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STUDIES ON THE CEREBRO-SPINAL FLUID.*

I. INTRODUCTION.

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Our knowledge of the meningeal and ependymal coverings of the central nervous system, as well as of the part played by the fluid which circulates through and over them, has hardly kept pace with our knowledge of the nervous tissues which they envelop. Indeed, until the introduction in 1891 of Quincke's revolutionizing lumbar puncture, which gave clinical access to the fluid content of the spinal subarachnoid space, there was but little more than academic interest in the cerebro-spinal fluid, which might or might not serve as a waterbed for, or represent the lymph of, the brain and cord.

The existence of fluid in the cerebral ventricles was doubtless observed by the earliest anatomists. It was Galen's view that the fluid contained the animal spirits. Vesalius thought it a lubricant. Vidus-Vidius noted its presence, as did Valsalva. Varolius credited the choroid plexuses with the property of pumping water into the ventricles. Willis regarded it as a product of distillation of the pineal gland and choroidal plexuses, and Vieussens, who also observed the fluid, believed that the valve to which his name is attached separated the contents of the cerebral and subtentorial ventricles. There were, however, serious doubts as to whether the fluid existed in the living or was merely a post-mortem precipitation. Many, like Haller, believed that the cerebral

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ventricles contained a vapor capable of condensation, which gravitated as water into the spinal spaces. To Cotugno is usually given the credit of first demonstrating (1774) in the ventricles of the living animal the presence of fluid rather than of a vapor.

The modern period may be said to begin with Magendie's three notable communications, which appeared in 1825, 26 and 27, in the "Journal de physiologie expérimentale et pathologique." Magendie was doubtless the first to fully appreciate the physiological importance of the fluid, and for many years he devoted himself to its consideration, his comprehensive monograph on the subject being published in 1842, fifteen years after his original papers. (In an appendix to this monograph his pupil, Dr. Jodin, gives an historical summary, from which subsequent writers have largely borrowed.)

Even to-day, with the general acceptance of the fact that there is a constant production and circulation of the cerebro-spinal fluid, few have other than a vague idea of the source from which it is elaborated within, or the way in which it escapes from the cranial chamber. On the basis of their structure, it has been conjectured that the choroid plexuses are secretory structures, and the studies of Key and Retzius have left the impression that the granulations of Pacchioni represent portals of outflow for cerebro-spinal fluid; beyond this, even if we go thus far, most of us are rather hazy.

This is the more remarkable when the recent invasion of the cerebro-spinal space for experimental, diagnostic, therapeutic and operative purposes is taken into account. Quincke showed us how we might safely tap the lower spinal meninges, and for purposes of clinical diagnosis we have learned to estimate fluid tension, to look for microörganisms and to gauge the cytological and some of the chemical abnormalities of the fluid, but it is safe to say that many of those who carry out this procedure are not entirely clear as to whether the fluid is withdrawn from the subdural or subarachnoid space and have but a faint grasp of the idea that it is a circulatory medium.

Possibly these physiological considerations are of greater moment to the neurological surgeon than to others, for much of the success of his intracranial and spinal work depends upon the ways and means he adopts to overcome the difficulties brought about by cerebro-spinal fluid stasis, whether he is dealing with cerebro-spinal anomalies, with tumors, with infections, or what not. They are, however, of unquestioned importance to the physician, and are likely to become still more so as the intra-spinal treatment of cerebro-spinal disorders comes to be perfected. For since the employment of drugs for purposes of spinal anesthesia first pointed the way, some notable steps have been taken in this direction, and prominent milestones have been set up by Flexner and by Swift and Ellis.

There are many questions to be answered. Granting that the choroid plexuses are the chief source of the cerebro-spinal fluid — and this has not been conclusively proved — is the process, as some believe, a transudation, or an actual secretion, or, as Mestrezat regards it, a mere dialyzation from the blood? What conditions activate and what conditions inhibit these choroidal glands? Have they an internal as well as an external secretion? To what primary diseases are they subject? How early in embryonal life do they secrete? Why does the fluid which they elaborate differ so greatly from that secreted by most other glands? Why are the cells so impermeable to the passage from the blood stream of drugs and of substances such as the bile pigments which in conditions of jaundice quickly stain all other body tissues and fluids?

