Critical Review.

THE CEREBROSPINAL FLUID: ITS SOURCE, DISTRIBUTION, AND CIRCULATION.

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IF the credit of having first performed lumbar puncture rightly belongs to an American physician, as has recently been claimed,¹ it is nevertheless to Quincke² that we owe the perfection of the technique, and it is still his method, unchanged in any essential detail, which is universally employed at the present day. In the three decades which have elapsed since Quincke's discovery great advances have been made in the study of the cerebrospinal fluid, and from this progress neurology has not failed to benefit, for the introduction of a simple device for the removal of cerebrospinal fluid from the living body opened up a new avenue of approach for investigating the chemical and biological reactions of the nervous system, on which rests to so great a degree our hope of progress in the treatment of nervous disease. Despite, however, the full and fruitful results which have been achieved in the field of its pathology, the cerebrospinal fluid has until recent years suffered neglect at the hands of the physiologists, with the inevitable result that the problem of its origin and circulation is still a subject of much controversy. Fortunately signs are not lacking that with the development of modern experimental methods the process of unravelling the mysteries of its destiny is at last making headway, and that out of the confusion of the earlier investigations clarity is beginning to ensue.

The literature of the cerebrospinal fluid may be grouped on the one hand into a vast series of clinical observations largely concerned with its pathological changes, and on the other, in the report of a considerable amount of experimental work dating from the pioneer studies of Key and Retzius. A review from every aspect would therefore embrace so many ramifications that it seems wiser to confine the present article to certain anatomical and physiological principles which have been the subject of recent research.

ORIGIN.

The Rôle of the Choroid Plexus.—For many years the origin of

the cerebrospinal fluid has attracted attention, and, although the general consensus of opinion is that it is the product of the choroid plexuses, the problem is still far from being settled. The belief that the choroid plexus takes a prominent share in its elaboration was first expressed by Faivre,³ who based his opinion on the presumably glandular character of these structures. Each plexus consists of a highly vascular fringe, beset with a large number of villous projections, and clothed with a layer of cubical cells. Findlay⁴ and other workers have described granular inclusions, staining with osmic acid, which have been looked upon as evidence of cell activity, and under the influence of agents which stimulate secretion changes also occur in the cubical cells which might be interpreted in a similar way, were it not for the fact that the histological appearances differ considerably from those which are said to occur in other glands during physiological activity. Meek,⁵ who employed injections of pilocarpine and muscarine, found that the choroidal cells become larger during secretion, and their cytoplasm differentiated into a clear outer and an inner granular zone. In the case of an ordinary secreting gland, such as the parotid, the alveolar cells become smaller during activity, and the differentiation of the cytoplasm is exactly the reverse of that observed in the cubical epithelium of the choroid plexus. Such an apparent disparity in results naturally suggests some error, and, as Becht⁶ remarks, the increased height of the choroidal cells following the action of drugs which commonly produce secretion might with equal right be interpreted as proof of an absorptive function. An assumption of this character has indeed been seriously entertained by Loeper, Askanazy, and Hassin.⁷ The latter considers that the function of the choroid plexus is probably "to pick up from the cerebrospinal fluid harmful or other products of nervous metabolism, and to render them, as well as the fluid, more absorbable". Certain pathological changes in the subarachnoid space and choroid plexus from a case of polio-encephalitis are accepted by him as evidence for this view, but his inferences will hardly survive critical examination, and are totally opposed to the findings of Wislocki and Putnam⁸ in their experimental study of hydrocephalus. These observers induced closure of the ventricles in a number of kittens and young rabbits by injecting a suspension of lamp black into the cisterna cerebellomedullaris. Subsequently a readily diffusible solution was introduced into the dilated ventricles, and by tracing its distribution they were able to show that, while absorption does occur to some extent, from the ventricles of hydrocephalic animals, the choroid plexus plays no part in the process. Their results have since been confirmed by Nañagas,⁹ whose work we shall have occasion to refer to in a later section.

Pharmacological Experiment.—In addition to histological study, attempts have been made to investigate the possible secretory powers of the choroid plexus by observing the behaviour of the cerebrospinal fluid after the administration of certain drugs. In one method a needle or cannula is introduced into the subarachnoid space, and the rate of outflow in drops measured. It is obvious, however, that such a procedure offers more than one source of fallacy, for the mere introduction of a needle through the occipito-atlantoid ligament cannot afford conclusive evidence of the source of the cerebrospinal fluid, for that which escapes may come, not only from the choroid plexus, but from other subsidiary sources, such as the perivascular lymph spaces. To get over this difficulty Weed¹⁰ catheterized the aqueduct of Sylvius, and by the administration of certain pharmacological agents caused a flow of cerebrospinal fluid which lasted for several hours. In a later series of experiments Cushing and Weed¹¹ obtained access to the ventricular fluid by employing a mid-line puncture directly through the longitudinal sinus and corpus callosum, and in this way were able to avoid the disconcerting complications introduced by other methods of approach. Very similar results were again obtained, for the intravenous injection of desiccated pituitary extract was followed by a secretory response which appeared to be independent of both respiratory influences and hæmodynamic reactions. Halliburton and Dixon,¹² whose researches form one of the most important contributions to this subject, succeeded in demonstrating an apparent hormone action by injecting intravenously extracts of choroid plexus, and also noted that brain extract caused an increased secretion independent of blood-pressure changes. These experiments were subsequently confirmed by Frazier and Peet,¹³ who, in addition, claimed that they had caused an apparent specific inhibitory effect by the injection of thyroid extract.

