 mg./100 ml. plasma an hour after injection) the bromide ratio is

independent of the concentration of bromide in the blood.

The Sodium Ratio.—The sodium ratio is similar, meaning the ratio “serum sodium/C.S.F. sodium” at equilibrium. This is approximately 1.0.

Sodium Entry.—Sodium entry is used for the ratio

$$\frac{\text{Concentration of radiosodium in C.S.F.} \times 100}{\text{Simultaneous concentration in plasma}}$$

when measured after periods much shorter than that needed for reaching equilibrium between the C.S.F. and plasma. For samples taken at any given time and for values of 20% or less, where reverse diffusion has only played a minor part, the “sodium entry” forms a rough guide to the rate of entry of sodium to the portion of the subarachnoid space from which the samples were taken. In drawing inferences from these “rates of entry”, it must be remembered that while many of the substances present may have come from the membranes surrounding the site of sampling, a large fraction may also have come by admixture of C.S.F. from other parts of the subarachnoid space.

In defining the above it is assumed that the concentrations in plasma and C.S.F. were measured at the same time (as was usually the case). In comparing ratios obtained at different times after the intravenous injection, it is important to remember that the apparent rate of entry is governed not by the plasma concentration at the time of sampling but by the mean concentration existing during the period between injection and sampling. Where this interval was four hours or more, it is probably safe to assume that the changes in serum concentrations of sodium and bromide have marched roughly in unison (since the bromide space in the body is found to be almost identical with the sodium space as soon as 20 minutes after intravenous injection, if a correction is made for the more rapid entry of bromide into red cells (Berson

and Yalow, 1955)). But when considering short periods of different length, or when testing the accuracy of exponential formulae, great caution is needed, owing to the rapid changes in plasma concentration in the first hours after injection.

Bromide Entry.—Bromide entry is used similarly to “sodium entry”, but for bromide instead of sodium.

The term “four-hour” refers to samples of C.S.F. taken four hours after the intravenous injection of the substances concerned.

4. Factors Influencing Lumbar C.S.F.

For studies of this kind lumbar C.S.F. has the disadvantage of coming from an outlying cul-de-sac of the subarachnoid space. Its composition differs from that of ventricular fluid. Further, the time taken by fluid from the choroid plexus to reach the lumbar sac must vary not only with the activity of the plexuses but with the vigour and phase relationship of the cardiac and respiratory pressure waves, and with the size of the ventricles. However, the last should not influence the equilibrium concentrations, and, since enough cases were studied to give results which appeared highly significant when treated statistically, we feel justified in drawing certain conclusions.

We have found appreciable variations in the rate of entry of bromide and even larger ones in the entry of sodium. While much of this variation is of uncertain origin, we have found changes in rate of entry correlated with age, with diseases of the basal nuclei such as Parkinson's disease, and with tuberculous meningitis and other inflammatory diseases of the central nervous system.

TABLE I

LUMBAR C.S.F. CONCENTRATIONS OF RADIOSODIUM AND BROMIDE FOUR HOURS AFTER INTRAVENOUS INJECTION IN PATIENTS CONSIDERED NEARLY NORMAL

Case No.	Disease	Age	Na ²⁴ C.S.F. × 100 Plasma	Br C.S.F. × 100 Plasma	Protein C.S.F. (mg./100 ml.)
264 X	Epilepsy (mild)	17	40.7	15.3	30
296 X	Syncopal attacks	18	30.6	16.6	25
280 X	Epilepsy (mild)	19	38.0	17.2	63
263 X	“ “	19	31.8	17.9	62
135 S	Psychoneurosis	21	26.0	12.3	35
67 S	Hysteria	24	46.0	20.1	43
58 S	Anxiety state	24	41.6	—	38
57 S	Headache	33	50.4	15.7	20
314 X	Pre-operative (gynaecological)	33	23.1	17.2	48
151 S	Compensation neurosis	45	20.8	22.0	27
145 S	Headache	46	36.4	17.2	—
162 S	Myalgia	49	16.9	12.1	30
300 X	Pre-operative (gynaecological)	55	21.8	—	—
127 S	Headache and vomiting	55	34.0	15.2	21
53 S	Migraine	58	31.6	—	37
82 S	Ataxia	60	17.4	14.0	23
156 S	Dysphagia	62	33.8	—	16
166 S	Post-herpetic neuralgia	69	25.5	—	41
161 S	“ “	74	12.2	11.5	29
169 S	Trigeminal neuralgia	83	22.6	—	—
Mean values in 20 cases		43.2	30.06	16.02	34.6
Standard deviations		20.396	8.944	2.88	—
Coefficients of variation		29.7	18.0	—	—

FIG. 1.—Percentages of radiosodium in lumbar C.S.F. four hours after intravenous injection. Effect of age in patients with abnormal physical signs. The diagonal line provides an estimate of the most probable sodium entry for any given age. The cross shows the mean value for a group of 16 elderly patients with some mental deterioration but lumbar C.S.F. protein level below 61 mg./100 ml.

5. Findings in Patients without Progressive Disease of the Nervous System ("Normals")

For obvious reasons it has been difficult to establish figures for normal human subjects. We have, however, managed to collect a limited number of cases in which the tests were made in the course of investigations that failed to show any sign of progressive disease of the nervous system. The clinical diagnoses in these cases included various psychopathic conditions such as compensation neurosis and anxiety state, mild idiopathic epilepsy, neuralgia, and myalgia. In addition, tests were made on two patients who were given a spinal anaesthetic before gynaecological operations. For convenience, these patients will be referred to as "normals".

The four-hour entry of both bromide and sodium, together with the clinical diagnosis and the protein content of the C.S.F., are shown in Table I.

It is noticeable that there is a larger scatter of the sodium values than of the bromide, the coefficient of variation for sodium being more than twice as great as that for bromide. One reason for this is that the sodium entry is to some extent influenced by the age of the patient.

6. Correlation between Sodium Entry and Age

The black circles in Fig. 1 show the Na^{24} concentrations given in Table 1 for 20 normal patients, plotted against age. It is evident that, while at any given age there is a variation of about 2 to 1 in Na^{24}

entry, there is a general tendency for the Na^{24} concentration at four hours to fall with increase in age. The correlation coefficient between age and sodium entry for this group of patients is 0.570. The probability (P) that this is not due to random deviations is a little less than 0.01. The cross in Fig. 1 shows the mean values of age and sodium entry for a group of 16 elderly patients who, though not acutely ill, showed some degree of mental confusion. It comes close to the regression line for the normals.

On the (unproven) assumption that the relation between age and sodium entry is linear, the regression line of lumbar sodium upon age has been calculated, giving the equation:

$$\frac{\text{Lumbar sodium} \times 100}{\text{Plasma sodium}} = 40.81 - (0.2821 \times \text{age in years})$$

This gives at birth (age 0) sodium 40.81, at age 50 sodium 26.70, and at age 90 sodium 15.42.

Correlation between Age and Bromide Entry.—Age has little, if any, effect on the bromide entry. For the 15 cases in Table 1 for which data are available, the correlation coefficient is only 0.105 and is not statistically significant. In the total of 105 patients for which we have these data the correlation is also negligible.

7. Correlation between Age and Bromide Ratio at Equilibrium

In 153 cases of non-inflammatory nervous diseases the bromide ratio was found to decrease slowly with age, showing a correlation coefficient of 0.514. This is 6.3 times the standard error for 153 cases and is therefore highly significant. On the assumption that the relationship is linear (as is suggested by the detailed figures), the regression line of bromide ratio on age was calculated as:

$$\text{Bromide ratio} = 3.005 - (0.01025 \times \text{age in years})$$

This gives an average equilibrium bromide ratio of 2.80 at age 20, 2.49 at age 50, and 2.18 at age 80 for the patients concerned.

Since none of our patients was entirely healthy, these figures must only be taken as a rough guide. Their extension to ages below 15 or above 90 would be purely speculative, since we have too few data to show whether the relationship is even roughly linear in childhood or after 85.

Correlation between Bromide Entry and Bromide Ratio at Equilibrium.—It was unfortunately seldom possible to establish the equilibrium bromide ratio in the cases listed in Table 1. However, for those cases of non-inflammatory disease for which data are available—and these include 26 cases from among the special group of elderly patients—the

correlation between the bromide entry and bromide ratio at equilibrium was negligible. This lack of correlation contrasts strongly with the findings in the cases of inflammatory disease as described later in Section II.

8. Hypotheses Concerning the Effects of Old Age on the C.S.F.

The disparity between the effect of age on the Na^{24} and on the bromide entry is itself evidence that the mechanisms subserving the passages of sodium and of bromide differ from one another. The finding that the equilibrium bromide ratio falls as age advances although the bromide entry remains unaffected makes it unlikely that the low bromide ratio of old age is simply the result of a general increase in permeability. A decrease in the formation of sodium-rich fluid by the choroid plexus would, however, on the choroidal barrier theory, automatically lower the bromide ratio and would be consistent with the observed fall in the Na^{24} entry.