Granting that the fluid thus secreted by the choroid plexuses leaves the ventricles and spreads over the brain and down the cord in the subarachnoid spaces, does it receive accessions from elsewhere, from the ependyma or from pituitary or pineal glands? Are there lymph channels in the brain, and if not how does the central nervous system dispose of its products of tissue waste? If there are cerebral lymphatics do they discharge into the subarachnoid spaces and is the subarachnoid fluid therefore of the same character chemically, physically, and cytologically as the ventricular fluid?

Why normally is the fluid practically limited to the subarachnoid spaces, and under what conditions does it become subdural?

Granting that fluid may escape by way of the Pacchionian granulations, is this the chief or only manner of escape? If an important avenue, why are these structures lacking in the lower animals and in the human infant? Are these granulations therefore pathological processes and if so what are their precursors? Are there other means of fluid absorption along the nerves by way of the lymphatics, and if so how important are they? How do the spaces in the pia-arachnoid develop and do the choroidal glands mature and secrete before or after their formation? Are there faults of development at these meningeal outlets for fluid which can account for congenital hydrocephalus and for malformations such as spina bifida and cephalocele? Are there analogies in the fluid circulation of the eye to which we may attribute the disturbances of circulation of the intra-ocular fluids?

For some years these and allied questions have been under consideration by my co-workers and myself, and occasional brief reports having some bearing upon the main theme have been made from the Hunterian Laboratory in Baltimore by Crowe,[1] Goetsch,[2] Sundwald,[3] and Dandy.[4]

Meanwhile other laboratory workers in many lands have seriously devoted themselves to cerebro-spinal fluid studies, and although some comprehensive monographs have recently appeared, such as those by Mestrezat in French (1912), by Plaut, Rehm and Schottmüller in German (1913), almost all writings on the subject have a distinct flavor of uncertainty regarding the fundamental anatomical and physiological aspects of the question. It has seemed to us that the factors upon which primarily there must be a clear understanding and over which there is still confusion are two, namely, the source or sources of the fluid and the manner of escape from the cranial chamber. In the leading papers of the present series, by Weed and Wegefarth, it is hoped that something will be added to our meager and inexact knowledge of these matters.

In the course of some experimental studies on cerebral compression undertaken in association with Professor Kocher in 1900, I came to believe that there must be wide channels of outlet from the meningeal spaces directly into the sinuses, and conceived the view that particularly along the irregular and many channeled longitudinal sinus there might be obliquely placed valves which allowed the entry of the fluid but prevented a back flow of blood — structures, in other words, which operated in much the same manner as the valve at the entry of the thoracic duct into the subclavian vein. In no other way could I then account for the apparent passage not only of artificially introduced fluid but even of gas and metallic mercury from the meningeal spaces into the sinuses, jugulars, and right heart. (These substances in most of the experiments were introduced, according to the method of Leonard Hill, into the subdural space through a cannula snugly screwed into a small trephine opening in the cranial vault, and it is quite probable that their rapid escape from the meninges may have occurred in some cases directly into the opened diploetic vessels rather than through normal channels of outlet for the cerebro-spinal fluid. In this same way Sauerbruch found that air embolism occurred when he attempted, in the hope of lessening bleeding, to conduct intracranial operations with the animal's head in a positive pressure chamber.)

It was thought that an investigation of the cerebro-spinal spaces in the embryo would most likely shed light on the subject, and some unpublished studies in this direction were undertaken in 1904 and 1905 by Lewis L. Reford in Mall's laboratory in Baltimore. In living pig embryos of various ages low spinal india ink injections were made, either into the wide central canal or into the arachnoid space, and the embryos were subsequently cleared. It appeared from the course taken by the injection mass that the full development of the spinal arachnoid preceded that of the intracranial spaces, the impression being gained that the separation of the premature meninx into its layers occurred later over the cerebrum than over the cord and later over the cerebral vertex than in the basilar portion of the chamber. Still, I never felt quite convinced that the failure of injection of the meninges over the surface of the hemispheres in many of Reford's specimens was not due to the floating up of the brain against its envelopes by the introduction of the injection mass from below. However this may be, it was nevertheless apparent that a venous injection of the body of the embryo was often produced, and the impression was gained that a communication existed between the basal subarachnoid spaces and the precursors of the sinusoidal veins of the cranial chamber which empty into the jugulars. If due to an artefact from a vascular rupture, at all events the communication always occurred at the same point. Reford, moreover, in agreement with Cruveilhier, Reichert and Kölliker, came to doubt the existence of the foraminal opening described by Magendie, believing that the opening was an artefact and that the fluid escaped by seepage through a persistent membrane.