The method of determining the amount of fluid formed by measuring the rate of outflow was soon replaced by a second, in which an attempt is made to measure alterations in the pressure of the fluid by the use of a manometer. Partial emptying of the subarachnoid space is avoided, and when used in conjunction with apparatus for measuring arterial and venous pressure the manometer was found to give more satisfactory results. Nevertheless, its use is open to criticism, for the pressure conditions favour absorption of fluid along natural channels, and do not exclude the possibility that the pressure under which the fluid is formed may be so low as to be checked by that found at times in this method of determination. To eliminate this possible source of fallacy, Becht and Gunnar¹⁴ devised an instrument for measuring and recording graphically the amount of fluid in the subarachnoid space under pressures slightly less than

normal. Cerebrospinal fluid was allowed to flow out into a Mariotte bottle so arranged that they were able to measure accurately the volume increase of fluid within the bottle without modification of the pressure; the conditions of the experiment also permitted fluid to re-enter the canal with the minimum of interference. The importance of such a method is at once obvious, for if the fluid returns completely to the canal it gives the required proof that there can have been no new formation, as otherwise there should be no room in the canal for the fluid forced out. It was found that neither adrenalin, pituitrin, nor pilocarpine caused any increased formation of cerebrospinal fluid, as in all experiments the outflow during the early stage of the action was followed by a complete re-entry during the period of vascular adjustment. Becht⁶ points out that many of the positive results obtained by other workers may be due to wrong interpretation, *movements* of the fluid being mistaken for *formation* of the fluid. Thus, in the experiments reported by Weed and Cushing the fluid which was observed to escape through a transcallosal puncture may have merely represented preformed cerebrospinal fluid draining through the patent aqueduct of Sylvius from the subarachnoid space. It is also true that an escape of preformed cerebrospinal fluid leads to a consequent reduction of pressure, which in itself may be sufficient to produce changes in the rate of formation. For this reason it is particularly hazardous to draw conclusions from the slow escape of fluid from a needle, and clinical records of the loss of enormous quantities of spinal fluid from the nose or the ear are for the same reason of little value in estimating the normal rate of production.

Another and more serious objection to the outflow method is the inability to judge the effect on the fluid of vascular changes and readjustment. Since the brain is incompressible and enclosed by the bony calvarium, any alteration in the venous and arterial pressures within the skull is bound to exert a marked effect upon the cerebrospinal-fluid pressure, and consequently alter the rate of its escape. In this way the administration of hæmodynamic drugs—and it is significant that most of the agents described as having a stimulating effect upon the formation of cerebrospinal fluid belong to this category—may mechanically force out cerebrospinal fluid and lead to a wrong interpretation of increased formation. It is therefore essential, in all experiments of this kind, to measure both arterial and venous pressures within the skull, and the neglect of many workers to do so has undoubtedly led to erroneous conclusions. How sensitive the cerebrospinal pressure is to variations in venous pressure within the skull may be readily demonstrated by any clinician who has occasion to perform lumbar puncture: the slightest degree of constriction on the large veins of the neck leads to an immediate and

marked rise in cerebrospinal fluid pressure—part of the so-called Queckenstedt phenomenon.¹⁵ Becht and Matill,¹⁶ who have recently published the results of a very able investigation of this subject, conclude that all the changes which have been offered as proof of the secretory mechanism of formation can be logically explained by alterations in venous and arterial pressures within the skull. Their results after the injection of tissue extracts showed very convincingly that in every case where there was a decrease in venous pressure within the skull the fluid pressure also fell; similarly, an increase in venous pressure was always accompanied by an increase in fluid pressure. A parallelism of this kind suggests that the determining factor for the fluid must be venous pressure, and that therefore the fluid pressure changes because of the alteration in venous pressure. In other words, all the changes observed can be readily explained on a mechanical basis, there being no indisputable proof that any of the extracts employed have a specific action on the secretory activity of the choroid plexus.

Pathological Evidence.—Evidence of the secretory function of the choroid plexus may also be obtained from a consideration of certain pathological conditions.

In congenital hydrocephalus cerebrospinal fluid accumulates slowly, causing a progressive dilatation of the ventricular system. The frequency with which a co-existent basal meningitis is found suggests that this condition is caused by some obstruction to the outflow of fluid from the ventricles, and in a number of cases obliteration of the foramen of Magendie has been described. More often, however, the two subsidiary openings discovered by Luschka are sufficient to maintain free drainage from the ventricles into the subarachnoid space, thus explaining the apparent anomaly that obliteration of the foramen of Magendie may not be accompanied by hydrocephalus. Apart from the inflammatory conditions of the base, distention of the lateral and third ventricles is sometimes seen complicating intracranial tumours which are growing in the neighbourhood of the mesencephalon. Usually such a hydrocephalus is the result of obliteration of the mid-brain iter, but more rarely it follows an occlusion of the *venæ Galeni magnæ*, when it is due to an overproduction of fluid which is in some ways analogous to the ascites brought about by stenosis of the inferior vena cava. With this overproduction there is an actual enlargement of the foramina of Monro, Magendie, and Luschka, as there is no obstruction within the ventricular system to localize the dilatation.

Both these types of hydrocephalus have been successfully reproduced on animals. In one series of experiments undertaken in collaboration with Blackfan, Dandy¹⁷ introduced into the aqueduct

of Sylvius a small piece of cotton-wool enclosed in an oiled gelatin capsule. In every animal on whom this experiment was performed, dilatation of the ventricles anterior to the occlusion followed; and when the foramen of Monro was treated in a similar manner, a unilateral hydrocephalus developed. Such experiments afford conclusive proof that cerebrospinal fluid is formed in the lateral ventricles, that absorption in them is at least less than production, and that while the aqueduct of Sylvius is a necessary outlet from the third and both lateral ventricles, there are no collateral channels capable of assuming the function of the blocked iter.

It is evident, however, that this work does not prove the specific point of formation of the fluid, for increased formation might result not only from activity of the choroid plexuses, but from transudation from cerebral capillaries, or from stimulation of the ependymal cells lining the ventricles. In this connection it is interesting to note that Cushing¹⁸ has been able to see the choroid plexus at work in the human subject. "On one or two occasions", he states, "I have had the opportunity in man to observe the main plexus at the bottom of a large porencephalic cavity, emptied of its contents, and have seen the fluid exuding from the surface of the structure."