In later life the brain substance tends to shrink and the ventricles to enlarge (Böning, 1924), while calcification in the choroidal plexus becomes increasingly common as age advances (Dyke, 1930). Both enlargement of the ventricles and degeneration of the choroidal artery and plexus would be expected to cause a decrease in the four-hour lumbar sodium entry, although enlargement of the ventricles alone could hardly alter the bromide ratio at equilibrium. The decrease in this ratio with advancing age is therefore best explained on the basis of choroidal degeneration, while both choroidal degeneration and ventricular enlargement may well play a part in the decrease of the four-hour lumbar sodium entry. The choroidal barrier theory thus offers a ready explanation for the observed effects of age on the C.S.F.

The conditions other than advancing age in which we have found consistent departures from the normal are diseases of the extra-pyramidal system and, more especially, inflammatory diseases of the nervous system. This second group, indeed, differs markedly not only from the normals but also from the non-inflammatory cases. But before going on to describe our findings in these two groups it is convenient to present here further evidence in support of the choroidal barrier theory. This evidence is derived from a study of the cases as a whole, irrespective of clinical diagnosis, except that the inflammatory cases are distinguished.

9. Comparison of Samples Taken at 4 and 4½ Hours

Valuable information as to the modes of entry of Na^{24} and bromide into lumbar C.S.F. can be gained by comparing samples of fluid obtained at

four and at four and a half hours after the intravenous injection. Table II shows the results obtained in 29 tests in which a needle was left in the lumbar sac for half an hour and a second sample taken approximately 30 minutes after the first one.

Group I shows the findings in non-inflammatory cases, in which no major disorder of the C.S.F. dynamics would be expected and in which the lumbar protein was less than 90 mg./100 ml. Group II contains those cases where serious disturbance of the production of C.S.F. seemed likely. All but one of this group were inflammatory cases, and in all but two the protein level was greatly raised. In each group the cases are arranged in order of decreasing rate of entry of Na^{24} during the first four hours of the test.

The most striking feature in Group I is the difference between the behaviour of the Na^{24} and bromide. The rate of entry of Na^{24} during the four to four and a half-hour period (t^2) is in every case faster than the average rate of entry during the preceding four hours (t^1), (compare columns 6, 7, and 8). The average ratio of the two rates is 1.702 (Col. 8). On the other hand, in 14 out of 18 observations the bromide actually comes in more slowly during the second period (t^2), and the ratio rate B./rate A. averages 0.9 (Col. 13) for the 18 cases.

This seems clear proof that, in these cases, the mode of entry of Na^{24} into the C.S.F. differs from that of bromide. It lends strong support to the view that, between four and four and a half hours after intravenous injection, C.S.F. containing a higher proportion of Na^{24} to bromide than that first entering the lumbar region is travelling down the spinal canal towards the lumbar sac.

Minor points of interest are: (1) The rates of entry of Na^{24} during the first period (t^1) show a positive correlation with the rates for the second period (t^2) and a slight negative one with the ratio of the two rates. This would be expected if the higher rates during the first period are due to the earlier arrival of sodium from the ventricles. (2) Rates A. and B. for Na^{24} depart widely from the results which would be expected from a uniform process of entry controlled by diffusion.

If the rates of diffusion across the membranes were equal in both directions, the process would be defined by the equation $kt = \log(100 - C_1) - \log(100 - C_2)$ where t is the time interval between two samples giving concentrations C_1 and C_2 and k is a constant. Taking the mean value for C_1 (sodium) from Group I as 20.8, and calculating k from this, the equation gives a calculated value for sodium entry C_2 (calculated) — C_1 (observed) of 2.20, i.e., a little over half of the observed difference of 3.93. A similar calculation for bromide gives a value for

C_2 (calculated)— C_1 (observed) of 1.78 which differs relatively little from the observed value of 1.60.

In Group II there are several points of interest, although since they mostly relate to single cases their value is only suggestive.

The case of convalescent tuberculous meningitis, in which ventriculo-cisternostomy had been performed for a presumed mid-brain tuberculoma, shows a high rate of entry of sodium in the first period, followed by a rather slow rate in the second one. Of the two cases of infective polyneuritis one, with a lumbar protein of 375 mg.%, shows a very high rate of entry of both Na^{24} and bromide in the first period; the other, with a lumbar protein of 147 mg.%, shows normal rates of entry for the first period. Neither case shows an increase in bromide during the second period.

The case with cerebral vascular lesions and arteriosclerosis shows an abnormally slow rate of entry of Na^{24} and bromide in the second period, nor was this influenced by the inhalation of CO_2 . This case, and the cases of "healed" and convalescent meningitis already mentioned, are the only ones in which the rate of Na^{24} entry during the second period is slower than that in the first. In the whole Table, three tests show a rate of entry of bromide greater in the second period than in the first in a ratio of over 2 to 1. In each case the patient was under the influence of an alleged dilator of the cerebral blood vessels, either "priscol" or CO_2 . Since the highest ratio observed in tests without a dilator was 1.63, and all except two of these ratios were less than 1.0, this observation is interesting.

10. Ratio of Sodium to Bromide at Different Times after Intravenous Injection: Periods from 4 Hours Upwards

During the 24 hours after intravenous injection considerable changes occur in the ratio of Na^{24} to bromide found in the C.S.F. These are of especial interest in throwing light on the source of the fluid.

It has already been shown that at equilibrium the bromide ratio for patients without disease of the nervous system is about 2.6 (Taylor *et al.*, 1954); that in certain inflammatory conditions, and especially in acute tuberculous meningitis, it is much lower and may fall below 0.8 (Smith, *et al.*, 1955); and that it tends to fall with increasing age (*v.s.*, Section 8). Less is known about the equilibrium ratio between the concentrations of Na^{24} in blood and C.S.F. Most of our tests showed a Na^{24} ratio close to 1.0; but we encountered the difficulty that equilibrium was not always established within 24 hours, while, owing to the rapid decay of Na^{24} , samples taken at 48 hours had counts too low for

great accuracy if we were to be certain that there was no possibility of exceeding the safe dose.

In two cases Na^{24} ratios of 0.77 were observed, *i.e.*, the Na^{24} concentration in the C.S.F. was 130% of that in the serum. We have no reason to suspect any error greater than 10% in these two measurements and think the subject worth further study. Greenberg, Aird, Boelter, Campbell, Cohn, and Murayama (1943) noted that from 20 hours after intravenous injection the concentration of Na^{24} in the C.S.F. of dogs always exceeded that in the plasma. A slight excess would be expected, owing to the continued exchange of the body Na^{24} caused by dietary intake and renal excretion. This exchange is not normally fast enough to account for a difference of more than a few per cent. between plasma and C.S.F. The range of concentration in m.Eq./litre given by Hald (1946) is 134.2 to 141.0 for serum and Dailey (1931) gives a normal range of 131 to 149 m.Eq./litre for C.S.F.

In the following discussion we shall assume the sodium ratio to be 1.0, although 0.96 is very probably a normal value. This would not, however, alter the main trend of our argument.

Fig. 2 shows the bromide entry plotted against the Na^{24} entry in 105 cases of non-inflammatory disease (dots) and in 20 tests in 18 cases of inflammatory disease (crosses). In any case in which the Na^{24} entry equals the bromide entry, that is to say, when the ratio Na^{24} to bromide is 1.0, the point will lie on the higher of the two diagonal lines drawn across the figure.

The lower line indicates the value for the ratio of Na^{24} to bromide of 2.6. This is the line on which points would lie if Na^{24} and bromide entered throughout in the same proportions as those found at equilibrium (taking 2.6 as the average normal value for the bromide ratio). This follows because the ratio of Na^{24} entry to bromide entry is the quantity

$$\frac{\text{C.S.F. Na}^{24} \text{ concentration} \times 100}{\frac{\text{Serum Na}^{24} \text{ concentration}}{\text{Serum bromide concentration}} \times \frac{\text{C.S.F. bromide concentration} \times 100}{\text{C.S.F. bromide concentration} \times 100}}$$

Now, if at equilibrium the concentrations of sodium in serum and C.S.F. are equal, then this quantity simplifies to

$$\frac{\text{Serum bromide}}{\text{C.S.F. bromide}} \text{ i.e., to the bromide ratio}$$

The crosses denote cases of inflammatory disease which are discussed in Section 11. The dots represent the non-inflammatory cases. It is clear from Fig. 2 that not only do the majority of these lie closer to the upper than to the lower line, but that they lie

FIG. 2.—Percentages of bromide and radiosodium in lumbar C.S.F. four hours after intravenous injection.

to the left of the upper line. In other words, in the majority of cases the value of the ratio Na^{24} /bromide at four hours is nearer to unity than to 2.6, and, in many, bromide has actually entered the lumbar C.S.F. more rapidly than Na^{24} . It follows, then, that for the ratio Na^{24} /bromide to reach 2.6/1 by 24 hours, the Na^{24} must enter in a much higher proportion relative to bromide than it has done during the first four hours. That this change has already begun by the period four to four and a half hours after injection is shown by Table II, discussed above. The increase in Na^{24} relative to bromide that takes place as the interval after injection lengthens is also well shown by serial observations carried out on individual cases.

