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Source of cerebrospinal fluid : a review of the literature

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THE SOURCE OF CEREBROSPINAL FLUID
A REVIEW OF THE LITERATURE

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Since the first description of the spaces of the brain by Galen in the second century (35), there has been almost total disagreement concerning the content, source, mechanism, circulation, and absorption of the fluid in these spaces. Because of the lack of freedom for scientific investigation, it was not until the year 1591 that fluid was described within the brain cavities. Even then, the work was rebuked because of the long standing theory of Galen and others that the spaces were filled with an air-like substance (35). Although some progress was made in the next three centuries, it was the works of Key and Retzius that paved the way for the advancement of the modern concept of cerebral spinal fluid (CSF) and i s containers. These men showed that at the arachnoid villi, the CSF was separated from the venous system only by a thin epithelial layer of cells. They also made the statement that "the most important organ in the ventricles is clearly the choroid plexus" (35). These and other findings enabled such men as Dandy, Weed, Cushing, Quinche, and many others to formulate the concept which has been generally accepted for forty years and is now under challange from recent investigations using the radioactive substances.

It is not the purpose of this paper to say who is

right and who is wrong, but to review the pertinent work concerning the source of CSF, which has been done since the birth of the "modern concept" of CSF and to express the opinion of those men who are faced with the actual problems of research.

Since the turn of the century, it has been the opinion and teachings of the majority of medical lead-ers that the CSF is formed primarily in the choroid plexuses of the lateral, third, and fourth ventricles. It circulates through the lateral ventricles to the third ventricle by way of the foramina of Monro. Then it flows through the aqueduct of Sylvius to the fourth ventricle, and finally, into the cerebral and spinal subarachnoid spaces by way of the foramina of Luschka and Magendie. It then circulates in the subarachnoid space over the entire central nervous system (CNS) and finally absorbed into the venous system primarily through the arachnoid villi of the cranial subarachnoid space. At the present time, there is no conclusive evidence favoring the above theory or any of the other theories concerning formation, circulation, or absorption of CSF. By separating the experiments which are foremost in acceptance, we can review the arguments concerning these subjects.

THE SITE OF FORMATION OF CSF

Even as late as the year 1954 the literature is filled with such statements as follows: "Although no proof has so far been supplied, it may be accepted in view of the present state of opinion, that normally the choroid plexus---should be considered as the most important, if not the only, fluid-producing organ"(31). The experiments which led to this opinion started about the first of the century. In 1919, W.E. Dandy (12) pre-sented a paper concerning the experimental production of hydrocephalus, which he thought offered conclusive proof of the theory that CSF is formed by the choroid plexus. In this paper, Dandy says that although Magen-die described anatomical obstruction at the base of the brain in several cases of hydrocephalus, he could not explain why there was no dilatation distal to the ob-struction since he (Magendie) regarded the pia as the source of all CSF. From experiments on dogs, Dandy came to the following conclusions: 1) by blocking the aqueduct of Sylvius be deduced that CSF is formed in the ventricles at least faster than it is absorbed, the aqueduct of Sylvius is a necessary outlet of the first three ventricles, and there are no collateral channels which assume the function of the iter when it is occlud-

ed, 2)unilateral hydrocephalus can be produced by occluding one foramen of Monro, 3) occlusion of the foramen of Monro after choroid plexectomy showed no hydrocephalus. The ventricle remained dry, thus proving that the choroid plexus and not the ependymal linings is the source of CSF, and 4) obstruction of the aqueduct of Sylvius after bilateral plexectomy gave slowly developing hydrocephalus showing that the choroid plexuses of the third and fourth ventricles produce more CSF than all the ventricles can absorb.

The results and conclusions derived from these experiments have been generally accepted. Although nobody has successfully repeated these experiments it's advocators have been numerous (28). Experiments by such men as Putnam (34) showed that by cauterizing the choroid plexus, some cases of hydrocephalus were arrested and fontanels were depressed. Braunstein and Martin (10) and Kahn (29) stated that about one-half of the cases of congenital papilloma of the choroid plexus are associated with hydrocephalus. They give evidence to show that in their cases, there were no ventricular obstructions or significant meningitis noted. These findings lend strength to Dandy's work. Bakay (2) and others (27) in their experiments on dogs could not explain why all of

the animals in which they attempted a block between ventricles and subarachnoid space, did not develop hydrocephalus. Bakay also says that removal of the choroid plexus of the lateral ventricles does not diminish the hydrocephalus but he explains this on the basis of the remaining choroid plexus in the third and fourth ventricles. He also found CSF distal to the obstructions he developed or after choroid plexectomy and hints that there may be another method of CSF formation.

