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DISCUSSION ON THE PENETRATION OF DRUGS INTO THE CEREBROSPINAL FLUID

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Physiological Aspects of the Penetration of Drugs into the Cerebrospinal Fluia

The problem of the penetration of drugs into the cerebrospinal fluid is just one aspect of the more general problem of the nature of the barriers between blood, on the one hand, and the cerebrospinal fluid and central nervous tissue on the other, i.e. the so-called blood-C.S.F. and blood-brain barriers. When a substance is injected into the blood it finds its way rapidly into the extracellular fluids of most parts of the body; in the central nervous system, however, this penetration is usually much slower, so slow indeed with some substances that their presence cannot be detected either in the cerebrospinal fluid or in the central nervous tissue even after some hours. It is this phenomenon that has given rise to the concept of a barrier that slows down the passage of material from blood to the cerebrospinal fluid and nervous tissue. We must consider first, then, the anatomical pathways available for penetration from blood to cerebrospinal fluid. It is believed that the fluid is elaborated as a secretion of the epithelium of the choroid plexuses of the ventricles; the fluid is formed continuously, passes into the cisterna magna and thence through the rest of the subarachnoid spaces at the base and over the convexities of the brain, to be drained away into the dural sinuses. If the substance we are considering, for example a sulphonamide, is able to enter the secretory cells of the choroidal epithelium, we may expect it to appear in the primary secretion of cerebrospinal fluid and flow with it over the surface of the brain; if we maintain a constant concentration of the drug in the plasma over a long period we may therefore expect the concentration to rise in the cerebrospinal fluid continuously; it will rise more rapidly in the ventricles than in the subarachnoid fluid, and we may expect the subarachnoid fluid of the spinal cord to lag behind the fluid elsewhere if circulation of fluid here is less continuous and rapid. Experiments show, however, that there is another possible route of penetration from blood to cerebrospinal fluid; this is by way of the capillaries of the nervous tissue, into the extracellular space of the tissue and thence into the ventricles and subarachnoid space. In other words, penetration into the cerebrospinal fluid may involve passage through the *blood-brain barrier*. For convenience, we may describe the blood-C.S.F. barrier as the barrier between blood and C.S.F. in the ventricles, i.e. the epithelium of the choroid plexuses; the blood-brain barrier becomes the barrier between the capillaries of the nervous tissue and the extracellular fluid of this tissue—it may be the capillary endothelium or it may be the so-called pia-glial lining supposed to cover this endothelium.

In general, physiological experiments have shown that these two barriers are very similar, in the sense that if a substance passes rapidly into the one compartment, e.g. the cerebrospinal fluid, then it also passes rapidly into the other. As with cellular permeability it is essentially the degree of lipoid-solubility of the substance that determines its ability to cross the barrier; thus alcohol and urethane pass so rapidly that it is difficult to measure the rate at which the blood comes into equilibrium with the cerebrospinal fluid after an intravenous injection of either of these substances. It is for this reason that many sulphonamides pass readily into the cerebrospinal fluid; thus sulphapyridine and sulphanilamide have high lipoid-solubility and appear rapidly in the fluid after an intravenous injection. Sulphadiazine and sulphathiazole have lower lipoid-solubilities and penetrate more slowly. Penicillin has a very low lipoid-solubility and it is difficult to detect its penetration; Chloromycetin is quite lipoid-soluble and penetrates easily. In general, if a drug has a partition coefficient—Concn. in Oil/Concn. in Water—greater than that of sulphadiazine, namely 0·035, we may expect it to penetrate sufficiently rapidly to permit of its therapeutic use.

So much for the general problem; some particular aspects that may have an important bearing on the choice of a drug are as follows:

Different regions of the cerebrospinal system.—As indicated above, the ventricles may be considered to be the most favoured with regard to coming into equilibrium with the blood plasma. This is found to be true in practice, the lumbar fluid lagging well behind the cisternal fluid. The discrepancy becomes small, however, with substances that penetrate very rapidly. Thus, if a substance penetrates with some difficulty, e.g. sulphadiazine, then we may expect the concentration in the lumbar fluid to be much less than that in the ventricles.