The point is further illustrated in Fig. 3, which shows results observed in 55 patients with non-inflammatory disease. Here the ratio Na^{24} /bromide is plotted on the vertical scale and the percentage

of Na^{24} on the horizontal, first at four hours after injection, and secondly, at the right of the graph, after equilibrium has been reached.

While all points represent direct observations, the justification for treating the equilibrium set as representing the same relationship as is shown at four hours rests on the assumption discussed above that the sodium ratio at equilibrium is roughly 1.0 and the further assumption that Na^{24} behaves exactly as Na^{23} .

This figure has three features of interest, as follows:—

Whereas at four hours the relative concentrations of Na^{24} and bromide centre near 1.0 with a median at 1.02, at equilibrium they are in a very different proportion, with a median at 2.42. In other words, far more sodium in relation to bromide is found at equilibrium than at four hours (or at shorter periods, as our other results show). This change in ratio from

TABLE II
Na²⁴ AND Br⁸¹ IN LUMBAR C.S.F. AT FOUR AND FOUR AND A HALF HOURS AFTER INTRAVENOUS INJECTION

Case No.	Disease (1)	Sodium 24							Bromide						
		(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
		t_1 (min)	t_2 (min.)	c_1	$c_2 - c_1$	Rate A $\frac{c_2 - c_1}{t_2 - t_1} \times 60$	Rate B $\frac{c_2 - c_1}{t_2 - t_1} \times 60$	$\frac{\text{Rate B}}{\text{Rate A}}$	c_1	$c_2 - c_1$	Rate A $\frac{c_2 - c_1}{t_2 - t_1} \times 60$	Rate B $\frac{c_2 - c_1}{t_2 - t_1} \times 60$	$\frac{\text{Rate B}}{\text{Rate A}}$	Protein (mg./100 ml.)	Bromide Ratio
Group I															
123 S	Transverse myelitis (quiescent)	250	32	39.5	5.8	9.48	10.9	1.15	21.0	1.8	5.05	3.38	0.67	28	3.30
144 S	D.S.	240	30	28.7	5.7	7.17	11.4	1.59	23.6	4.8	5.9	9.6	1.63	40	2.44
121 S	D.S.	240	30	26.6	3.8	6.65	7.6	1.14	13.5	1.3	3.37	2.6	0.77	26	2.81
135 S	Psychoneurosis	240	30	26.0	4.5	6.50	9.0	1.38	12.3	1.2	3.08	2.4	0.78	35	3.33
211 X	Senile	275	30	26.0	3.2	5.68	6.4	1.13	21.3	0.5	4.65	1.0	0.22	15	—
50 S	D.S.	240	30	24.3	4.1	6.07	8.2	1.35	18.0	0.0	4.50	0.0	0.00	31	—
146 S	D.S. (with CO ₂)	240	30	37.5	5.6	9.37	11.2	1.20	12.3	3.1	3.07	6.2	2.02	40	3.16
133 S	D.S.	240	30	21.5	5.0	5.37	10.0	1.86	20.0	1.7	5.0	3.4	0.68	35	—
139 S	Hypertension	238	30	21.2	4.4	5.35	8.8	1.65	21.9	2.6	5.5	5.2	0.94	45	—
68 S	D.S.	245	30	20.2	3.8	4.95	7.6	1.54	19.8	1.5	4.85	3.0	0.62	75	2.18
128 S	D.S.	247	43	17.7	7.6	4.30	10.6	2.47	15.6	2.3	3.78	3.21	0.85	55	—
212 X	Senile	305	20	21.3	3.0	4.18	9.0	2.15	16.8	0.4	3.30	1.2	0.36	36	—
142 S	Neurosis	244	31	15.5	3.9	3.81	7.55	1.98	—	—	—	—	—	20	2.60
222 X	Senile	223	16	11.4	2.4	3.07	9.0	2.93	14.3	0.8	3.85	3.0	0.78	61	2.06
116 S	D.S. (advanced)	240	30	11.2	1.8	2.80	3.6	1.28	13.25	1.15	3.32	2.3	0.69	50	2.29
10 S	"	244	30	8.35	2.55	2.05	5.1	2.48	12.5	1.2	3.07	2.4	0.78	82	3.18
"	"	245	30	9.3	1.9	2.28	3.8	1.66	11.0	1.0	2.69	2.0	0.74	31	—
"	" (with "prisco")	245	32	9.1	2.5	2.23	4.68	2.10	10.3	2.9	2.52	5.44	2.16	52	—
	Means	246.7	29.7	20.4	3.93	5.06	7.82	1.702	16.26	1.60	4.01	3.36	0.900	43.1	2.735
Group II															
110 S	T.B. meningitis convalescing	243	30	46.5	3.5	11.50	7.0	0.61	—	—	—	—	—	—	2.36
134 S	Infective polyneuritis	255	30	47.8	7.2	11.22	14.4	1.285	39.5	0.0	9.3	0.0	0.0	375	1.73
132 S	Cerebral syphilis	245	30	27.6	8.6	6.76	17.2	2.55	18.2	0.0	4.36	0.0	0.0	147	—
140 S	Infective polyneuritis	250	30	19.4	3.8	4.66	7.6	1.63	18.8	0.5	4.60	1.0	0.22	14	2.78
125 S	Severe meningitis leaving gross damage	245	30	16.2	1.6	3.96	3.2	0.81	12.1	2.3	2.96	4.6	1.55	51	2.93
126 S	Cerebral thrombosis	240	30	15.4	1.0	3.85	2.0	0.52	12.6	0.5	3.15	1.0	0.32	105	—
"	" (with CO ₂)	242	30	17.8	0.2	4.42	0.4	0.09	12.5	0.5	3.10	1.0	0.32	205	1.71
106 S	D.S., arachnoiditis, laminectomy	257	70	12.9	6.9	3.01	5.9	1.97	18.2	1.6	4.25	1.37	0.32	220	2.48
"	" Plus CO ₂	246	30	19.0	4.4	4.64	8.8	1.90	12.7	3.8	3.10	7.6	2.45	118	2.48
210 X	Healed T.B. meningitis	260	30	8.2	1.6	1.89	3.2	1.70	10.2	1.8	2.35	3.6	1.53	153	1.66

Col. (2) The time t_1 between intravenous injection of Na²⁴ and Br and the taking of the first lumbar sample.
 Col. (3) The time between first and second lumbar samples.
 Col. (4) and (9) The concentrations of Na²⁴ and Br in the first samples expressed as C.S.F. $\times 100$ /plasma.
 Col. (5) and (10) The increase in concentrations of Na²⁴ and Br between first and second samples.
 Col. (6) and (11) The average rise per hour in percentage concentrations during the first four hours.
 Col. (7) and (12) The average rise per hour in percentage concentrations during the second period.
 Col. (8) and (13) The ratio of the average rates of entry during the first and second periods.
 Col. (14) The lumbar protein concentration in the first sample.
 D.S. = disseminated sclerosis.

1.0 to 2.42 is far greater than could be accounted for by any differences between the equilibrium sodium content of C.S.F. and serum that have yet been described or found in any of our tests. It can be explained by the assumption that there are two sources of C.S.F., of which one contributes a much higher ratio of sodium to bromide than the other and only affects the lumbar region later.

The figure also shows that in every one of these 55 cases the ratio of sodium to bromide was higher at equilibrium than at four hours. Since this was not self-evident for the five cases with a four-hour ratio above 1.50, lines are shown connecting these

points with the values found at equilibrium for the same patients.

A third point of interest is that the four-hour points show a positive correlation between the ratio Na²⁴/bromide and the Na²⁴ entry. It follows that the higher of these rates of entry of sodium are not merely due to a single process admitting both sodium and bromide more freely, but are due to some process favouring sodium entry preferentially.

No single uniform mode of entry or exit can bring about these changes in the relative rates of entry of Na²⁴ and bromide. They could, however,

FIG. 3.—This figure shows the change in the relative proportions of sodium and bromide entering the lumbar C.S.F., which occurs after the first few hours in patients without inflammatory disease of the nervous system. Fifty-five cases are shown.