One important chronological relationship which we wished to establish was that between the period of primary secretory activity of the choroid plexuses, the development of the dural sinuses and the cervical lymphatics, the breaking down of the ventricular roof with the establishment of the foramina of Magendie and Luschka, the separation of the meninx into its two layers, and the formation of the points of escape for the fluid into the sinusoidal vessels. This relationship we did not succeed in establishing to our entire satisfaction, though it is quite probable that secretion of the cerebro-spinal fluid not only antedates the formation of the lymph channels but that it plays a part in the rupture of the ventricular roof as well as in the formation of the cysternæ, the lesser arachnoid spaces, and so on. In the settlement of these points, it seems to me, lies the explanation of many of the congenital deformities associated with cerebro-spinal fluid disturbances — particularly the various forms of spina bifida, cephalocele, and "essential" hydrocephalus. Without more exact information on these matters than we now possess it is fruitless to speculate upon the causation of these lesions, and past attempts to relieve them by operative measures have for the most part been made blindfold.

Surgical removal of one of the major forms of spinal or cranial meningocele usually serves to accelerate the accompanying hydropic distension of the cerebral ventricles, and the futility of many of the measures directed toward the cure of so-called idiopathic hydrocephalus by drainage are sadly familiar to all. It is generally supposed that the failure of formation of Magendie's foramen or occlusion of the same by some prenatal or early inflammation is the usual cause of these forms of hydrocephalus, and on this basis most of the earlier surgical procedures have been undertaken, such as the making of communications between the ventricles or the subdural space and the subaponeurotic layers of the scalp, or between the dilated lateral ventricles and the subdural space, recently modified in the form of a callosal puncture. From our own experience, however, as I have elsewhere pointed out,[5] in most of these cases it is possible to empty the ventricles as freely by a lumbar as by a direct ventricular puncture, which shows that their fluid content already has access to the subarachnoid spaces and that prevention of escape lies elsewhere than at the foramen of Magendie. It was in view of this finding that my early efforts to drain the spinal subarachnoid space into the loose retroperitoneal tissues were undertaken.

In spite of the emphasis laid by Cathelin and some others upon the important part played by the lymphatics in cerebro-spinal fluid absorption, it is our impression, as will be gathered from Weed's papers, that they exercise a relatively minor part in the escape of fluid. However great may be the importance of the pericranial lymphatics as portals of infection, their part in fluid absorption apparently is not an important one. When the fluid is let out under the scalp, and probably also when it escapes into the loose retroperitoneal spaces, the early widespread edema which occurs is followed by the gradual formation, about the primary area of outflow into the tissues, of an endothelial-lined cavity from which the fluid no longer is absorbed into the adjoining lymphatics. More nearly corresponding with the actual manner of escape have been the attempts, first by McClure,[6] at my instigation, to establish a vascular anastomosis between the cerebellar cysternæ and the external jugular, by Payr between the lateral ventricle and the longitudinal sinus, and by Haynes between the median cerebellar cystern and the torcular.

Wegefarth, as will be seen, advances the proposal that direct punctures be made through the sinuses with the expectation that the opening will remain patent and that under all circumstances, except those of lowered intracranial tension, the current will be from the cerebro-spinal fluid into the sinus. If his suggestions prove to be feasible — and the procedure has been undertaken in one case — it is my impression that its success will depend upon the occlusion of the puncture openings by arachnoid tissue, with the formation at these points of functionating villi. This suggestion is based on the, to us, new interpretation of the manner of escape of the fluid by way of the arachnoidal villi, which are particularly numerous in the neighborhood of the sinuses, though they occur elsewhere as well. It has of course long been recognized that chemical substances in solution can pass freely from the cerebro-spinal space into the dural sinuses, though granular substances are checked, but so far as I am aware no histological demonstration of the points at which the absorption occurs has heretofore been satisfactorily made. Weed's studies of the arachnoidal villi have effectively exploded my preconceived ideas in regard to the escape of the fluid by valvular action and have brought us back to the view of seepage through the arachnoid projections into the dura as the chief manner of fluid outflow. With the conception of these structures gained through his studies it is readily understood how easily the outflow of fluids at these points may become occluded by products of arachnoidal inflammation. The fact that, in the few cases of essential hydrocephalus which we have had the opportunity of studying, there appears to be an absence of the arachnoidal projections or villi into the sinuses suggests that the developmental fault, at least in some of these cases, occurs at this portion of the circulatory channel rather than at the ventricular foramina. (The idea has been advanced that in some cases hydrocephalus is due to an oversecretion of the fluid, and this has led to carotid ligations (Stiles) in the hope of lessening the circulation in the plexuses. To be sure, there are certain mechanical conditions which must be explained. For example, if the obstruction of fluid outflow occurs from malformation or incompetence of the arachnoidal villi why do we not have an external rather than an internal hydrocephalus? Possibly this can be explained on the basis that the primary secretion into the ventricles fills them out and holds the hemisphere against the envelopes and prevents the external accumulation of fluid. Even the making of a large direct opening through the thin cortex between subdural space and dilated ventricle rarely transfers the internal into an external hydrocephelus; for though it may sometimes do so the thin cerebral wall usually floats back again against the pachymeninx.)