Evidence of this character, although instructive and no doubt valuable, fails to carry conviction, for if the oozing of fluid from an exposed surface is to be regarded as proof of secretion, then we must also ascribe a secretory function to the arachnoid membrane, which almost always shows some degree of 'sweating' when exposed by operation. More direct and conclusive proof that the choroid plexus is related to the formation of cerebrospinal fluid should be furnished by the experimental removal of the plexuses, but until recently the mechanical abuse which is inevitable in an operation has led to inconclusive results. The credit of having surmounted these difficulties belongs to Dandy,¹⁹ who in a recent independent study has shown that the plexus is one of the points of origin of the cerebrospinal fluid. By means of a transcortical incision he removed the entire choroid plexus of one ventricle, at the same time blocking the corresponding foramen of Monro. After the lapse of three months the animal was killed. It was then found that the blocked ventricle had collapsed to the dimensions of a mere slit. In some animals on whom unilateral choroidectomy had been performed, Dandy obliterated both foramina of Monro, and so obtained a striking contrast between the two sides, one hemisphere showing a collapsed ventricle, and the other a hydrocephalic distention. Dandy's results, therefore, seem to settle the question in favour of the view that cerebrospinal fluid is elaborated by the choroid plexuses of the lateral ventricles, and probably by those of the third and fourth ventricles as well. In this connection

we get little help from morbid anatomy, for although the choroid plexus is subject to cystic degeneration, tumour formation, etc., no cases have been recorded in which the entire structure has been destroyed.

The data derived from microscopic study are still far too meagre to permit any definite conclusions, but a recent communication by Taft²⁰ is highly suggestive. Histological study of the choroid plexus taken from cases of general paralysis showed a progressive fibrous change, beginning with general increase of connective tissue, and followed eventually by an obliteration of the capillaries and formation of fibrous tufts. In view of these findings, and of the abundance of cerebrospinal fluid in this disease, Taft asks whether we are justified in concluding that the persisting ependymal cells are capable of functioning in the rôle of gland-cells in the absence of the capillaries with which they normally stand in relation.

In order to escape from the difficulties encountered in interpreting the above experiments, so contradictory in their results, an alternative hypothesis may be framed without entirely depriving the plexus of the importance usually ascribed to it. It has been estimated by Bard²¹ that the surface area of the choroid plexuses amounts approximately to one square metre, and it is legitimate to assume that the cuboidal cells of so large a surface may play the part of a dialysing membrane quite adequate for a constant supply of cerebrospinal fluid, whose rate of formation will be governed by the physical laws of permeability rather than by the factors which govern secretion.

In this connection the observations of Mestrezat²² are more than usually instructive. In his monumental thesis he points out that the cerebrospinal fluid presents nothing comparable with the products of a differentiated gland, and that its composition may be calculated by taking count only of the dialysable elements of plasma. Furthermore, with the assistance of Mlle. Ledebt²³ he has shown *in vitro* that the fluid obtained by dialysing horse serum through collodion has the characteristic composition of cerebrospinal fluid and aqueous humour. Experiments on living animals also yielded similar results; dialysing sacs introduced into the peritoneal cavity of the dog, rabbit, or guinea-pig became filled with a colourless, limpid, non-albuminous fluid which in its chemical composition was exactly similar to cerebrospinal fluid. Corroborative evidence of the same order was also obtained by an analysis of the contents of a gall-bladder containing 'white bile'—a condition which sometimes follows occlusion of the cystic duct—and Mestrezat concludes by stating that the cerebrospinal fluid, considered from all points of view, is a pure dialysate, there being no evidence to show that it is a true secretion.

RELATIONSHIP OF CEREBROSPINAL FLUID TO NERVOUS SYSTEM.

In man large amounts of cerebrospinal fluid may be obtained by lumbar puncture, and it seems scarcely credible that the enormous quantities which have been observed to drip from the nose in pathological states have had their sole origin in the choroid plexus. Under normal conditions the flow of the ventricular fluid must be very small, for both the aqueduct of Sylvius and the foramen of Magendie are of surprisingly narrow calibre. Furthermore, the possibility of a subsidiary source of supply is suggested by the chemical difference between the ventricular and spinal fluids; that in the ventricles contains a higher percentage of sugar and a lower percentage of globulin than the spinal fluid. The difficulty in explaining these differences has accordingly led to the suggestion that the fluid contained in the subarachnoid space receives an increment from the perivascular spaces, and possibly from the pia-arachnoid itself. It has been known for many years that the blood-vessels of the brain have certain peculiarities of structure not encountered in any other region of the body. Although comparatively thin-walled vessels they are surrounded by an adventitial sheath which extends throughout their whole length down to the minute capillaries. In addition, there are said to be present spaces—the Virchow-Robin spaces—between the media and adventitia which are believed to communicate directly with the subarachnoid space. There is also described a second canalicular system between the adventitia and the brain tissue itself, forming, as it were, a fluid sleeve for the cerebral vessels. By puncture injection of the nervous system His²¹ succeeded in distending the latter system, and was able to follow the injection mass to a plexus beneath the pia. When excessively developed by pathological conditions of the brain, these adventitial spaces of His give rise to a condition which Durand-Fardel²⁵ named *état criblé*. By many authorities the His spaces are regarded as artefacts; Mott,²⁶ however, was able in cases of experimental anæmia not only to present evidence of their functional existence, but to demonstrate a connection between the perivascular system and the spaces surrounding the nerve-cells. From chemical and histological evidence, he was led to believe that cerebrospinal fluid circulates in these spaces and acts as a medium of gaseous exchange between the blood and nervous tissues. He also suggested that cerebrospinal fluid is absorbed into the cerebral capillaries. More recent work, however, favours the view that the flow is in reality in the opposite direction, the perivascular channels contributing to the cerebrospinal fluid waste products of nerve-cell metabolism. To establish such a theory it is necessary to postulate

a direct communication between these spaces and the subarachnoid space, and in support of such an arrangement existing, Weed²⁷ offers evidence from experiments on animals. He injected into the subarachnoid space a solution containing potassium ferrocyanide and iron ammonium citrate. After completion of the experiment the brain with its meninges was fixed in a formalin solution containing 1 per cent of hydrochloric acid, and in microscopic sections the resulting precipitate of ferric ferrocyanide (Prussian blue) appeared as fine bluish granules. In typical observations in which the ferrocyanide solution was injected under very low pressures for several hours, practically no granules were found in the perivascular spaces. When, however, higher pressures (50 mm. Hg) were employed, the precipitated material could be traced in a continuous collection from the subarachnoid spaces into the perivascular channels. In some cases granules could be identified in the pericapillary spaces, while in others diffuse collections occurred around the nerve-cells. No evidence of passage of the deposits into the cerebral capillaries could be found, and Weed therefore concludes that the flow is towards the subarachnoid space, the perivascular channels serving to carry away products of nerve-cell metabolism, and so in part contribute to the formation of cerebrospinal fluid.