(a) At four hours after the intravenous injection (towards the left of the chart), and (b) at equilibrium 24 hours or more after the injection (at the right of the chart). In every case the ratio sodium entry/bromide entry is much higher at equilibrium than at four hours. To show that this holds for the uppermost of the four-hour points, these have been joined by lines to the equilibrium points for the same patients. The median of the four-hour ratios is 1.02 and that of the equilibrium points 2.40.

be caused by the intervention of a second process after a delay period. Thus, they will result if bromide-poor fluid reaches the lumbar sac either from the choroid plexus or from the blood vessels of the central nervous system, provided that there is a time-lag due to the displacement of fluid from the ventricle, or from the perineural and perivascular spaces, before the bromide-poor fluid mixes with the fluid from the meninges.

11. Na^{24} and Bromide Entries in Diseases of the Extrapyramidal System

In the course of our studies of the entry of Na^{24} and bromide in various neurological diseases certain departures from the normal were noted in

cases of Parkinsonism and allied conditions. These changes consisted of a reduction in Na^{24} entry into lumbar C.S.F. at four hours greater than that expected from the age of the patient, and accompanied by a reduced bromide entry but a normal equilibrium bromide ratio. In presenting these findings we do not imply that they are pathognomonic for diseases of the basal nuclei: on the contrary, a reduction in the Na^{24} entry was observed in several cases of advanced neurological disease. But as the changes in the extrapyramidal group were not only consistent but in some cases were found early in the illness, before the patient's general health was affected, it was thought that they merited attention.

TABLE III

LUMBAR CONCENTRATIONS OF RADIOSODIUM AND BROMIDE FOUR HOURS AFTER INTRAVENOUS INJECTION IN CASES OF PARKINSONISM AND OTHER DISEASES OF THE BASAL NUCLEI

Case No.	Disease	Age	Na ²⁴ C.S.F. × 100 Plasma	Br C.S.F. × 100 Plasma	Br at Equilibrium		Protein (mg./100- ml)
					C.S.F. × 100 Plasma	Plasma C.S.F.	
194 S	Choreoathetosis since infancy with some dementia	25	19.1	11.0	37.6	2.66	64
188 S	Progressive dementia with extrapyramidal signs	29	15.9	10.7	32.3	3.09	70
174 S	Wilson's disease	32	12.75	12.3	36.8	2.72	20
186 S	Congenital athetosis	39	16.0	17.3	39.1	2.56	52
163 S	"	41	11.02	—	—	—	17
286 X	Parkinson's, atypical	45	14.3	15.0	—	—	105
172 S	" ? post-encephalitis	47	13.5	12.3	31.0	3.22	21
195 S	"	48	14.3	10.5	37.2	2.69	31
177 S	" certainly post-encephalitis	51	33.1	19.5	33.3	3.00	27
158 S	" ? post-encephalitis	51	10.2	9.8	—	—	—
137 S	" Arteriosclerotic	53	10.6	13.4	48.8	2.05	35
164 S	"	54	12.4	—	42.1	2.38	30
181 S	"	54	15.4	—	—	—	—
168 S	" idiopathic	56	18.0	12.7	34.6	2.89	39
154 S	" (early)	62	13.8	11.0	—	—	55
173 S	" Arteriosclerotic	65	20.6	14.4	33.8	2.96	30
302 X	"	69	10.6	13.9	—	—	41
301 X	"	70	10.2	11.1	—	—	35
288 X	"	77	7.75	9.0	33.6	2.98	22
272 X	"	81	11.4	15.2	53.7	1.86	82
Mean values in 20 cases		52.45	14.55	12.89	38.0	2.70	41

The results obtained in 15 cases of Parkinsonism, four cases of congenital athetosis, and one case of Wilson's disease, are shown in Table III and Fig. 4. Cases of paralysis agitans and atherosclerotic Parkinsonism are included as well as three cases in which a diagnosis of post-encephalitic Parkinsonism was made. In one of these (No. 177S, aged 51 years) the diagnosis was beyond question, since the records of the acute attack in 1920 were available.

In every case but one the four-hour entry of Na²⁴

Fig. 4.—Percentage of radiosodium in lumbar C.S.F. four hours after intravenous injection in cases of disease of the extrapyramidal system. The line is in the same position as in Fig. 1 and shows the most probable values of sodium entry for normal patients.

is considerably lower than in the majority of the normal cases, while the exception is the one case with the conclusive history of encephalitis lethargica.

The mean value of the Na²⁴ entry in these 20 patients is 14.55, *i.e.*, only just over half the figure of 30.06 found for normal patients. For Na²⁴ the difference between the means for normal patients and for Parkinson's is 5.82 times the standard error of the difference, *i.e.*, is highly significant. Some of the difference is presumably due to the cases of Parkinson's disease having a mean age of 52.45 years while the "normals" average 42.3 years. The difference is, however, still significant if the mean value for normal cases is calculated only from the 13 patients with the same mean age as the patients in this group.

The bromide entries show a smaller difference between the two groups, being 16.02 for the 14 normal patients for whom we have figures, and 12.89 for the patients with Parkinson's disease. Though smaller, this is 3.8 times the standard error of the difference and is therefore still significant.

Equilibrium Ratios for Bromide.—The ratios of bromide concentrations in serum and C.S.F. at equilibrium are also shown in Table III. The C.S.F. concentration averages 38% of that in the serum, and the mean bromide ratio is 2.70. This does not differ significantly from the values for those few normal cases in which we have the bromide ratio.

12. Hypotheses Concerning Effects of Extrapyramidal Disease on the C.S.F.

We have considered three possible explanations for the low rates of entry into the lumbar C.S.F.

encountered in these cases. First, that the thoracic immobility characteristic of Parkinson's disease retards the mixing of spinal and ventricular C.S.F. This is unlikely, since some of the patients were hyperkinetic rather than immobile, while in others the disease was still at an early stage. Nor would this account for the reduction in the four-hour bromide entry.

A second explanation might be that atrophy of the basal nuclei may be accompanied by some degree of ventricular dilatation, causing a longer period than usual to intervene before fresh fluid secreted by the choroid plexus reaches the spinal canal. A moderate enlargement such as might escape comment could, we think, account for the unexpected combination of a reduced lumbar sodium four hours after injection with an equilibrium bromide ratio fully equal to the normal value.

A third explanation is that disease of the anterior choroidal artery (and in some cases of the posterior choroidal artery also) may reduce the rate of secretion from the choroid plexuses. This hypothesis would explain why the cases of athetosis and Wilson's disease showed the same features of reduced sodium entry as did those of Parkinsonism. It would not, however, explain why the bromide entry should also be reduced, nor why the equilibrium bromide ratio should be as high as 2.7, unless the choroidal arteries are responsible for the supply not only of sodium but also of bromide to the cranial C.S.F. Bering (1952) showed that in dogs bilateral removal of the choroid plexus caused practically no change in the very rapid entry of deuterium into the ventricles,

and more recently (Bering, 1955) has produced similar evidence for Na^{24} . Entry is presumably through the ependymal capillaries, and if these play a part in the formation of C.S.F. they may well pass the bromide ion as readily as the meningeal capillaries. In some of our own tests the early appearance of bromide in the ventricles has suggested this route of entry.

13. Findings in Inflammatory Disease of the Nervous System

By contrast with the low Na^{24} and bromide entries found in disease of the extrapyramidal system, in inflammatory disease of the nervous system both entries were markedly and consistently increased. This contrast is illustrated by Fig. 5, which shows the distribution of the Na^{24} and bromide entries in both groups of cases as compared with the normal.

Table IV shows the results obtained from 23 tests carried out in 21 cases of inflammatory disease. Since it has been shown that the bromide ratio is affected both by the stage of the disease and the aetiology of the inflammation (Smith *et al.*, 1955), the cases are grouped according to these factors. Groups I, II, and III are made up of cases of tuberculous meningitis; in Group I the tests were done during the first month of treatment; in Group II after several months of treatment but at a time when the infection was thought to be still active; and in Group III during convalescence. In two of the cases in Group II and one in Group III a complete manometric spinal block was present at the

FIG. 5.—Lumbar entry of sodium and bromide at four hours in normals, diseases of basal nuclei, and inflammatory disease.