In regard to the formation of the fluid and its accessions we may start with the choroid plexuses, the anterior portion of which secretes directly into the lateral ventricles and the posterior into the subtentorial cysternæ. Though absolute proof is wanting, there can be little doubt but that the modified ependymal cells which cover these structures have an active secretory function — a view which was advanced by Faivre sixty years ago and shortly afterwards by Luschka, and which has been upheld notably by Pettit and Gerard, by Studnicka, Galeotti, Cavazzani, Capelletti, Meek, and Pallizzi: Mott has recently summarized the arguments in its favor. On two or three occasions 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. In one such case associated with an apparent occlusion of the foramen of Monro the plexus was removed, and in another the entering vessels were ligated, with immediate cessation of the secretion. These patients were under ether anesthesia; and the inhalation anesthetics, as others have pointed out and as we also have observed, are among the few substances which definitely activate choroidal secretion. Indeed this single fact that ether anesthesia stimulates the outpouring of fluid from the plexuses, thus increasing the very tension difficulties which an operation may have been planned to overcome, and at the same time increasing, through the rise of intracranial tension, the difficulty of the anesthetization itself, is a simple enough illustration of the importance of this subject to cerebral surgery.

We have already made certain attempts to determine what other substances either stimulate or inhibit the secretion, and studies of a like nature have been reported by Capelletti and by Dixon and Halliburton, with whose findings ours largely agree, although some of our preparations of pituitary extract are potent in activating the secretion, whereas the results of the latter investigators were negative in this respect.

It will be important to know against what pressure the glands are capable of secreting, for doubtless pressure influences play a considerable part, and it is presumable that when a certain degree of intracranial tension is reached secretion ceases. All are familiar with the fact that a cerebro-spinal fluid fistula, whether of surgical or accidental origin, or one arising from a pathological process as in cerebro-spinal rhinorrhea, may discharge a large quantity of fluid in the twenty-four hours, though it is not clear whether this corresponds with the amount of fluid normally secreted during the same period. It is also well known that the withdrawal of fluid from a lateral ventricle in obstructive hydrocephalus is followed by its rapid reformation — two hundred or three hundred cubic centimeters and possibly more in twenty-four hours — often under greater tension than before. Apparently the lowering of intra-ventricular tension activates, and it certainly leads to changes in, the choroidal cells, which become swollen and often cystic. Insufficient attention has been paid to the routine histological examination of the plexuses at autopsy, and doubtless such studies will yield much information. That an actual functional hypertrophy of the plexus may occur, with an amount of secretion in excess of what may be readily absorbed by the normal channels of exit, leading to the so-called condition of meningism, may possibly be an underlying factor in the so-called "wet brains" and cerebral edemas of uremia and of acute alcoholism, and in the amicrobic meningitis serosa — conditions which are capable of marked relief by a single lumbar puncture.

W. E. Dandy, working in the Hunterian laboratory in 1911, found it possible to produce an experimental internal hydrocephalus by slipping a pledget of cotton, or cotton enclosed in a small absorbable capsule, directly into the iter — a method followed by Wegefarth in some of his surgical experiments recorded in this series. Weed has enlarged upon this idea, and in his experiments has directly catheterized the iter so that the intraventricular secretion from the plexuses can be studied and the influence of drugs upon it observed without the complexities which arise when the observations are made upon the fluid in the posterior cerebellar cystern tapped through the occipito-atlantoid ligament — the usual point of drainage in such studies.