Grattarola (20), experimenting on cats, eliminated the supply of blood to one choroid plexus and then blocked the ventricles. In some cases symmetrical hydrocephalus was formed indicating a possible source other than choroid plexus, at least in pathological cases. Hyndman (26) says that as a result of tearing the lamina of the choroid plexus, decreasing hydrocephalus is obtained. This is because a communication is formed from the lateral ventricle through a space (cisterna venae parvae) in the tela choroidea to the cisterna venae magna and cisterna ambiens, and thus the entire subarachnoid space.

Studies concerning the formation of spinal fluid using dyes are not too revealing except for those in which fluorescein was used (35). Following injection

intravenously, in animals, dye was actually observed emitting from the choroid plexus and also from the pia of the spinal subarachnoid space (30). In this experiment, the results indicate that a great part of the CSF is formed by the choroid plexus while a smaller part is formed elsewhere.

One of the methods of study of CSF formation has been by the histopathological technique. Weed (44) presented work done in this manner and states that there is a possible mechanism for the CSF elaboration in the choroid plexus. Later (46) he states that it cannot be proved histologically that the choroid plexus elaborates CSF but by pharmacological means it can be shown that the plexus changes in character under stimulation of certain drugs. Other investigators (4) have supported this contention. Hassin (23) utilized the histological technique to come to the following conclusions: 1) CSF represents the tissue fluid of the brain, 2) it includes the contents of the Virchow-Robin spaces which originate in the tissue fluids and which are discharged into the cerebral ventricles and the subarachnoid space, and 3) the function of the choroid plexus is not to secrete fluid but to excrete or eliminate from it noxious substances and thus make it possible for the perineural

spaces to absorb the CSF. Since earlier authors referred to the perineural spaces as a source of CSF, this last statement was of particular interest and importance, and numerous experiments were done to show relationship between the spinal subarachnoid and perineural spaces.

Attempts have been made to show a relationship between blood and tissues and CSF utilizing the technique of ionic identification. The first experiments with this method were done using ions foreign to normal CSF. Colloidal palladium has been used (25) but the results are not conclusive. Ion distribution has been demonstrated using bromide, iodide, and thiocyanate. In the first experiments (21),(41),(42) with such materials it was concluded that the extracellular fluid of the brain and cord has a quantitative composition similar to CSF but differs from the extracellular fluid elsewhere in respect to the passage of the ions into it from the blood stream. These authors found that although there is no barrier to the passage of ions out of the CSF, there seems to be selective permeability as well as a certain threshold to the same ions passing into the CSF. It was also noted that passage of certain ions from serum to CSF is slower than their passage into other tissues and that the concentration of ions in

CSF is always lower than it is in the blood serum.

Wallace and Brodie (42) attempted to show that Br_2 and I_2 normally pass from the serum to the extracellular spaces of the brain and cord and from there to the CSF. To do this they placed needles in various parts of the CNS and CSF chambers and withdrew small amounts of fluid for assay at scheduled intervals following intravenous injection. Their results showed: 1) immediately each ion distributed evenly throughout the CNS extravascular system, 2) later the ions were found to be more concentrated in the tissues immediately surrounding the cisterna magna, 3) bromide ions enter the CSF even below a ligature at the cisterna magna, and 4) iodide ions appear promptly in the brain extravascular fluid and lateral ventricles in equal concentrations while there was some lag in the concentrations of the ions in the supracortical subarachnoid fluid and in cisterna magna fluid. From these results, they concluded that the anions tested entered the CSF as readily from the brain capillaries as from the ventricular choroidea. Thus the ions passed from plasma to pericapillary spaces to perineural spaces and to CSF. These authors considered the ventricular choroidea to play only a minor role in the formation of CSF.

Before considering more recent experiments concerning CSF formation, it will be of value to examine some of the other aspects of the problem under consideration, namely the mechanism of formation, the circulation, and the absorption of CSF.