TABLE IV
FINDINGS IN INFLAMMATORY DISEASE

	No.	Age	Diagnosis	Protein (mg./100 ml.)	Four Hours			24-48 Hours			Na ²⁴ /Br	Comments
					Na ²⁴ %	Br%	Na ²⁴ /Br	Na ²⁴ %	Br%	Na ²⁴ /Br		
Group I	345 X	13	Tubercular meningitis early in treatment	430	98.4	118	0.83	—	—	—	—	
	253 X	20	ditto	148	92.5	93.5	0.99	112.2	96.1	1.16	1.04	
	417 X	23	ditto	337	78.4	96.4	0.8	102	98.7	—	1.01	
	333 X	16	ditto	119	62.0	68	0.91	101	93	1.08	1.07	
	447 X	21	ditto	190	55.7	63.8	0.87	—	—	—	—	
	334 X	23	ditto	166	53.5	65.5	0.8	101	96	1.05	1.04	
Group II	462 X	19	Tubercular meningitis late in treatment	1000	109	96.2	1.03	92	109	—	0.92	Complete spinal block
	247 X	16	ditto	280	60.0	69.4	0.95	99	74.5	1.18	1.34	
	73 X	53	ditto	225	56.0	—	—	101.5	110	0.9	0.91	
	194 X	5	ditto	297	51.8	46.5	1.1	90.3	85.6	1.05	1.17	Gross hydrocephalus
	228 X	19	ditto	700	—	125	—	—	127	—	0.79	Complete spinal block
	187 X	7	ditto	45	54.2	56.7	0.95	—	—	—	—	ditto
Group III	431 X	8	Tubercular meningitis convalescent	45	56.2	26.9	2.05	98	36.5	—	2.73	
	213 X	19	ditto	83	40	33.2	1.2	96.3	56.5	1.7	1.77	
	199 X	21	ditto	425	28.7	35.6	0.81	93.7	81.2	1.14	1.23	Complete spinal block
	247 X	16	ditto	119	25.9	26.3	0.98	89.5	51.1	—	1.96	
Group IV	326 X	18	Pneumococcal meningitis	112	48	46	1.0	129	71	1.8	1.4	
	244 X	38	Micrococcal meningitis	620	33.7	41.5	0.8	—	89	—	1.12	
Group V	275 X	9	Post-varicella encephalitis, congenital cerebral palsy	48	58.5	33	1.4	98.9	68	1.4	1.47	1 month after onset
	275 X	9	ditto	63	30.8	32.4	0.93	86.5	53.7	1.4	1.86	3½ months after onset
	205 X	18	Meningo-encephalitis	120	53.7	—	1.35	131	52	2.4	1.88	3½ months after onset
	448 X	19	ditto	70	36.3	29.1	1.2	102	50	2.0	2.0	Treated with cortisone
Group VI	134 S	51	Acute infective polyneuritis	375	45	37.2	1.2	—	56.2	—	1.78	

time of the tests. In one case, No. 247X, two separate tests were done, one during the active phase of the disease and the other towards the end of convalescence. Group IV contains two cases of active purulent meningitis, one pneumococcal and the other micrococcal. Group V contains two cases of meningoencephalitis of unknown aetiology, in one of which the patient was under the influence of cortisone at the time of the test, together with two separate observations made at an interval of almost three months in a case of post-varicella encephalitis superimposed on congenital choreo-athetotic cerebral palsy. The single case in Group VI is one of acute infective polyneuritis in the active phase of the disease.

For these 23 tests the mean four-hour Na²⁴ entry is 55.8, which is 1.85 times the mean value for the normals; and the mean bromide value is 59.5, which is 3.7 times the value for the normals (Table I). This striking increase in the rates of entry of both Na²⁴ and bromide is well shown in Fig. 2, where the values found in these inflammatory cases are plotted as crosses. With three exceptions, all the

inflammatory cases show a higher bromide entry than any of the non-inflammatory cases, and of the three exceptions two were cases of tuberculous meningitis in advanced convalescence and the third was the case of meningoencephalitis under treatment with cortisone. The overlap between the rate of entry of Na²⁴ for the inflammatory and non-inflammatory cases is a little greater, but, even so, it is apparent that in the inflammatory cases it is as a rule also greatly increased.

As with non-inflammatory cases, so the value of the ratio of Na²⁴ to bromide at four hours is, as a rule, close to unity. But as Table IV shows, this value tends to be preserved at equilibrium: in other words, the progressive increase in Na²⁴ relative to bromide found in the non-inflammatory cases (Fig. 3) is seldom seen. Table IV also shows that the approximation of the ratio between Na²⁴ and bromide at 24 hours with the equilibrium bromide entry is reasonably close.

In Fig. 6 the bromide entry is plotted against the equilibrium bromide ratio both for these inflammatory cases (crosses) and for the other group of

FIG. 6.—Lumbar bromide entry at four hours plotted against bromide ratio in inflammatory and senile cases.

cases in which a low bromide ratio was found, namely, the special group of elderly patients with mild mental changes referred to in Section 2 (dots). The mean value for normals is also plotted. In the inflammatory cases it is clear that the bromide entry rises as the equilibrium ratio falls. In the group of elderly patients, on the other hand, the low bromide ratios are not accompanied by a high bromide entry. Thus, in none of the inflammatory cases is the entry below 25% and in only two is it below 30%, while in only one of the elderly patients is it as high as 25%, and this in spite of a considerable overlap for the values of the equilibrium bromide ratio. It is also worth noting that, as in both groups of cases the four-hour Na^{24} /bromide ratio usually approximates to unity, the relationship shown in Fig. 6 would hold for the Na^{24} entry.

This seems clear proof that the depression of the bromide ratio in these two groups of cases is brought about by different means. It was argued in Section 8 that the findings in the elderly can be explained on the hypothesis of degeneration of the choroid plexus. The findings in inflammatory cases, on the other hand, are readily explained on the assumption that when the capillaries of the meninges are dilated in inflammation they pass both sodium and bromide more freely than normal. It has been shown elsewhere that in tuberculous meningitis the equilibrium bromide ratio is more regularly and more profoundly depressed than in other varieties of meningitis (Taylor, *et al.*, 1954), and also that when the infection is overcome the bromide ratio returns to normal (Smith *et al.*, 1955). Table IV shows that the same is true for the rates of entry of

bromide and, to only a slightly lesser degree, of Na^{24} . Thus, Groups I and II show the highest rates of entry of bromide of any of the inflammatory cases and, with two exceptions, of Na^{24} also. But in Group III, in which convalescence was well advanced at the time of the tests, the rates of entry of both Na^{24} and bromide have fallen steeply. Case 199X is perhaps of particular interest (see Table V). Although the tuberculous infection had been obsolete for many months and convalescence was well advanced, a residual manometric spinal block was still present. The low lumbar Na^{24} entry relative to that of bromide, and an equilibrium bromide ratio of only 1.23 in the absence of any active infection, strongly suggest that the spinal block was preventing the arrival from the ventricles of sodium-rich fluid secreted by the choroid plexus.

14. Results in Cases with Complete Manometric Spinal Block

That bromide can enter the lumbar C.S.F. freely without the intervention of the choroid plexus has been shown by tests carried out on patients in whom the lumbo-sacral cul-de-sac was isolated from the intracranial cavity by a complete manometric spinal block. Complete manometric spinal block was diagnosed when jugular compression produced no rise in the pressure of the spinal C.S.F., although a free rise and fall could be produced during and on release of abdominal compression. In the great majority of our cases the presence of a block was confirmed either by the intrathecal injection of contrast media (air or "myelodil") or by direct inspection at operation or necropsy.

As Table 5 shows, the bromide ratio was low, ranging from 1.29 to 0.81, and it was always lower

than that for the cisternal sample. The mean rates of bromide entry per hour were high, reading 14.4% per hour in the first two hours for Case 26X and 10.4% for the first hour in Case 199X. In the latter case the sodium entry figures are also available and at 6.8% in one hour and 28.7% in four hours are very close to the average value of 30.06 at four hours shown in Table I for normal cases. (The cross nearest to the left side of Fig. 2 shows the four-hour values for this case.) The ratio bromide entry/sodium entry is in this patient 1.53 at one hour and 1.24 at four hours.

These results show that in cases where fluid from the ventricle either fails to reach the lumbar sac, or only does so in small amounts, the bromide may enter the lumbar C.S.F. rather faster than the sodium, and that the equilibrium bromide ratio is fairly close to 1.0. In the tumour case (No. 26X) the bromide entry per hour during the first two hours averages 14.4% per hour, which is 3.59 times the mean rate of 4.01 (Table II) for non-inflammatory cases. In Case No. 199X (with persistent block but no evidence of active tuberculosis) the bromide entry at both one hour and four hours was considerably greater than in normals, while the sodium entry at 28.7% was close to the mean value although rather lower than the value of 35.0 expected at age 21.