It is extraordinary what an effective barrier the uninjured plexuses are against the entry into the cerebro-spinal fluid of substances which may be present in the circulating blood, whether introduced for therapeutic purposes or products of pathological states. Thus the agglutinins of typhoid fever, the bacterial toxins such as that of tetanus, and hemolytic amboceptors, do not pass the plexus and enter the fluid. It has been found, moreover, that many poisons are far more toxic when introduced into the cerebro-spinal space than when they reach the nervous tissues by way of the blood stream. Particularly significant is the fact that drugs such as potassium iodide do not pass from the blood stream into the fluid, and to this the prevalence of cerebro-spinal para-syphilis following old methods of antiluetic treatment is doubtless attributable. Salvarsan likewise does not pass from the blood into the cerebro-spinal spaces and is very toxic when put directly into the subarachnoid fluid. Hence has arisen Swift and Ellis's procedure of treating cerebro-spinal syphilis by the lumbar subarachnoid introduction of salvarsanized serum. The importance of the cerebro-spinal fluid in the conveyance of drugs to the nervous tissues becomes more apparent with the realization of the peri-neuronal communications with the subarachnoid spaces.

As shown by Crowe in 1909, hexamethylenamin is one of the few known drugs which when taken internally readily traverses the barrier of the plexuses; though to accomplish the purpose we hoped it might have in antagonizing infections some chemical modification of the substance may be necessary, for it seems from the studies of others that it is not broken up into formaldahyde in other than acid media and that as hexamethylenamin in the cerebro-spinal space it has but a feeble, if any, bactericidal power. However, according to Cavazzani the alkalinity of the fluid is only half as great as that of the blood, and possibly it may become acidulated in the presence of some of the infective acid producing organisms, and the drug may actually break up and become therapeutically useful. The matter needs further investigation.

We have observed, as have others, that after tapping a hydrocephalic ventricle there occurs a slight increase in the normally insignificant albumin content of the fluid. This is true also of the substance which reduces Fehling's solution, first observed by Claud Bernard and thought to be glucose, and the presence of which has been variably noted by others. (Halliburton formerly regarded the substance as pyrocatechin but, according to Mott, he has come to believe, with others, that it is actually glucose.) Jacobson's studies, to be recorded in this series, will show that in many conditions the sugar percentage in the fluid is practically the same as in the blood, whether there is a coexistent hyper- or hypo- glycemia. This percentage equalization, however, seems to take place more slowly than would be the case did the exchange occur by dialization through the plexuses, and it is possible that the blood sugar reaches the fluid by filtration from the capillary bed in the nervous tissues and thus primarily reaches the combined rather than the ventricular fluid. In this connection, however, it may be said that his comparative studies of spinal and ventricular fluid show that there is a slightly higher percentage of sugar in the ventricular than in the subarachnoid fluid, whereas the reverse is true of the albumen content.

One matter which has interested us greatly has been the question of the possible passage into the cerebro-spinal fluid of the secretion from the pars posterior of the hypophysis. With Emil Goetsch, a report was made in 1910 which assembled the arguments favorable to this view, but they were subsequently questioned, on insufficient grounds we believe, by Carlson. We have since made further confirmatory studies, and of particular interest in this connection is Weed's demonstration of the fact that posterior lobe secretion, as well as ether, pilocarpin, choroid extract, and a few other substances, stimulates choroidal secretion.

The first reports in this present series of papers deal with questions of fluid outflow rather than with fluid formation. The method of injection and precipitation which Weed has employed is so far superior to other methods which have been utilized in studying drainage from serous cavities that it was certain to give results in his skilful hands, particularly in the less carefully studied and more complex mesothelial cavities of the central nervous system. He has demonstrated with apparent conclusiveness that the arachnoidal prolongations, tufts or villi, which project into the dura are the essential elements in the fluid outflow. These tufts, capped by clusters of mesothelial cells, have been described by M. B. Schmidt and others, but by none has their specific function as fluid filters been so clearly made evident. It is true that Reiner and Schnitzler in their experiments also made use of potassium ferrocyanide injections and demonstrated that the drug passed from the cerebro-spinal space into the blood stream, but, heretofore, so far as I am aware, no satisfactory histological demonstration of the channels of outflow has been offered.