The abnormal barrier.—In meningitis it is considered that the barrier between blood and cerebrospinal fluid is broken down; presumably the blood vessels of the pia mater allow material to escape into the subarachnoid fluid. Under these conditions drugs that were unable to cross the barrier in the normal subject do penetrate the cerebrospinal fluid in measurable amounts.

Measurement of drug penetration.—For results to be of general value it is desirable that the concentration of the drug in the blood plasma be measured at intervals during the penetration of the drug into the cerebrospinal fluid. Thus, if a single intravenous injection is given, and blood is sampled say one, fifteen, thirty and sixty minutes later and the cerebrospinal fluid just once at sixty minutes, it is possible to compute a transfer constant that permits comparison with other values. It is worth noting, also, that the blood-aqueous barrier, i.e. the impediment to penetration from blood into the aqueous humour of the eye, is very similar to the blood-cerebrospinal fluid barrier. If it is known that a drug penetrates rapidly into the aqueous humour it can be accepted that it will also penetrate rapidly into the cerebrospinal fluid.

Dr. Honor V. Smith (Department of Neurology, Radcliffe Infirmary, Oxford):

The fact that certain substances normally present in blood, or artificially introduced into the blood stream, either do not appear in the cerebrospinal fluid (C.S.F.) or do so only in minute amounts is one that has an important bearing on both the pathogenesis and treatment of certain neurological diseases. Dr. Davson has discussed the basic physiological problems of this blood-C.S.F. barrier, and I shall attempt to describe briefly certain studies carried out in recent years in Oxford, and to consider some of their clinical implications.

Of the substances we have studied, the first in clinical importance are those used in the chemotherapy of neurological infections. It is now established that, when the meninges are normal, none of the usual chemotherapeutic agents except the sulphonamides and iso-nicotinic acid hydrazide (I.N.A.H.) will enter the C.S.F. in anything except negligible quantities. It is, however, widely held that inflammation of the meninges greatly increases the permeability of the barrier, and that therefore penicillin or streptomycin, when given systemically in cases of active meningitis, will appear in the C.S.F. in therapeutic concentrations. This important assumption clearly requires careful verification. Unfortunately penicillin and streptomycin are not themselves ideal indicator substances to use in studying the effects of inflammation and other conditions on the permeability of the blood-C.S.F. barrier, since they can only be estimated quantitatively by biological methods that, of necessity, carry a considerable margin of error.

We have, therefore, studied the partition of bromide, magnesium and calcium between blood and C.S.F. in a large variety of neurological conditions. These are all substances that can be accurately estimated in body fluids even in very low concentrations (Hunter, 1955; Hunter and Stott, 1956). In many cases, too, we have studied the rate of passage of radioactive sodium, Na^{24}, from blood to C.S.F. Much of this work is still at an early stage, but we have already found consistent departures from the normal in old age, in diseases of the basal nuclei such as Parkinson's disease, and in inflammatory conditions of the nervous system (Bourdillon *et al.*, 1957). It is with these last that I am particularly concerned to-day.

Cohen's law.—Earlier workers have found that in active meningitis substances normally present in higher concentration in blood than C.S.F. increase their concentration in the C.S.F., whereas those that are normally at a higher concentration in the C.S.F. decrease (Cohen, 1924). This generalization is sometimes known as Cohen's law. It may be expressed by saying that whatever the normal ratio of the C.S.F. concentration to that of the serum, this ratio is altered in meningitis in the direction of unity. Table I shows the

TABLE I

	Magnesium		Calcium		Bromide	
	No. of cases	C.S.F./S.	No. of cases	C.S.F./S.	No. of cases	C.S.F./S.
"Normal"	17	1·35	13	0·51	34	0·39
Tuberculous meningitis	15	0·94	13	0·64	15	0·96

mean values for the ratio of C.S.F. to serum concentration for magnesium, calcium and bromide, in 15 cases of active tuberculous meningitis compared with 17 so-called "normals". These latter were cases in which lumbar puncture was indicated in the course of their investigation, but where no evidence of progressive neurological disease was found.