15. Comparison of Lumbar and Ventricular C.S.F.

A simple method of determining whether bromide passes the choroid plexus with difficulty while entering freely elsewhere would appear to be by comparing simultaneous rates of entry of bromide into lumbar and ventricular C.S.F. Some of our earliest experiments were devised to this end, but

TABLE V
RESULTS IN CASES WITH COMPLETE SPINAL BLOCK

			Lumbar Sample (Below Block)			Cisternal Sample (Above Block)		
Case No.	Age	Time between Injection or Last Oral Dose and Sampling	Protein (mg./100 ml.)	Br Ratio	Br %	Protein (mg./100 ml.)	Br Ratio	Br %
<i>A. Block from Spinal Tumours</i>								
6 X	52	24 hr.	300	1.23	81.3	260	1.65	60.7
26 X	54	2 hr.	285	—	28.9	47	4.15	24.1
		6 hr.	273	—	59.2	41	2.46	40.7
81 X	61	23 hr. oral	212	0.89	112	175	2.26	44.3
25 X	70	4 days oral	420	1.05	95.4	130	2.41	41.4
<i>B. Block from Tuberculous Meningitis</i>								
187 X	7	25 hr.	85	0.81	124	15	1.74	57.5
135 X	9½	24 hr. oral	—	0.87	115	—	1.28	78.3
112 X	20	22 hr. oral	—	0.96	104	Cisternal	1.49	67.2
						L. ventricular	1.58	63.3
199 X	21	8 weeks	520	1.08	—	—	—	—
		1 hr.	425	—	10.4	—	—	—
		4 hr.	393	—	35.6	—	—	—
		24 hr. 7 min.	225	1.23	81.2	—	—	—
71 X	21	2-3 days oral	4,400	1.01	99	87	1.48	67.7
			4,250	0.92	109	150	1.08	92.5
		19 days	3,950	1.06	94.5	56	2.57	39.0
		3 days	1,200	1.29	77.5	20	3.45	29.0

while the results were entirely compatible with this theory most of these experiments had to be confined to cases of meningitis and encephalitis, in which the formation of the C.S.F. is greatly affected by the disease.

An example of these tests is given by a child of 9 years who had been treated for seven months for tuberculous meningitis and in whom the infection was considered obsolescent. She had developed a severe hydrocephalus during the course of the illness. Advantage was taken of a therapeutic lumbar and ventricular puncture to determine the relative rates of entry of bromide into both ventricle and spinal canal. Samples of ventricular and lumbar C.S.F. and of venous blood were first obtained and then 4 g. NaBr and 1 ml. isotonic Na^{24}Cl were given by intravenous injection. Samples of both ventricular and lumbar C.S.F. were withdrawn at frequent intervals during the first five hours after the injection and again on the following day.

Unfortunately, blood samples were only obtained at 0, two, five, and 24 hours after the injection. Hence the earlier samples of C.S.F. were compared with the serum taken at two hours instead of at simultaneous times. The results are shown in Table VI. At equilibrium, that is to say, at 0 and 24 hours, the bromide content of the lumbar C.S.F. exceeded that of the ventricle in the ratio 1.2–1.6 to 1, a finding in line with our previous experience in tuberculous meningitis (Smith *et al.*, 1955). Immediately after the intravenous injection, however, the excess of lumbar over ventricular bromide rose sharply, as shown graphically in Fig. 7, in which the ratio between the concentration of bromide found in the lumbar C.S.F. and that in the ventricular C.S.F. is plotted against time.

In this and in similar cases bromide appeared in the lumbar C.S.F. much more rapidly than in the ventricular. Thus, six minutes after the injection the lumbar C.S.F. already contained 3.09 mg./ml., as against an initial value of 1.03 mg./ml., while the ventricular C.S.F., which contained 0.8 mg./ml. initially, showed no significant increase in the bromide concentration. Even allowing for the

possible effect of dilution in the greatly dilated ventricle, this difference, which was maintained to a considerable degree even at 24 hours, is very strong evidence that bromide reached the lumbar C.S.F. directly without passing through the ventricles.

The rise in concentration of Na^{24} was also more rapid into the lumbar than into the ventricular C.S.F. But, slow as was entry of Na^{24} into the ventricle, it was always higher than that of bromide, as shown by the serial values for the ratio Na^{24} /bromide for ventricular fluid (Table VI). By contrast, in the lumbar C.S.F. the bromide entered nearly 1.5 times as fast as the Na^{24} ; that is to say, they entered at rates roughly proportional to the mobility of the two ions. We have seen this in other cases of tuberculous meningitis.

Table VII shows the results of estimations of both Na^{24} and bromide in samples of C.S.F. obtained by simultaneous ventricular and lumbar punctures. The cases are divided into three groups, according to the interval between the intravenous injection and sampling, and within each group are arranged in order of decreasing rate of entry of Na^{24} into ventricular fluid.

Group I comprises two cases of meningo-encephalitis with a moderate degree of ventricular dilatation, and two cases of tuberculous meningitis in which the tests were done early in treatment when the hydrocephalus was negligible, together with three observations made on two extremely advanced cases of tuberculous meningitis with gross hydrocephalus. In the first four cases the entry of Na^{24} into ventricular fluid was very much more rapid than into the lumbar C.S.F., while the reverse was true for bromide. Moreover, in the ventricular fluid the entry of Na^{24} was invariably and considerably greater than that of bromide; indeed, in one case (No. 205X) the ventricular Na^{24} at 35 minutes after the injection was 50.1% while the bromide was too low to be distinguishable with certainty from the trace initially present. In lumbar fluid, on the other hand, the bromide entry sometimes exceeded that of Na^{24} .

In the remaining cases in Group I (below the

TABLE VI
LUMBAR AND VENTRICULAR FINDINGS IN CASE NO. 186 X

Time (Hr. Min.)	Lumbar			Ventricle			BrS/CSF.L	BrS/CSF.V
	Na^{24} (%)	Br (%)	Na^{24} /Br	Na^{24} (%)	Br (%)	Na^{24} /Br		
0 6	3.4	5.4	0.63	0.6	0.1	6.0		
0 11	10.2	13.6	0.75	1.4	0.6	2.3		
0 21	19.1	27.7	0.68	2.4	2.8	0.85		
0 40	32.0	41.8	0.76	3.9	3.8	1.0		
2 0	35.3	47.2	0.74	11.9	9.2	1.3		
5 11	60.8	57.1	1.04	30.8	19.0	1.6		
24 0	88.5	72.0	1.2	79.4	43.0	1.8	1.37	2.2

Base-line values for bromide (mg./100 ml.): Serum = 1.61; L. C.S.F. = 1.03; V. C.S.F. = 0.79

FIG. 7.—A comparison of lumbar and ventricular bromide concentrations following intravenous bromide injection. Case 186X.

dotted line) the disease was long-standing and the hydrocephalus extremely advanced. The entry of Na^{24} into ventricular fluid was very much lower than in the first four cases, though in two of the three observations it was still just in excess of the bromide entry. In the lumbar fluid, on the other hand, bromide entered more rapidly than Na^{24} and both more rapidly than into ventricular fluid.

In the cases in Group II, where the interval between injection and sampling was four hours, the same relationships hold, namely, the Na^{24} entry is greater into ventricular than into lumbar

fluid, while the entry of bromide is greater into lumbar than into ventricular fluid. Once again, the entry of Na^{24} into the ventricle was invariably and often markedly greater than that of bromide, while in the lumbar fluid the entry of bromide often equalled or exceeded that of Na^{24} .

The four observations listed in Group III were all made in very advanced cases of tuberculous meningitis with severe hydrocephalus, comparable to the cases below the dotted line in Group I. The relationships described above for those cases remain unaltered, even when the interval between injection and sampling is increased from approximately half an hour to between five and five and a half hours.

While care is needed in applying to normal persons findings obtained from cases of inflammatory disease or hydrocephalus, the results of these tests lend strong support to the view that the initial rate of entry of sodium into the ventricle exceeds that of bromide, but that in the lumbar sac the reverse is the rule. As Table VII shows, we have found wide variation in ventricular ratios, depending presumably on the state of the choroid plexus and perhaps best exemplified by the cases included in Group I. Thus, the greatly depressed ventricular entry of Na^{24} in advanced, hydrocephalic cases of tuberculous meningitis and the approximation of the ratio of Na^{24} /bromide to unity, is in marked contrast to the findings early in the disease and in the non-tuberculous cases. Tubiana *et al.* (1951) also found that the Na^{24} entry into ventricular C.S.F. was depressed in tuberculous meningitis,