While it would be unfair to ignore the outstanding merit of Weed's experiments, it can hardly be said that they afford very satisfactory proof of his contention. The injection of solutions under considerable pressure into the delicate tissues of the brain constitutes at the best a rather crude experiment; and because a true solution can be forced into the perivascular spaces, it is surely not legitimate to conclude that there is a normal flow of fluid from these spaces into the subarachnoid system. Further, as the injected ferrocyanide solution required for its demonstration in the perivascular spaces both a preliminary cerebral anæmia and a pressure of 50 mm. Hg—none being found when low pressures were employed—it is more than possible that communications were opened up which in the normal brain have no existence. Again, if granules can travel readily into minute cerebrospinal channels there seems to be no reason why organisms should not do so also; yet in various types of meningitis where the cerebrospinal fluid is heavily infected, it is most unusual to find evidence of their presence even in the widest perivascular spaces. Dercum,²⁸ who is a vigorous opponent of those who believe that these spaces are in direct communication with the subarachnoid space, points out that if the cerebrospinal fluid is the nutrient fluid of the brain it should bear in its constitution some evidence of the fact; yet under normal conditions it contains no products of nerve-tissue metabolism. Lastly, if, as Weed suggests, cerebrospinal fluid

is partly formed by exudation from the blood into the perivascular system, it should carry with it any diffusible drug or poison which may be present in the circulation. As is well known, there is great difficulty in introducing drugs via the blood-stream into the cerebrospinal fluid, and this difficulty becomes readily comprehensible if it be assumed that there is no communication between the perivascular and subarachnoid systems. That such may, indeed, be the case is indicated by some instructive experiments performed by McIntosh and Fildes²⁹ in an investigation of the factors governing the penetration of arsenic and aniline dyes to the brain. Certain dye substances were found to pass directly from the blood to the brain substance proper without entering the cerebrospinal fluid, a result which it seems impossible to explain if the existence of an intramedullary canalicular system filled with cerebrospinal fluid be granted.

Early writers, impressed by the similarity of the meningeal spaces and the larger serous cavities of the body, looked upon the cerebrospinal fluid as a secretion of the meninges, which they thought might possibly function in a manner analogous to the peritoneum. A contribution from such a source would explain the difference in composition of the spinal and ventricular fluids referred to above, but there seems to be good reason for supposing that the meninges cannot function in this manner. They are histologically unlike any other membrane, for, of their two components, the arachnoid is non-vascular, and the pia is said to possess no capillary bed.

It is customary to ascribe the failure of drugs to penetrate into the nervous system to the barrier imposed by the epithelium of the choroid plexus, which is assumed to exercise a selective activity towards certain substances circulating in the blood. At one time it was thought that only alcohol, acetone, chloroform, and urotropine were able to pass this barrier; but recent investigation has shown that the choroid plexus is permeable to a large number of substances. Spirochætal agents appear to pass through in a certain percentage of cases, for Hall³⁰ and his associates found arsenic in the spinal fluid of 25 to 35 per cent of a series of cases undergoing salvarsan treatment, and iodine has also been found in appreciable amounts by Osborne.³¹

In lower animals the permeability of the choroid plexus has been fully investigated by Stern,³² who found that among a large number of substances, sodium bromide, sodium salicylate, sodium sulphocyanide, sodium picrate, strychnine, morphine, atropine, santonin, and bile salts regularly make their appearance in the spinal fluid. The chief interest of Stern's work concerns not so much the barrier-like action opposed to the entry of various drugs into the cerebrospinal fluid as the relationship of this fluid to the brain substance.

All the experiments were performed on animals which had been subjected to a preliminary double nephrectomy, and the drugs were administered in massive and often lethal doses. Their presence in the spinal fluid did not therefore necessarily mean that they would reach the cerebrospinal fluid under normal conditions; but it was a remarkable fact that whenever a substance introduced into the general circulation was found in the spinal fluid it was also present in the nervous tissue, and, conversely, in every case in which a given substance entered the nervous tissues it could also be demonstrated in the spinal fluid. Moreover, Stern was never able to detect the presence of a given substance in the brain, either by signs of nervous disorder or by microchemical analysis, if it had failed to penetrate into the cerebrospinal fluid, whereas on the other hand every agent introduced into the cerebrospinal fluid could be demonstrated in the brain by the effects which followed or by appropriate analytical methods.

These results are of considerable importance, for they seem to settle in a most conclusive manner that in its relation to the nervous system cerebrospinal fluid plays the same rôle as lymph, and that every substance contained in the blood must first penetrate into the cerebrospinal fluid before exercising its effects on the nerve elements.

In the interpretation of these experiments there are two possible sources of fallacy which appear to have escaped Stern's notice. In the first place, it is not unreasonable to suppose that the nerve elements of the brain are protected against noxious agents circulating in the blood by the electivity of both the choroidal epithelium and the cells of the brain capillaries. The existence of such a blood-cerebral barrier would give results precisely similar to those observed by Stern; it would not, however, throw any doubt on the validity of Stern's conclusion that substances contained in the blood must reach the cerebrospinal fluid before they can affect the nerve elements. We have already seen that McIntosh and Fildes could not find certain dye substances in the cerebrospinal fluid, although they passed readily from the blood to the brain substance, and Stern's admission that his results with methyl violet were very conflicting probably indicates that this method of experiment is subject to many defects.

One other source of fallacy is the difficulty of making sure that a given substance injected into the cerebrospinal fluid does not reach the brain tissue indirectly—that is to say, by absorption from the subarachnoid space into the general circulation and thence to the blood-vessels of the brain, and until this is shown not to occur, Stern's conclusions must be accepted with caution.