THE MECHANISM OF FORMATION OF CSF

Every worker who has experimented with the formation of CSF has also tangled with the problem of mechanism. Most of these men favor one or the other theories but none have presented conclusive proof that CSF formation takes place by one definite mechanism. In 1927, Fremont-Smith (19) presented a paper favoring the dialysis theory. He states that this theory was championed by Mestrazat in 1912 but was not accepted by all. Boyd claimed that dialysis was the mechanism to be considered under normal conditions while secretion was the result of stimulation of the choroid plexus. He favored dialysis because of the fluid formation pressure ratio, but also it had been shown that when a hypertonic salt solution is used intravenously, that the direction of flow through the choroid plexus could be changed. Although several men backed this line of reasoning (33), most of them sided with the secretion theory (31). Flexner (18), considering equilibrium

activity and concentration of the constituents of the CSF, attempted to analyze the problem by separate analysis of the blood and CSF. It has also been demonstrated that at different pressures, CSF production varies (18) and certain drugs also effect the production rate (4). The latter alone has been evidence enough for some (46). Flexner goes on to say that assuming CSF and plasma are not in complete equilibrium, then the formation of CSF involves an expenditure of work. This suggests that CSF is not a dialysate in equilibrium with the blood nor an ultrafiltrate because the capillaries in the choroid plexus have too small of a pressure to account for the energy change which takes place in the formation. This leaves only a secretion to be considered.

Working with radioactive phosphorus and sodium Boldrey (9) and others (14) have reported that in cases with complete block between ventricles and subarachnoid space they could show formation and absorption occurring in both spaces, absorption being greater in the lumbar space than in the ventricles. Because both absorption and formation occurred, it would seem to minimize the objection that this is a diffusion phenomena. However, there was a barrier against phosphorus while sodium passed freely, suggesting secretory activity.

In his book, in 1954, Lups (31) states that the question is undecided and lists the arguments for the two prominent theories. In favor of secretion are: 1) it is possible to increase the production of fluid by means of administering certain pharmaceutical products and to decrease this production by others, 2) substances are present in the fluid which cannot be found in the blood, 3) fluid production is not influenced, or only slightly influenced by the arterial pressure, and 4) the histological investigations of the cells of the choroid plexus also point to active secretive processes. In favor of the dialysis theory are: 1) the fluid is isotonic with the blood plasma and attempts to maintain this equilibrium, and 2) by making the blood plasma strongly hypertonic it is possible to cause the fluid in the ventricles to flow back into the choroid plexus and to the blood stream. The CSF is apparently quantitatively different than that of the plasma.

THE CIRCULATION OF THE CSF

Before beginning the discussion of circulation, it will be of assistance in evaluation, if the work of Schurr, McLaurin, and Ingraham in 1953 (37), be presented at this time. In their experimental study on the circulation of CSF, they made a comparison between

species using dogs, cats, and the rhesus monkey. Briefly, they showed three main pathways of absorption (and thus circulation) in dog which are: 1) arachnoid villi leading to the blood stream, 2) and 3) perineural channels of the optic and olfactory nerves leading to the lymphatics. These pathways were given equal importance. In the cat, the dye (pantopaque) used did not enter the optic or olfactory sheaths at all but in the monkey, it enters the optic sheaths. The amounts of fluid between dog and monkey which circulate in these cranial nerves and are absorbed there lead these men to state that a comparison between dog and man is not a reliable method.

Since the experiments of Key and Retzius in the last century, the general consensus of opinion is that after leaving the ventricles, the fluid circulates over the CNS and back into the arachnoid villi. In 1922, Weed (44), summarized this work by saying that after elaboration in the ventricles and passage through the foramina of Luschka and Magendie, the CSF then circulates everywhere about the CNS in the central canal of the spinal cord and in the tortuous mashes of subarachnoid space. These channels are all clothed with a special cell, which is fluid-retaining so to maintain a true circulation.

It must also be recognized that hydrocephalus can be produced by blocking the passageways from the ventricles as shown in previous experiments (35) using dyes and contrast media and also in clinical experience with communicating hydrocephalus. Most of these men agree that the rate of circulation is not rapid but very sluggish, varying with arteriole and venous pressure with the force for movement being changes of intracranial pressure, both in body movement and heart beat.