In broad outline these findings conform to Cohen's law. Thus, with calcium, where normally the concentration in the C.S.F. is only about half that of serum, in tuberculous meningitis the C.S.F. concentration increases so that the ratio of C.S.F. to serum rises. Magnesium, on the other hand, is normally present in higher concentration in C.S.F. than blood; and the effect of the meningitis is to lower the ratio. Cohen, discussing the alteration of the chloride distribution in meningitis, stated that he never found the C.S.F. chloride concentration to fall below that of the serum, but, as our figures show, the magnesium

ratio can actually be reversed. This effect may be even more marked with the bromide ratio. Although in the normal the C.S.F. concentration is only about one-third that of blood, in active tuberculous meningitis not only are ratios of the order of unity the rule, but on occasion they may be as high as 1·4.

Tuberculous meningitis as opposed to other varieties of meningitis.—It cannot, however, be assumed that similar results will be obtained in all types of meningitis, irrespective of their ætiology. On the contrary, experience has shown that the blood-C.S.F. barrier is more profoundly and more consistently affected in tuberculous meningitis than in other varieties of meningitis showing comparable changes in the C.S.F. The difference is indeed sufficiently well marked to serve as the basis of a useful diagnostic test (Hunter *et al.*, 1954).

The one other condition in which the effect on the barrier seems to be consistently of the same order as in tuberculous meningitis is neoplasia of the meninges. Thus, although in cases of brain tumour as a whole the bromide ratio has been normal, in 2 cases of oligodendrogliomatosis and one of carcinomatosis of the meninges the ratio was unity.

The effects of a specific inflammation on the blood-C.S.F. barrier.—It is clear, then, that except in the most general terms, no rule can be formulated as to the result of meningeal inflammation as such on the permeability of the blood-C.S.F. barrier. But not only does the effect on the barrier vary with the ætiology of the inflammation: we have evidence that the effect of a given inflammation is not necessarily the same for all substances. This is well seen when the effects of the intrathecal tuberculin reaction of the blood-C.S.F. barrier are considered (Smith *et al.*, 1955). By the intrathecal tuberculin reaction is meant the transient wave of sterile meningitis that follows the introduction of tuberculin into the spinal fluid of a subject sensitized to tuberculin. We have used intrathecal tuberculin in the treatment of various diseases; and since, on the whole, the changes provoked in the C.S.F. have proved remarkably constant in both occurrence and pattern, we have taken advantage of these reactions to study the effects of a given inflammation on the permeability of the blood-C.S.F. barrier.

Systemic versus intrathecal tuberculin.—In the first place, the barrier to tuberculin itself appears to be absolute. In the sensitized guinea-pig the cisternal injection of tuberculin is followed by an intense inflammation involving not only the meninges but also the perforating vessels of the neuraxis (Bosanquet *et al.*, 1953). If, however, a fatal dose of tuberculin is given by intraperitoneal injection, no significant meningeal exudate is found *post mortem*. In man, intramuscular tuberculin, when given as an adjuvant to the chemotherapy of systemic tuberculosis, produces no concomitant changes in the C.S.F.; nor is the passage of either penicillin or bromide from blood to C.S.F. in any way affected (Swithinbank *et al.*, 1953; Fig. 13).

Changes with intrathecal tuberculin.—Contrast this with the effects of tuberculin when given as the Purified Protein Derivative, P.P.D., directly into the cerebrospinal fluid of a highly sensitized subject (Smith *et al.*, 1955; Fig. 1). Twenty-four hours after an injection of 3·75 mg. of P.P.D. the C.S.F. typically contains many hundreds or, more commonly, thousands of cells and the protein content is also markedly increased. Both the cell counts and protein content then fall abruptly until towards the end of the first week, when a second rise takes place. During the first phase of the reaction most of the cells are polymorphonuclear leucocytes; during the second phase they are virtually all lymphocytes. The first phase is accompanied by a sharp rise in the bromide ratio, to the order of unity, and this rise usually continues to increase until the second phase of the reaction is beginning to subside. Even then it may be many weeks before the barrier is fully restored.

One of the reasons why bromide has proved such a useful tool in studies of this kind is that it is excreted so slowly that there is ample time for equilibrium to take place between blood and C.S.F., while in these concentrations the ratio is independent of the absolute amounts of bromide present (Hunter *et al.*, 1954; Fig. 1).

In summary then, the intrathecal tuberculin reaction exerts a dramatic effect on the blood-C.S.F. barrier to bromide; but while the permeability of the barrier increases most rapidly during the first phase of the reaction, the maximal increase in permeability is delayed until the second phase has developed.