THE AVENUES OF ESCAPE.

It is obvious that if under normal conditions cerebrospinal fluid is being constantly secreted by the choroid plexuses, there must exist a mechanism for its return to the general circulation of the body. Regarding the actual course which the fluid takes, there seems to be general agreement that the pathway of escape is a double one, the major portion of the fluid being absorbed by the blood, and a smaller quantity by the lymphatic stream.

The evidence for this view rests partly on anatomical and partly on physiological grounds. Quinke,³³ one of the earliest workers in this field, recorded in 1872 his experiments on drainage of the subarachnoid spaces after the injection of cinnabar. He was able to trace an injection mass along the sheaths of the upper spinal nerves and along those of the optic nerves as far as the episcleral space of Schwalbe. Cinnabar granulations were also found in the Pacchionian granulations which project into certain venous sinuses, but none could be identified in the general circulation or in the visceral organs of the body. Later, Key and Retzius,³⁴ by skilful injection of coloured gelatin solutions, furnished evidence of the part played by the Pacchionian bodies. They were able to demonstrate an epithelial covering, and supposed that cerebrospinal fluid passes through stomata between the endothelial cells into the dural sinuses. When, however, it came to be realized that Pacchionian bodies are never found in lower animals, it was felt that this theory of absorption was inadequate, although all the available evidence suggested an actual passage of cerebrospinal fluid into the venous system. At a later date interest in this problem was revived by Leonard Hill's³⁵ contribution to the physiology and pathology of the cerebral circulation. He reported that saline solution coloured with methylene blue and introduced into the cerebrospinal spaces passed straight into the venous sinuses, and after a varying interval could be identified in the bladder and cervical lymphatics. Very similar experiments performed by Cushing³⁶ demonstrated that globules of mercury are able to pass from the subarachnoid space through the cerebral sinuses, diploic and jugular veins, into the right chambers of the heart. The peculiar valvular arrangement at the point of entry of the chyle into the left jugular vein suggested to him that there might be an analogous mechanism of obliquely placed valves along the superior longitudinal sinus, permitting the entry of cerebrospinal fluid, but preventing a flow of blood in the opposite direction.

Another pathway for absorption was put forward by Mott in 1910. This theory, already alluded to, conceives a passage of fluid through the walls of the cerebral capillaries from the surrounding

adventitial spaces; but since recent investigations have shown that the pressure in the blood capillaries of the brain is considerably higher than that of the cerebrospinal fluid, it seems fair to assume that the flow, if any, must be in the opposite direction, that is, from a point of higher pressure (brain capillaries) to a point of lower pressure (subarachnoid space). Dandy and Blackfan¹⁷ studied the rate of absorption of solutions of phenolsulphonaphthalein from the subarachnoid space, and concluded that the absorption of cerebrospinal fluid is a diffuse process from the entire subarachnoid space; but their assumption is rather discounted by the recent researches of Weed,³⁷ whose methods mark a distinct advance on those of his predecessors. Using the technique which we have already outlined, he was able to trace fine bluish granules of ferric ferrocyanide from the subarachnoid space into the great sinuses, but could find none in the cerebral veins or capillaries. One of the most important findings in these experiments was the discovery that the Pacchionian body is in reality a pathological transformation of a microscopic arachnoid villus which normally projects from the leptomeninges into the walls of the large intracranial sinuses. It consists of a delicate web-like structure of many interlacing cords continuing the outer arachnoid membrane into the dural walls, its basework being composed of a very fine connective tissue, reticular in structure, and with the general staining qualities of myxomatous tissue; capping this on all sides is a mesothelial covering of arachnoid cells which serve to keep intact the structural characteristics of the arachnoid projection, and in places to act as a cellular filter into the great sinuses. Such villi are invariably met with in normal children, and at all ages in man, being only evident to the naked eye when they have undergone a hypertrophic enlargement—the Pacchionian granulation. Weed was able to exclude the possibility of fluid passage through stomata between the mesothelial covering cells, but on the whole the results seemed to indicate that the process of drainage is through a cellular membrane. Weed concludes with the statement that the chief mode of return of cerebrospinal fluid is by a process of filtration through arachnoid villi into the great sinuses. In other words, the cranial portion of the nervous system seems to contain the efficient mechanism for the absorption of cerebrospinal fluid.

The Accessory or Lymphatic Pathway of Absorption.—Not only have the cranial and spinal nerves a leptomeningeal sheath for varying distances, but there is also around each a perineural space which can be injected from the subarachnoid system, and by using his ferrocyanide method Weed succeeded in demonstrating the possibility of absorption through the lymphatic system. Granular material was traced along the sheaths of the olfactory nerves to the walls of the

nasal cavity, and in experiments in which the fluid was under very high pressure, fluid was observed to drip from the nose of the animal. In the optic and other cranial nerves the findings were on the whole very similar, and the blue precipitate could be traced into the lymph nodes of the neck. With regard to drainage from the spinal subarachnoid space, the anatomical conditions found there are rather different from those in the cranial cavity, there being neither dural sinuses nor arachnoid villi. In a large series of spinal subarachnoid injections Weed was never able to observe the passage of granules into any spinal vessels, but there was an obvious perineural deposit which could be followed a short distance along the anterior and posterior roots. It is therefore likely that the sole pathway of escape from the spinal meninges is along lymphatic channels, and that therefore drainage from the spinal subarachnoid space is a very slow process.

Another possible spinal path of absorption has been suggested by Kramer,³⁸ who claims to have shown that if methylene blue be injected into the spinal subarachnoid space the tissues about the central canal become stained, the dye-stuff having apparently ascended in the canal from a patent caudal metapore. Confirmation of his experiments is lacking at present, but it is interesting to recall that in certain fishes the central canal opens into the surrounding tissues.