Hassin (23) had some radical theories on CSF in general and made the statements that CSF is actually lymph carrying away the waste products of the CNS and there is no central force to set the CSF into circulation under normal conditions. He explains the flow of injected materials by saying that this is a passive process set in motion by a lumbar or other puncture. Hassin's findings were based on histopathological technique and had few backers until the discoveries with radioactive substances were presented. Even then Eichler and Linder (15) attempted to show some circulation using radioactive sodium. They demonstrated that after intrathecal injection, the concentration drops slowly at the injection site and increases rapidly 22 cm cranially to it, followed by a rapid drop. They thus con-

cluded that besides a cranial to cervical current, there is a lumbar to cervical current. In the same year, Becker (5), using India ink could demonstrate only a caudal direction of flow. Further research is, of course, needed to prove or disprove the currents suggested or even their very existance.

The difference in the composition of the fluids in the ventricles, cisterna, and lumbar spaces strongly suggests circulation of the fluid in a cranial to caudal direction (24),(40).

One of the interesting aspects of formation and circulation is the determination of protein in the different parts of the ventricles and subarachnoid space. Wagner (40) showed the relationship between protein in obstructed and unobstructed cases and stated that with a block, the lumbar proteins were increased in most cases. Schaltenbrand (35) in a review of the literature stated that the CSF changed considerably in constitution during its migration from ventricles to subarachnoid space in the lumbar area. Blockage does not prevent fluid formation below the block, but the fluid is of different composition than that of normal CSF. An electrophoresis of CSF shows the same proteins as blood but in different proportions with decreased globulins

and increased small albumins. This small albumin molecule is apparently formed in the ventricles for it's concentration decreases as the CSF sampling approaches the lumbar area. It is also absent below a complete block. He theorizes that this may be a function of the choroid plexus. This difference in protein composition may also figure into the mechanism of circulation with relation to some osmotic phenomena.

THE ABSORPTION OF CSF

Weed (43), in 1914, reviewed the works of Key and Retzius and stated that because of their work, it was generally believed that the CSF escapes along lymphatic pathways. He states that the past methods used are open to adverse criticism and no exact pathway has been agreed upon. Weed's experiments in that year led him to believe that CSF was returned to the general circulation by a filtration process through arachnoid villi into the great sinuses. He also showed there was insignificant amounts absorbed into the lymphatic system. He saw no evidence of CSF escape into the cerebral veins or capillaries but did note that the absorption is much more rapid and much more in amount in the cranial subarachnoid space than in the spinal portion.

Many men (3) could not accept this theory and advocated that the CSF was absorbed through the linings of the ventricles and subarachnoid spaces. Among these men was Dandy who, in his classical work on the choroid plexus and experimental hydrocephalus in 1919 (12) showed that in a case of communicating hydrocephalus, dye was absorbed from the subarachnoid space at about 1/5 the normal rate of the entire space. This is due to a decrease in absorptive area to 1/5 normal because of a block of the cranial subarachnoid spaces as indicated by dye injection into the lumbar space. Weed (44) still maintained his former theories as did a number of investigators (33),(17), (36), but states that there is also absorption by the perivascular channels and by the ependymal lining of the cerebral ventricles into the capillary bed of the nervous system, but only after the use of intravenous hypertonic solutions (45). In 1929, Dandy (13), tried to disprove Weed's theory by separating the cerebral hemispheres from all attachments of longitudinal, transverse, or circular sinuses. This separates the subarachnoid space from any venous outflow. All of his experiments showed no collection of fluid. Even with the injection of certain dyes, there was no absorption by the granulations. He also notes

that if a dye is injected into the spinal canal, 20-25% will be absorbed before it reaches the granulations. Thus, Dandy says, it must pass directly into the blood stream. Weed and his followers answered these statements by saying that Dandy overlooked the villi in the spinal subarachnoid space which took over the load.

Katzenelbagen (30) suggested that the choroid plexus might be considered an organ of reabsorption, as well as production, but added that the experiments of Dandy were seemingly conclusive and that there was very little absorption in the ventricles.