Though the arachnoidal villi are clustered in special number in certain places, particularly along the sinuses, where they occur with or without association with the cortico-dural anastomotic veins, they are also found scattered elsewhere over the brain, and are doubtless capable of being newly formed where adhesions occur or where there is opportunity for the arachnoid to project into the dural crevices. It is into these villi that the minute cortical herniations take place in cases of increased intracranial tension, and those which occur in the lateral lacunæ of the sagittal sinus commonly spoken of as Pacchionian granulations, are the largest and most often commented upon. However, they occur in many other places, being especially numerous, for example, over the temporal lobes, where they project into the dural sinuses of the middle cranial fossa, and they are also frequently seen distributed along the course of the meningeal veins over the convexity. The reason why these villi and pathological herniations have received scant notice in post-mortem studies is doubtless a two-fold one, due on the one hand to the fact that the brain is rarely hardened in situ before its removal and on the other to the fact that it is rarely removed with the meninges intact.

All neurological surgeons are familiar enough with the fact that the blood which exudes from a denuded dura is watery in character, even in the absence of subdural fluid, for the arachnoid tubes connect the subarachnoid space with the vessels of the widely channeled dura, some of which have communication with the diploetic vessels of the bone. Moreover, on delicately lifting the dura from the cortex, even over the free hemisphere, transparent arachnoidal tubes, often mistaken for fine pathological adhesions, may be seen, if care is taken not to rupture them. They readily empty if put under tension, and may be seen to fill again when the tension is relaxed. Surgeons too are familiar with the fact that under circumstances of tension in which the delicate villi have become hypertrophied and show histologically the characteristic myxomatous core, it is often possible to dislodge the villous tufts from their pockets between the cross-hatched mesh of dural fibers of the parasinoidal zones, with but a minimum of bleeding or with no bleeding whatsoever if the manipulations are carefully conducted, except in those cases when they are associated with a vessel bridging from cerebral cortex to sinus or to dura.

These points of fluid filtration through arachnoid membrane prove to be very similar to the structures at the so-called filtration angle of the anterior chamber of the eye, and, using Weed's technic, Wegefarth has been able to draw a very illuminating analogy between the intra-ocular and the intra-cranial fluid conditions. He describes for the first time mesothelial villi, similar in structure to those of the arachnoid, which actually project into the canal of Schlemm, and this vessel therefore in the case of the eye plays the same part as do the dural sinuses in being a circulatory pathway for both blood and fluid.

As indicated in a foregoing paragraph there are reasons for believing that there may be recognizable differences in the two fluids — ventricular and subarachnoid — under normal as well as under experimental or therapeutic conditions, owing to the possible accretion to the ventricular fluid of waste substances during its passage through the subarachnoid perivascular and perineuronal spaces. It is a difficult problem to attack, particularly in animals, owing to the small amount of fluid normally in the ventricles, but it is not an insurmountable one. This idea of a double source of fluid has been hinted at also by Mott in his admirable Oliver-Sharpy lectures.[7] In his words, " a canalicular system surrounding the cells and vessels of the brain exists which is in direct communication with the subarachnoid spaces." Adopting Mott's method of showing these spaces in an anemic brain, Weed has succeeded in precipitating Prussian blue in these perivascular and perineuronal channels after an arachnoid injection of the ferrocyanide solution. We gather, however, that it is Mott's idea that cerebro-spinal fluid is absorbed into the circulation by the capillaries which this system surrounds, whereas it is our conception that the flow is in the opposite direction, namely, toward the arachnoid spaces. We, however, agree fully with him in the view that fluid secreted by the plexuses is not the same in composition as that contained in the cerebro-spinal spaces, in view of the probable increment it must receive from these perivascular " lymphatics."

There are a number of arguments in favor of the flow toward the subarachnoid spaces rather than from the surface toward the subcortex. As Weed points out, his potassium ferrocyanide solutions do not pass into the perivascular and perineuronal tracts unless the brain is rendered anemic, in which case there must naturally be a suction from the subarachnoid spaces to fill the spaces and make up for the loss of fluid in the brain due to the anemia. Then again we are accustomed to see, on histological study of brains which have been under great tension, as from tumors, and which have therefore become flattened against the dura — the so-called dry brain of the surgeon's parlance — that the perivascular and perineural spaces are especially dilated, as though fluid which accumulated in the spaces escaped with difficulty. And, moreover, after decompressive operations under circumstances of this kind, fluid from this intra-cerebral source, which is rich in albumen and presumably in waste products, accumulates in areas on the arachnoid surface of the cortex, where it is imprisoned, owing to the cortical herniation. Under these same circumstances, furthermore, it is very common to see dilated spaces in the substance of the brain tissue itself, due apparently to extreme dilatation of these passages, which under normal conditions are of microscopical dimensions.