TABLE VII
RESULTS OF ESTIMATIONS OF Na^{24} AND BROMIDE BY SIMULTANEOUS VENTRICULAR AND LUMBAR PUNCTURES

No.	Age	Diagnosis	Ventricle			Lumbar			Bromide Ratio		Comments
			Na ²⁴ %	Br %	Na ²⁴ /Br	Na ²⁴ %	Br %	Na ²⁴ /Br	S/V	S/L	
Group I: 25-35 minutes after injection											
205 X	18	Meningo-encephalitis	50.1	Trace	750	13.4	2.3	5.8	—	1.88	Late in treatment
275 X ₍₁₎	9	Meningo-encephalitis	39.1	13	3.0	17.6	15	1.17	—	1.4	Early in treatment
213 X	19	Tubercular meningitis	35.4	12.6	2.9	6.8	7.8	0.87	—	1.16	" " "
253 X	20	" "	33.1	16.0	2.07	19.2	28.9	0.66	—	1.04	" " "
194 X	5	Tubercular meningitis	3.75	3.7	1.0	25.5	27.7	0.9	1.79	1.17	Late in treatment
187 X ₍₂₎	7	" "	2.8	5.4	0.52	20.7	29.9	0.68	2.7	—	Gross hydrocephalus.
187 X ₍₁₎	7	(in remission) " Tubercular meningitis in recrudescence	1.58	1.0	1.58	4.01	5.6	0.7	—	—	? spinal block Gross hydrocephalus, Spinal block
Group II: 4 hours after injection											
269 S	58	Hemisphere glioma	101	19.5	5.1	32.8	19.5	1.6	—	—	
327 X	18	Tubercular meningitis	95	19	5.0	75	69	1.08	—	1.0	Early in treatment
326 X	18	Pneumococcal meningitis	86	19	4.5	48	46	1.0	1.3	1.4	Blood in ventricle ? old
275 S	49	Post-trauma dementia	74.4	12.3	6.0	39.6	13.5	2.9	4.4	2.8	
417 X	23	Tubercular meningitis	49.1	21.7	2.2	96.4	78.4	0.8	3.85	1.0	Early in treatment
275 X ₍₂₎	9	Meningo-encephalitis	28.0	16.0	1.8	32.0	33.1	0.96	3.3	1.8	Late " "
Group III: 5-5½ hours after injection											
95 X	5	Tubercular meningitis	23.5	12.1	2.0	74.0	84.1	0.88	3.0	0.94	All 4 cases very late in treatment.
88 X ₍₁₎	3	" "	12	30	0.4	39	40	1.0	—	1.29	Gross hydrocephalus
88 X ₍₂₎	3	" "	12	7	1.7	49.4	45	1.1	3.38	1.5	" "
98 X	5½	" "	10.1	9.0	1.1	41.1	49.8	0.82	3.0	0.94	" "

but do not specify the stage of the disease at which their observations were made.

To what extent the composition of ventricular C.S.F. was modified by diffusion or by reflux of C.S.F. is not known. In our tests we have been unable to estimate the rate at which reflux of C.S.F. occurred from cistern to ventricles. That reflux can occur must be inferred from previous work (Cairns, Duthie, Lewin, and Smith, 1944; Smith, Duthie, and Cairns, 1946; Cairns and Russell, 1946). In any event, its effect must be small when the interval between injection and sampling is reduced to a few minutes.

17. Effect of Drugs and CO₂ Inhalation on Production of C.S.F.

When it became apparent that the rates of entry of both Na²⁴ and bromide were significantly reduced in cases of Parkinsonism, the possibility was considered that this might be an effect of the drugs of the hyoscine group which many of these patients were receiving. A few pilot observations, however, coupled with consecutive tests on patients with and without "artane", made it clear that our findings could not be accounted for in this way. Similarly, it was shown that the bromide itself was not exerting a significant influence on the rate of entry of the Na²⁴. Our studies on the possible effects of different drugs on production of the C.S.F. are still at an early stage, but the results obtained with CO₂ were sufficiently constant to warrant description.

Inhalation of CO₂.—Since carbon dioxide is known to dilate the cranial blood vessels (Shenkin and Novack, 1954; Gibbs, Gibbs, and Lennox, 1935), it might be expected to increase the rate of entry of C.S.F. Table VIII shows results obtained when the subject inhaled 5% CO₂ in oxygen for five minutes in every 15 during the four-hour test period. The CO₂ caused only small rises in blood pressure, similar to those found by Kety and Schmidt (1948). In every case the four-hour con-

centration of sodium was increased, while in all cases except the last that of bromide was diminished. On the assumption that the choroid plexus forms a fluid containing more sodium and less bromide than that directly entering the lumbar sac, these results may be due either (1) to the deeper breathing caused by the CO₂ increasing the rate of mixing of lumbar and cranial C.S.F., or (2) to more active secretion by the choroid plexus. The rise of bromide concentration in the last patient may be related to the subnormal rates found in the first half of his test. While we think it highly probable that these results show a real effect of CO₂, they are too few to be conclusive.

18. Theories of the Production of C.S.F.

Until recently it has been widely assumed that the C.S.F. was secreted mainly by the choroid plexus and, to a less extent, by the meninges or blood vessels of the central nervous system and meninges, as a fluid of the composition found in the subarachnoid space, with the addition of protein and possibly waste products from the central nervous system. However, work with deuterium (Bering, 1952, 1954), radiosodium, and other isotopes (Greenberg *et al.*, 1943; Sweet and Locksley, 1953) has shown that the individual components of the C.S.F. enter at widely different rates and that water at least enters very freely and rapidly from widely-spaced sources—probably through all parts of the membranes surrounding the subarachnoid space. The ionic concentrations observed are often said not to satisfy the Donnan equilibrium for a static system, and, for this and other reasons, it is now considered probable that some of the ionic constituents are secreted by the cells of the choroid plexus by the process now called "active ion transfer". It is known that the sodium ion may be thus "secreted" across other membranes, *e.g.*, the red cells and the neurone, and, since electrical neutrality must be maintained, it follows that an equivalent number of anions must enter at the same

TABLE VIII
THE EFFECT OF CO₂ INHALATION ON RATE OF ENTRY OF SODIUM AND BROMIDE TO LUMBAR C.S.F.

Disease	Age	C.S.F. Protein (mg./100 ml.)	Four-Hour Sodium Entry C.S.F. × 100 Serum			Four-Hour Bromide Entry C.S.F. × 100 Serum		
			Without CO ₂	With CO ₂	Change %	Without CO ₂	With CO ₂	Change %
D.S.	33	68	23.5	26.6	+ 13	20.5	14.1	- 37.2
D.S.	37	36	17.0	28.6	+ 68	15.2	11.0	- 27.6
Cerebral thrombosis	45	200	15.4	17.7	+ 15	12.6	12.4	- 1.6
D.S.	43	40	24.3	37.5	+ 54	18.0	12.3	- 31.7
Syringomyelia	45	30	19.2	27.2	+ 43	18.6	18.3	- 0.1
Parkinson's	54	30	12.4	16.2	+ 31	—	—	—
D.S.	33	82	8.2	32.2	+ 293	12.3	14.9	+ 21.1
Means	41.4		17.1	26.6	(+ 73.9)	16.2	13.8	(- 12.8)

D.S. = disseminated sclerosis.

time (except in so far as K or other cations are leaving the system). The known excess of chloride in the C.S.F. would suggest that this ion might also enter by "active transfer", but such transfer of this ion is not recognized in other systems, and most of the phenomena concerned can be explained by assuming that the "active" transfer is primarily one of sodium ions.

The outflow of the C.S.F. from the subarachnoid space is generally assumed to occur through the arachnoid villi and Pacchionian bodies into the sagittal sinus, and to a less extent through the spinal roots. The arachnoid villi are supposed to pass large molecules as freely as small ones, and to return the C.S.F. into the veins by simple mechanical flow, which can occur easily owing to the reduced pressure in the veins concerned. The proof that deuterium can pass very freely through the membranes of the subarachnoid space, coupled with the finding that sodium and chloride ions enter the C.S.F. much more slowly, makes it clear that the production of obstructive hydrocephalus is due to the fact that osmotic equilibrium between C.S.F. and plasma will inevitably be approximated, and therefore that if more solute particles enter the C.S.F. than leave it in a given time, the volume must increase owing to the entry of water.

Theories of the Bromide "Barrier".—The ionic mobility of the bromide ion is closely similar to that of the chloride ion, and (in water) is 1.56 times that of the sodium ion. In so far as entry into the C.S.F. occurs by diffusion, one would therefore expect that bromide and chloride would enter equally freely and be found in the same proportions in the C.S.F. as in plasma. However, as Walter (1925) showed, the bromide ratio plasma/C.S.F. is of the order of 2.5 to 3.0. This can be explained in several ways, as suggested below.

(1) *That Bromide Diffuses through Meninges More Slowly than Chloride.*—This view is rendered most improbable by the low ratio for sodium entry/bromide entry after an intravenous injection. In meningitis it is also disproved by the low equilibrium values found for the bromide ratio (Hunter *et al.*, 1954). These data show that bromide passes the spinal blood vessels or meninges at least as easily as sodium. That bromide and chloride pass at roughly the same rate is also rendered probable by the work of Greenberg *et al.* (1943) which showed the rates of entry of sodium and bromide into dog's C.S.F. as almost equal, and that of Wang (1948), who showed that the rates of entry for sodium and chloride were closely similar both into dog's C.S.F. and into the aqueous humour.

(2) *Active Transference of Sodium into C.S.F.*—It is clear that, as Davson (1956) has pointed out, a selective deficiency of a substance in a closed space cannot occur merely from any partial resistance to its entry, since that would only lengthen the time needed for that substance to reach equilibrium. But if, in addition, that substance has a route of exit from the space, then any deficiency may occur. Thus, if the chief exit for solutes from the C.S.F. is the supposedly non-selective route through the arachnoid villi, the partition of substances between plasma and C.S.F. would vary directly according to their rate of entry. It is of course the average rate of entry over the whole system that is concerned rather than that at any one point. It is thus easy to explain the observed lumbar bromide ratio of 2.6 to 1 by assuming that the lumbar C.S.F. is formed by the admixture of 1.5 volumes of fluid from the choroid plexus, containing one part of sodium with chloride bicarbonate, etc., but no bromide, and one volume from the meninges and other blood vessels containing one part of sodium, with bromide in the same proportion as in the plasma.