The penetration of penicillin.—The effect of the reaction on penicillin is rather different, in that the increase in penetration during the first phase of the reaction is often negligible while during the second phase a considerable increase in penetration takes place. Indeed, the increase in the penicillin content of the C.S.F. appears to be dependent on the second phase of the reaction; and in anomalous reactions, where the lymphocytic phase did not develop, the C.S.F. was never found to contain more than a trace of penicillin, even though thousands of polymorphs might appear during the first phase of the reaction, with a sharp increase in the permeability to bromide.

It appears, then, that intrathecal tuberculin exerts a specific effect on the blood-C.S.F. barrier; nor have we been able to find any record of a comparable effect with any other

factor. This appears the more significant as the amounts of tuberculin given are probably of the same order as those present in tuberculous meningitis.

The effect of cortisone.—The effect of intrathecal tuberculin appears to be antagonized by cortisone. Thus in one case 2 reactions were produced at different times to the same dose of P.P.D. in the same subject. Before the second reaction 50 mg. cortisone was given by mouth the same morning as the P.P.D. The polymorphonuclear component failed to develop though the second phase of the reaction was unaffected. Even under the influence of this single small dose of cortisone the barrier was less affected than in the unmodified reaction and was restored more rapidly (Smith *et al.*, 1957; Fig. 4).

Conclusions.—These findings go some way towards explaining the divergence of opinion that still persists as to the necessity or otherwise of giving penicillin and streptomycin by intrathecal injection in the treatment of meningitis. To take the question of penicillin first: As the results obtained in the intrathecal tuberculin reaction show, the penetration of penicillin into the C.S.F. does not run parallel with the intensity of the inflammation as measured by height of the pleocytosis and the protein content of the C.S.F. In fact, during the first or polymorphonuclear phase of the reaction, when the C.S.F. is often indistinguishable from that in a case of purulent meningitis, little or no penicillin may be found in the C.S.F. This is in line with our clinical experience, that the passage of penicillin from blood to C.S.F. is far too erratic to be depended upon in the treatment of such a serious disease as purulent meningitis. For example, though it is often claimed that pneumococcal meningitis can be adequately treated by intramuscular penicillin, we have failed to detect more than a trace of penicillin in the C.S.F. of a child of 7 months, weighing 7·7 kg., who was suffering from pneumococcal meningitis and who was receiving 5,000,000 units of penicillin by intramuscular injection every two hours (Smith, 1951). Moreover, reports of sizable series of unselected cases of pneumococcal meningitis in which the mortality has been reduced to the order of 10%, have, so far as I know, still only come from centres where intrathecal medication is given.

The position with regard to streptomycin is rather different. In untreated tuberculous meningitis we have frequently found from 5–15 units per c.mm. in the C.S.F. six hours after the intramuscular injection of a gram of streptomycin. This is well above the *in vitro* bacteriostatic level for virulent human bacilli. Yet it has been conclusively shown that the results obtained in the treatment of tuberculous meningitis with streptomycin alone are significantly better when both intrathecal and intramuscular injections are given than when the systemic route is used alone (Medical Research Council, 1948). It therefore seems logical to ascribe the improved results to the very high concentrations in the C.S.F. that persist for some hours after an intrathecal injection.

It is often said that the advent of I.N.A.H. has made the intrathecal administration of streptomycin unnecessary. Though this is not the time to discuss the merits of systemic treatment alone versus combined systemic and intrathecal medication (Smith *et al.*, 1956), it is perhaps worth saying that at Oxford, where combined treatment is still given, we have seldom been kept so busy with requests from elsewhere to take patients whose response to treatment has been disappointing as during the last year to eighteen months. It is tempting to relate this increased demand for our services to the growing tendency to dispense with intrathecal therapy.

It has now been shown that the increase in barrier permeability caused by meningitis varies both with regard to different substances and with regard to the ætiology of the infection. Before, therefore, any one drug can be accounted effective in the treatment of any case of meningitis, it must be shown that, in that particular infection that particular drug is capable of crossing the blood-C.S.F. barrier in therapeutic amounts. It must also be remembered that if cortisone is used in treatment the effect may well be to restore the barrier at the very time when maximal penetration of the drug is most urgently required.

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