The Normal Rate of Absorption.—There is probably no question which offers greater difficulties than that which concerns the rates of formation and absorption of the cerebrospinal fluid. In the case of the blood it is a comparatively easy matter to devise an instrument for measuring the velocity of its flow, but the difficulties in investigating the rate of circulation of the cerebrospinal fluid are very great, for not only is the fluid confined to a system placed in a most inaccessible region, but the total amount in circulation is never very much, especially in the case of lower animals. Hence it is not surprising to find opinion much divided, some authorities holding that the cerebrospinal fluid is renewed four or five times in the course of twenty-four hours, and others maintaining that there is little or no movement unless the pressure of the fluid be artificially lowered.

One of the most important methods of attacking the problem is that in which certain drugs or dyes are injected into the subarachnoid space, and records made of the time required for their appearance in the blood or urine. Leonard Hill³⁵ found the urine coloured in less than twenty minutes after an injection of methylene blue into the cisterna magna, and more recently Frazier and Peet,³⁹ using intraventricular injections of phenolphthalein, obtained an excretion of about 50 to 60 per cent of the dye within two hours. Very similar results were recorded by Dandy and Blackfan⁴⁰ in their study of

experimental hydrocephalus. After subarachnoid injection the dye appeared in the blood in three minutes, and in the urine in six minutes, about 35 to 60 per cent being recovered in the latter situation at the end of two hours.

Mehrtens and West⁴¹ observed that diseases of the nervous system cause a lengthening of the appearance time to as much as seventy minutes in some cases, and in cases of dementia præcox Webster⁴² found that the time varied from twenty-three to a hundred and four minutes in the case of the former, and from twelve to sixty-eight minutes in the latter. The dye remained in the lumbar or thoracic regions, and was completely absorbed or destroyed before it could reach the cranial region, as repeated cisternal punctures made at six-hour intervals showed in every case a clear fluid free from all trace of colour.

The little which we know at present concerning the metabolism of the nervous system suggests that katabolic processes are more active in the cerebrum than in the caudal segments of the cerebrospinal axis, and that therefore on the convex surface of the brain a larger provision must be made for the discharge of waste products than is necessary elsewhere. That such an arrangement has been provided by nature is indicated by the large number of venous sinuses and arachnoid villi in this neighbourhood. Their importance as avenues of escape is clearly shown by the ease with which communicating hydrocephalus may be produced experimentally. By enclosing the mid-brain of a dog with a strip of gauze saturated with an irritant, Dandy⁴³ found it possible to prevent the passage of the cerebrospinal fluid to the subarachnoid spaces over the cerebral hemispheres. The area in which the absorption of cerebrospinal fluid could occur was thus limited to about one-fifth of the normal amount, and rapid dilatation of the ventricles ensued. On the other hand, exclusion of the spinal subarachnoid space has had little or no effect on the rate of absorption, for Weed found that dye-stuffs injected into the cerebellar cistern could be recovered from the urine in a period hardly longer than when the whole system was functioning. Potassium ferrocyanide could be detected in the urine twenty minutes after its introduction in the lumbar region, but when the cranial mechanism was excluded by ligature of the cord in the lower cervical region the dye was not excreted until the lapse of seventy-five minutes.

In the course of their experiments on the cerebrospinal fluid, Dixon and Halliburton⁴⁴ employed substances of different molecular size, and found that those which disappeared from the fluid did so by a process of diffusion, whose rate was slower or faster in proportion to the size of the molecule of the agent injected. The introduction of substances like adrenalin, nicotine, and atropine produced

characteristic physiological effects almost as rapidly as if introduced into the venous circulation, while other non-diffusible substances, such as proteins, failed to give rise to characteristic effects.

Next in historical sequence come the experiments of Becht,⁶ who covered much the same ground as Dixon and Halliburton. He found no satisfactory proof of rapid absorption from the subarachnoid space, for neither adrenalin nor nicotine caused any characteristic rise in blood-pressure. These substances could still be identified in the spinal fluid several hours after the experiments, for in every case where the fluid was withdrawn from the canal and injected intravenously the usual blood-pressure changes followed, clearly showing that an absence of effect after intrathecal injection was not due to a failure to inject the drug nor to a failure of response on the part of the animal. It is to be regretted that these experiments have not been confirmed by other workers, since Becht concludes that so far no indisputable evidence of the source or circulation of the cerebrospinal fluid has been furnished, and does not hesitate to attribute the results recorded by others to faulty technique or wrong interpretation. As an illustration of his vigorous criticism we may quote from his remarks on the rate of absorption of the fluid.

“Attempts to get at this problem indirectly have led to questionable and we believe erroneous conclusions. Frazier and Peet, working with phenolsulphonephthalein, found that if the drug is injected into the ventricles under normal conditions about 50 to 60 per cent is excreted into the bladder within two hours. They then conclude: ‘If we assume that the cerebrospinal fluid is absorbed proportionately as rapidly as the amount of phthalein injected, *and there is no reason for believing otherwise*, we are led to the conclusion that at least 50 to 60 per cent of the cerebrospinal fluid is absorbed every two hours’. We cannot agree with this conclusion. The absence of proof that an assertion is untrue does not prove that the assertion is true. In this instance it cannot be assumed—it must be proved—that all of the constituents of the cerebrospinal fluid are absorbed in the same proportion to the whole of the drug; otherwise the possibility of the selective absorption of a foreign material is not eliminated. It would be just as sound reasoning to assume that since from 50 to 60 per cent of the phenol-sulphonephthalein has been excreted from the kidneys in two hours, 50 to 60 per cent of the water and other constituents of the blood had been eliminated in that time. Assuming the weight of the blood to be one-tenth of that of the body for animals, and the blood to be two-thirds plasma, then in a man of 60 kilos weight there should occur in two hours the excretion of 2 to 2.4 litres of urine, or 24 to

28·8 litres in twenty-four hours. This is of course preposterous, and proves that the drug must be selectively excreted from the kidney and is not excreted in proportion to all the other constituents of the blood. This same activity must be proved to be absent before the conclusions of Frazier and Peet become at all convincing."

THE CIRCULATION OF THE CEREBROSPINAL FLUID.