Many of our tests were designed with a view to checking this hypothesis. They have given strong reasons for thinking that the choroid plexus (at least that of the lateral ventricles) does secrete fluid containing a low ratio of bromide to chloride, *i.e.*, a high ratio of sodium to bromide, and that the spinal meninges pass bromide rather more freely than sodium, possibly even in the ratio of their ionic mobilities, 1.56 to 1.

Our chief evidence favouring this is as follows: (1) The change in the median values of the lumbar ratio "sodium entry/bromide entry" (shown in Fig. 4) from 1.02 at four hours to 2.40 at equilibrium (for non-inflammatory cases); (2) the increase in rate of entry of sodium coupled with a decrease in rate of entry of bromide during the ninth half hour after intravenous injection, as shown in Table III and Section 10; (3) the increase in bromide ratio, *i.e.*, decrease in bromide concentration, in the C.S.F., which is almost invariably found in ascending the neural axis from lumbar sac to cisterna magna and again from there to the ventricle (Hunter *et al.*, 1954); (4) the fact that lumbar C.S.F. taken below a complete spinal block shows an equilibrium bromide ratio not far from 1.0, *i.e.*, when the access of ventricular fluid is prevented the proportion of bromide is nearly equal to that of sodium.

Summary

The concentrations of bromide and of radio-sodium in the C.S.F. have been determined at

varying times after the intravenous injection of these substances.

An extensive series of tests on patients in a neurological clinic have shown regularities in the lumbar C.S.F., as follows:—

1. In meningitis and encephalitis the rate of entry of bromide is considerably higher than in the non-inflammatory diseases studied. The highest rates are seen in tuberculous meningitis, and in this disease the entry of sodium is also much increased.

In both meningitis and encephalitis the equilibrium bromide ratio falls as previously reported (Hunter *et al.*, 1954).

2. In non-inflammatory cases increasing age is accompanied by a fall in the four-hour lumbar sodium, but not in the four-hour bromide, and by a corresponding fall in the bromide ratio at equilibrium. The regression line of sodium upon age, at four hours after injection, is shown for a group of 20 patients showing only slight disease.
3. In advanced disseminated sclerosis and other severe non-inflammatory nervous disease, the four-hour concentration of sodium and bromide tends to be reduced, but no regular correlation of this type has been demonstrated.
4. In diseases of the basal nuclei, Parkinsonism (15 cases out of 16), congenital athetosis (three cases), and Wilson's disease (one case) abnormally low figures were found at four hours both for sodium and bromide. Since the equilibrium bromide ratios are normal, this appears to be due either to a moderate enlargement of the ventricles or to degeneration of the anterior choroidal artery, or to both.
5. In non-inflammatory cases the relative rates of entry of sodium and bromide into the lumbar sac show an important change with time. During the first few hours the bromide concentration rises proportionately as fast or faster than the sodium. At about four hours after intravenous injection the rise in sodium concentration becomes faster, while the rise in bromide becomes slower, with the result that at equilibrium the bromide ratio becomes about 2.6/1 instead of about 1/1 as is found at four hours.
6. It is concluded that this change gives very strong evidence for the belief that the solute contents

of C.S.F. come from two (or more) types of source of which the "higher" one (presumably the choroid plexus of the lateral ventricles or of all four ventricles) secretes sodium with a much smaller proportion of bromide than the other sources. Other theories are discussed.

7. In a few cases comparison has been made between the rates of entry into the lateral ventricles, cisterna magna, and lumbar sac. The results give further support to the theory just mentioned.
8. The inhalation of 5% carbon dioxide in oxygen was accompanied by an increase in the rate of entry of sodium in all the six cases tested and usually by a decrease in the bromide.

We should like to acknowledge our debt to our colleagues in the Department of Medicine and the Medical Research Council Unit for their share in this work, and particularly to Drs. Ritchie Russell and R. M. Acheson and Drs. Hunter and Stott. We are also most grateful to Dr. Philip Bedford for his help and interest in this work.

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disorders one has the impression that psychotherapy is the treatment of choice, for E.C.T. receives scant mention. It comes somewhat as a surprise, therefore, to read further on in the same chapter that the authors feel that they can dispense with instructions about the maintenance of the physical health of depressed patients because "the advent of shock therapy . . . makes patients' symptoms evolve so rapidly . . ."

The literature surveyed is almost exclusively American: on the subject of post-traumatic syndromes, for instance, one reads with astonishment that "according to verbal reports from the Office of Scientific Research and Development", the duration of the period of unconsciousness following head injury is the best guide to the severity of the post-traumatic changes. In these days of fast travel, it should not take 23 years for Ritchie Russell's work to cross the Atlantic.

All in all, a very uneven book, likely to confuse rather than educate.

The Clinical Examination of Patients with Organic Cerebral Disease. By R. Klein and W. Mayer-Gross. (Pp. xiii + 96; 9 figures. 15s.) London: Cassell. 1957.

The examination of the patient with organic cerebral disease often falls between the two stools of psychiatry and neurology. While the neurologist is interested in dysphasia and its ramifications, he is often uninterested in or ignorant of confusional states and their content. The psychiatrist on the other hand may recognize clearly enough the confusional state and assign a correct psychogenesis to some of its contents while missing the element of agnosia or apraxia that is playing a part in the clinical picture. It is just such a borderland that this small book deals with. Its systematic approach will be useful to both neurologists and psychiatrists who do not meet a great many of such cases, although those who see many may feel that many aspects really require rather fuller treatment than is here afforded. It can be recommended as an introduction to the subject, particularly to students for the Diploma of Psychological Medicine.

Pneumoencephalography. By E. Graeme Robertson. (Pp. xxi + 482; 34 plates, 209 figures. 110s.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

This book is the third to be written on air encephalography by this author since he became interested in the subject over 20 years ago. He is well known as one of the originators of modern techniques of air encephalography which have greatly increased its safety and decreased its discomforts. Other workers have tended to simplify the technique and have adapted it to investigate patients with raised intracranial pressure, a practice which the author himself deprecates.

This volume contains clear descriptions of the author's technique of air encephalography, of the normal brain anatomy disclosed by air injections, and of his theories on the mechanism of ventricular filling. Much of those

sections appeared in previous volumes, but their reproduction is welcome because copies of the author's first book ("Encephalography") have been unobtainable in this country for several years. This present book also contains excellent descriptions of the abnormal conditions likely to be encountered, including injuries, vascular disease, congenital lesions, and diseases in childhood. The section on space-occupying lesions shows the reasons for the various abnormal signs produced by masses in different situations, rather than giving mere lists of changes. The author pays particular attention to information obtained from deformity of the basal cisterns in all his descriptions. There is also a very useful chapter on the causes of failure to obtain air-filling of the ventricles and on the remedies to be applied.

The book is well printed and is profusely illustrated with clearly coloured plates and excellent radiographs. It should become a standard text-book on the subject of air encephalography and should appeal to all those who are interested in neuroradiology.

Tranquillizing Drugs. Arranged and edited by Harold E. Himwich. (Pp. viii + 205; 32 figures.) London: Bailey Bros. & Swinfen. 1957.

This small volume represents the outcome of a symposium on tranquillizing drugs arranged jointly by the American Psychiatric Association and the American Physiological Society. Experimental investigations in animals of some of the electrophysiological effects are reported. Clinical aspects of the drugs, especially in the treatment of psychotic states, are also described, and some problems of dosage and side-effects are mentioned. The book will be of interest to psychiatrists and neurologists wishing to know something of applied biochemistry in this field.

Correction

In this paper, "The Entry of Radiosodium and of Bromide into Human Cerebrospinal Fluid" (*J. Neurol. Neurosurg. Psychiat.*, 20, 79) by R. B. Bourdillon, M. Fischer-Williams, Honor V. Smith, and K. B. Taylor, Figs. 1 and 4 have been transposed, though the legends are in the correct positions. Thus the legend under the present Fig. 1 explains the graph shown as Fig. 4 and *vice versa*. In addition, the legend to Fig. 1 should read: Effects of age in patients with *no* abnormal physical signs.

Società Italiana di Neuro Chirurgia

The Società Italiana di Neuro Chirurgia will hold its ninth congress in Florence on April 24 and 25, 1958. Two subjects will be discussed:—

- (1) Cerebral abscesses and suppurative encephalitis
- (2) Cervical discal herniations and cervical spondylosis

Further information may be obtained from the Secretary (Dr. Giulio Morello, Via Celoria 11, Milan, Italy).