It is quite possible that differences in the two fluids may be shown in various ways. Thus, an example suggesting a difference in their bactericidal properties was given by the writer with Sladen [8] in a case of cerebro-spinal fever with subsequent hydrocephalus, occurring in a child in whom after four months the diplococcus intracellularis was found to be still living in the fluid of the dilated ventricles, whereas the organisms had been killed off from the subarachnoid fluid. Another recent experience is equally suggestive of a chemical disparity in the fluids. A patient of middle age, with focal epilepsy and a negative Wassermann reaction from the blood and lumbar cerebro-spinal fluid, was suspected of having a brain tumor. The operation disclosed a certain amount of convolutional atrophy, with thickening of the lepto-meninges and an excess of subarachnoid fluid, enough of which for a Wassermann reaction was secured from the subarachnoid spaces after pricking the membrane. The reaction from this fluid was positive, whereas fluid subsequently taken from the lumbar subarachnoid was negative.

We unfortunately know little of the fluid currents in the spinal region, where there are apparently no villi to constitute points of outflow and where the lymphatic perineural drainage is certainly no more important than from the cranial chamber. Does the fluid from the ventricles tend first to gravitate into the spinal subarachnoid and then to pass back to the intracranial space? May credence be placed upon a possible current in the central canal of the cord, as upheld by Kramer? Is there any discontinuity between subdural or subarachnoid spaces in the two regions? Is fluid from some source actually elaborated in the spinal region?

Onlookers at neurological operations are familiar with the appearance of "sweating" of the exposed arachnoid except under those conditions in which there is a tense dry brain with flattened convolutions. This, however, does not imply that with normal hydrostatic conditions and a closed skull and dura the same process will occur. It shows, however, how permeable the arachnoid membrane actually is to the passage of fluid when, as in the case of the specialized points of the membrane constituting the villi, it is not in contact with an unresisting surface. As a matter of fact, as Weed emphasizes, the subarachnoid and subdural spaces are practically discontinuous so far as the cerebro-spinal current is concerned, and any excess of fluid in the subdural space is probably always due to pathological conditions.

All are familiar too with the appearance of the subarachnoid spaces when they are crowded with the products of suppuration in cases of basilar meningitis, no subdural involvement whatsoever being apparent; and still more striking are the extraordinary conditions of gliomatous invasion of the subarachnoid spaces, the process often extending the full length of the spinal cord in addition to covering much of the cerebral base, without, however, any extension through the arachnoid membrane.

As will be seen, chief emphasis in our present series of papers is laid upon the arachnoid and its villi and the escape of fluid through these channels. These structures, moreover, as will be pointed out, are not only of physiological importance but also of pathological significance, for, as has been mentioned, we believe they are the precursors of the Pacchionian granulations, and also that it is from them that the so-called dural endotheliomata arise — lesions therefore which have their origin in arachnoid rather than dural mesothelium. We find that the same mesothelial whorls and psammoma bodies which characterize these growths are demonstrable in the normal membranes of animals as well as in those of man.

Certainly nothing could have served to retard our understanding of the meningeal physiology more effectively than the method long cherished in the post-mortem room of removing the unhardened brain from which the dura has been stripped away and each hemisphere of which is promptly laid open by successive sweeps of a long knife, after which the sliced organ is gathered up and put away in a fixative for future study. Fixation in situ with intracarotid injections and removal of the organ intact within its meninges is absolutely essential to any study which pretends to determine the relations of the structures in question.

The following significant foot-note appears in connection with Magendie's introduction, in his later monograph, to the chapter on the cerebro-spinal fluid in disease: "Cet enfant a de l'eau dans le tête, dit le vulgaire: cet enfant est hydrocéphale, dit gravement le médecin, répétant littéralement par un mot grec ce que dit l'ignorant dans sa propre langue. Mais quelle est cette eau? d'où vient-elle? Voilà ce dont les médecins auraient dû s' occuper." As a matter of fact we have not occupied ourselves with the subject, and as regards the cerebro-spinal fluid we stand in much the same position as did the pre-Harveian phlebotomist in regard to the circulation of the blood.

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