We have already seen that a large amount of experiment and pathological observation points strongly to the choroid plexuses as the chief source of the cerebrospinal fluid, and that the evidence for its escape through arachnoid villi and lymphatics is no less definite. There now remains for consideration the probable course taken by the fluid between its points of origin and exit. Surrounding the central nervous system and acting as an efficient fluid cushion, the cerebrospinal fluid lies wholly within delicate spaces between the arachnoid and pia mater. These spaces are lined everywhere by flattened mesothelial cells. Upon the surface of the cerebral hemispheres the confined fluid is present only as a capillary layer, but at the base of brain the arachnoid trabeculae widen to form the arachnoid cisterns.

The stream of cerebrospinal fluid is believed to start within the ventricles and to pass out through the foramen of Magendie and those of Luschka into the subarachnoid spaces. The fluid in both lateral ventricles flows freely through the foramina of Monro into the medially situated third ventricle, and thence it escapes through the aqueduct of Sylvius into the fourth ventricle. The existence of the three openings in the roof of the fourth ventricle has at various times been called into question; but recent morphological studies indicate that they are true anatomical openings in the velum, and not artefacts caused by the histological methods employed for their demonstration. Moreover, experiments have shown that if phenol-sulphonaphthalein is injected into the lateral ventricle it will quickly make its appearance in the subarachnoid space. If air, in the place of coloured solutions, be introduced, it will pass externally into the cisternæ, and with the aid of the *x* rays Dandy⁴⁵ has been able to demonstrate its actual passage through the foramen of Magendie. What happens to the fluid after it has reached the cisterna magna is somewhat doubtful, but it is generally assumed to pass in two directions, upwards over the cerebral hemispheres and downwards into the spinal subarachnoid space. In the former locality it bears important relationships to the dura mater, for the arachnoid villi come to lie directly beneath the vascular endothelium of the large dural sinuses, and are so in a position to facilitate the escape of cerebrospinal fluid into the blood. On the other hand, in the spinal

system there are neither dural sinuses nor arachnoid villi, and consequently the fluid must either pass backwards to the cranium or escape through the lymph channels in relation to the spinal nerve-roots.

The question of how far the cerebrospinal fluid serves as the lymph of the brain is one of great practical importance in view of the attempts which have been made to influence syphilitic disease of the brain by intraspinal therapy, but unfortunately it cannot as yet be answered. The conflicting views of Mott and Weed have already been referred to, and most recent work does not make the presentation of this problem any clearer. Monakow⁴⁶ introduces further complexity by suggesting the existence of two distinct circulatory systems within the nervous system. In the first place he assumes that the ventricular fluid passes outwards between the lining ependymal cells into the brain substances, where it bathes the nerve-cells prior to its discharge through the perivascular spaces of His into the subarachnoid space. Secondly, another canicular system represented by the Virchow-Robin spaces is thought by him to be concerned with the removal of foreign particles, undissolved products of degeneration, etc., which are ultimately carried by scavenger cells through meningeal lymphatics to the lymphatic glands of the neck.

To a certain extent Monakow's speculations are confirmed by the observations of Stern³² on the relations of the cerebrospinal fluid to the nervous system and general circulation. Certain substances injected into the ventricles were found to give effects more pronounced, more enduring, and much earlier in their appearance than when injection was made into the subarachnoid space. Furthermore, microscopic examination showed that while ferrocyanide of potassium readily penetrated the brain substance in the neighbourhood of the ventricles, none could be identified in the nerve-tissue if the injection was given beneath the dura mater. Stern concludes that under normal conditions the current of cerebrospinal fluid is directed from the cerebral ventricles towards the subarachnoid space, the former being the afferent and the latter the efferent path of the system. The relationship between the cerebrospinal fluid, the nerve elements, and the blood may therefore be represented schematically as follows :—

Blood → ventr. cs. fluid → nerve elements → subarachnoid cs. fluid → blood.

At the same time Stern is willing to allow that this schema does not rule out the possibility of a circulation through the various foramina connecting the ventricles and basal cisterns, but he claims that the view put forward by him explains in a more satisfactory manner the lack of results attending the injection of certain substances into the subarachnoid space. A careful

perusal of his paper, however, shows that the anatomical relationships of the cerebrospinal fluid as conceived by him are totally different from those of the majority of workers. This is clearly indicated in the paragraph devoted to a discussion of the possible identity of the fluid in various localities, for he states: "En parlant du liquide céphalorachidien nous avons eu en vue l'ensemble de liquide remplissant les espaces *sous-duremériens*, intraventriculaires, périvasculaires, et péricellulaires" (italics ours). He then passes on to compare the effects of various agents injected intraventricularly with those produced by subdural injection, and notes that the exciting agents when introduced beneath the dura were often without effect, or at the most induced a very delayed result. Now if there is one point on which all observers are agreed, it is that the subdural and subarachnoid spaces are anatomically and physiologically distinct, with no communication of any kind between them. The arachnoid membrane appears to be a rigid and impenetrable barrier, and hence Stern's experiments with subdural injections do not in any way prove that absorption is more rapid in the ventricles than in the subarachnoid space.

Before concluding this section, reference must be made to the work of Nañagas⁹ on absorption in the closed ventricles of hydrocephalus. It had been previously shown by Weed and McKibben⁴⁷ that intravenous injections of salt solutions of varying concentrations had a very definite and rapid effect on cerebrospinal-fluid pressure. A 30 per cent solution of sodium chloride caused a marked reduction of pressure, the fall in some cases being below zero, and, conversely, intravenous injections of distilled water were followed by a marked and sustained rise of pressure. These discoveries suggested to Nañagas that the interesting problem of absorption in the closed ventricles might be studied experimentally. Having produced hydrocephalus in kittens by subarachnoid injection of a suspension of lamp black, careful records were taken of the intraventricular pressure before and after the administration of salt solutions. It was then shown that intravenous injections of hypertonic solutions caused a marked fall in pressure, and that the opposite effect could be obtained when hypotonic solutions were given.

Having in this way established physiological proof that the volume of cerebrospinal fluid in the closed ventricles may be increased or diminished experimentally, Nañagas proceeded to investigate the way of absorption from the ventricles, using for this purpose the injection method of Weed. In microscopic sections the precipitate of Prussian blue was found to be most abundant in the neighbourhood of the ependyma of the lateral ventricles. It could also be traced in zones of diminishing intensity in the grey matter of the brain for a

varying distance from the ventricles, but in no cases was the cortex affected. Blue granules were found within the cytoplasm of the ependymal cells, in the tissue intervening between them, in the interior of minute capillaries, and, further away, in vessels which were identified as veins. The cerebral arteries and the vessels of the choroid plexus were entirely free from precipitate. In control animals not subjected to experimental hydrocephalus the replacement of the ventricular fluid by ferrocyanide solution brought about an absorption very limited in distribution, and Nañagas is compelled to admit that intraventricular absorption in the normal animal must be of almost minimal physiological importance.

Apart from the established fact that in hydrocephalic animals fluid can escape into the capillary bed of the brain, there is little in the work of Nañagas to confirm the hypothesis put forward by Monakow. It is, also, more than likely that the tremendous osmotic pull exercised by the hypertonic solutions brings about a state of affairs totally different from that which obtains in the normal brain. Nañagas himself points out that hypotonic solutions have an effect the opposite of that seen when strong solutions of sodium chloride are injected. Instead of being aspirated into the shrinking nervous system, the cerebrospinal fluid receives a marked accession of fluid from those same capillaries which are credited with an absorptive function when hypertonic solutions are employed. In other words, his experiments seem merely to prove that by varying the osmotic pressure of the blood it is possible either to force cerebrospinal fluid from the ventricles into the cerebral capillaries, or to cause a flow of fluid from the latter in an exactly opposite direction.

In one particular the results reported by Nañagas are in direct conflict with those of Weed. The latter was never able to find particles of Prussian blue in the cerebral vessels, although they almost filled the perivascular spaces, and this distribution was used to support his belief that there is no absorption of cerebrospinal fluid into the vessels of the brain. The explanation of such divergent results appears to be simple : Weed performed his experiments under conditions imitating as far as possible the physiological, whereas Nañagas used a method whose effects have no possible counterpart in the normal animal. Such considerations serve to accentuate the incompleteness of our knowledge of this subject, and suggest that the experiments outlined above require to be supplemented by further research before they can be accepted as proof of an intracerebral circulation of cerebrospinal fluid.

Circulation in the Spinal Subarachnoid Space.—From what has preceded it is evident that the rate of absorption from the spinal subarachnoid space is very much slower than in other localities. The spinal fluid may, indeed, be compared with a nearly stagnant canal

ending blindly and discharging its contents through a limited number of minute channels. Nevertheless, attempts have been made by various writers to prove that not only does the cerebrospinal fluid circulate briskly in this region, but that it follows a downward and upward course through very definite channels. Propping,⁴⁸ for example, thought that the flow was downwards along the anterior aspect of the spinal cord, and in a reverse direction in the posterior compartment of the arachnoid sac. He believes that fluid movements are brought about by the influence of respiratory changes on the veins inside the spinal canal; during inspiration they collapse, and so cause a suction of cerebrospinal fluid out of the cranium; during expiration the return of this aspirated fluid is prevented by a kind of valve placed anteriorly, and in consequence spinal fluid flows from the caudal end of the sac upwards along the posterior surface of the cord. Such a theory receives no support from anatomical, physiological, or clinical observation. In the first place, the anterior and posterior compartments of the spinal subarachnoid space are very incompletely separated from each other by the ligamentum denticulatum and other septa. Then again, not only do the veins of the spinal canal collapse during inspiration, but also those within the cranium, and it is therefore impossible to understand how any suction effect can be produced. Lastly, if a true flow in special paths occurs, the injection of anæsthetic substances for securing regional anæsthesia would be anything but a satisfactory procedure.

That the degree of movement of the spinal fluid is almost negligible is indicated by the work of Weigelt⁴⁹ on the composition of the cerebrospinal fluid in different regions of the subarachnoid space. For the details of his work the reader must be referred to the original paper; it is sufficient to state that he spent two years examining fluids from the ventricles, the cisternæ, and the cervical, dorsal, and lumbar regions of spinal sac, making in all 1500 punctures. In both normal and pathological fluids the number of cells and the amount of albumin showed a progressive increase from the cervical to the lumbar region, a finding hardly consistent with the view that fluid circulates in the spinal subarachnoid space. Certain experiments by Becker⁵⁰ seem to establish the fact that although the spinal fluid has no true circulation, it is nonetheless far from being altogether at rest. This worker claims to have shown that during ventricular systole rhythmic expansion of the brain causes a movement of fluid towards the caudal end of the subarachnoid system, followed during diastole by a return in the opposite direction. The effect of the pulsating spinal vessels is very slight, but those of the brain give rise to oscillations which, after conversion into sine waves, are propagated through the cerebrospinal fluid at a rate of about 3 metres per second. To a lesser extent respiratory waves

pass in the same direction, and may compound with those of vascular origin. There is thus promoted a constant ebb and flow sufficient to ensure a certain degree of mixing of the fluid and its contents.

SUMMARY.

1. On the whole there is almost complete unanimity of opinion that the choroid plexuses are the chief source of the cerebrospinal fluid. This conception rests not on any single conclusive piece of evidence, but on well-established data derived from histological, pharmacological, and pathological observation.

2. The question of whether the cerebrospinal fluid is a true secretion or a dialysate cannot as yet be fully answered.

3. The possibility of subsidiary sources of supply, either by drainage from the perivascular spaces or from the membranous surfaces of the brain must be considered.

4. Conclusive proof that the cerebrospinal fluid functions as the lymph of the brain is at present lacking.

5. Thus far the methods devised for computing the rates of formation and absorption are unreliable.

6. Absorption of cerebrospinal fluid takes place by a process of diffusion through microscopic arachnoid villi into the large dural sinuses, and to a lesser extent through the lymph sheaths of the cranial nerves.

In the spinal subarachnoid space the fluid is drained by way of the lymphatic system only.

7. Cerebrospinal fluid circulates in the ventricles of the brain and in the subarachnoid space surrounding it. Whether it also circulates in the substance of the brain remains to be established. Movements of the fluid in the spinal subarachnoid space are probably minimal in degree.

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