Somberg (38), in 1947, used methylene blue, intrathecally, in 12 humans just before they died and serial micro-sections failed to show any communication beyond the spinal ganglion, at which point the meninges fused. Sections also were made which showed no communication between the subarachnoid and subdural spaces. Hassin (21) rebuked this work by saying that the experiment was not good technique because of poor dye distribution and the failure to obtain certain necessary micro-sections. Also, in the presence of such a barrier as Somberg describes, some of the severe types of spinal defects are seen. Hassin belittles the excuse that the sections were too minute for the equipment used by

Somberg, and says that the pathways do exist but must be demonstrated microscopically.

In 1948, Hassin (23) stated that absorption was not through the villi or pacchionian bodies but through the perineural spaces of the cranial nerves and spinal roots. Most of the investigators had given this route some minor significance but not the entire role.

In 1950 and 1951, Brierley (11) and others (6) worked with histological sections after injection of India ink in saline into the cisterna magna. He showed that a cul-de-sac exists but he could not support Hassin on the subarachnoid continuity with tissue or perineural space. He does however show continuity between the subdural and sub-perineural spaces, with free passage of the matter from subarachnoid to subdural and then to peripheral nerves. He concludes that some CSF must escape by this latter route but the amount is small. He does say that some of the dye was seen in the perivascular spaces of the CNS showing some connection here.

Howarth and Cooper (24) experimented with cats using a variety of radioactive ions and concluded that the substances were passed into the general circulation by direct venous drainage. This was probably the most important work at this time.

RECENT STUDIES ON CSF

In the past ten years, the use of radioactive substances and heavy water has become a milestone in the effort to provide a correct answer to the problem of CSF formation and absorption. Whether this will prove to be the last word can only be told by the test of time. The following studies appear to be fairly conclusive in nature and seemingly answer many of the riddles of the problems related to CSF.

The first extensive studies came in 1951 from such men as Maass, Adams, Boldrey, Low-Beer, and Stern (1),(9),(32), who carried on studies with radioactive phosphorus and sodium. In one case report, in which the patient had a complete block between ventricles and subarachnoid space, the conclusion, after studying this patient was that fluid was formed in both spaces. Absorption was also active in both spaces but more in the lumbar areas than in the ventricle. The exact site however was not determined. In another series of cases (32) evidence was presented to show that the absorptive bed for CSF is not the arachnoid villi of the pacchionian granulations, but lies distal to this point and is presumably the capillaries and possibly the small veins of the pia arachnoid.

The most conclusive experiments with radioactive phosphorus (P^{32}) injected intraventricularly or intracisternally showed the following results. From samples of blood from the superior sagittal sinus, the uptake of P^{32} after intraventricular or intracisternal injection was great in the first five minutes, dropped rapidly to 15 minutes and then tapers off. Samples of arterial blood (carotid a.) demonstrated slower uptake and less concentration after intraventricular or intracisternal injection. The A-V equilibrium was reached in about 70-80 minutes. This level in arterial blood suggested that the uptake reflects the absorption from the entire brain rather than the absorptive bed drained only by the superior sagital sinus (surface of the hemispheres). The time element suggests that absorption of CSF takes place through the pia arachnoid membrane rather than villi. There also were samples of cortex of brain tested. In this study, absorption of intraventricular P^{32} was markedly slowed but could be increased by the use of hyaluronidase.

Bering (7),(8) has added much to our knowledge of water exchange in the CNS and CSF. He injected, intravenously, D_2O prepared as 0.8% NaCl and analyzed samples of arterial blood, superior longitudinal sinus

blood, Ventricular CSF, cisterna magna CSF, subarachnoid CSF, and CNS tissue. In the normal state he found that D_2O appeared simultaneously in the three CSF spaces but concentrated more rapidly in the cisterna magna. The time interval for CSF to reach equilibrium with blood varied, increasing with the age of the experimental animal. Half-times (time required for solution tested to reach 50% of tracer containing solution) were: Ventricles, 2-37 minutes; cisterna magna, 1.5-6 minutes; lumbar, 7-38 minutes. This showed that the choroid plexus definitely was not the only source of the water component of CSF. Even after choroid plexectomy, no change in water exchange was detected, suggesting that the role played by the choroid plexus in water exchange was small.

Cases of isolated spinal subarachnoid space were also tested and the half-times of lumbar exchange were within normal variation. This exchange was more rapid than could be explained by circulation alone suggesting exchange at the surface of the CSF.

In attempting to show something of blood, brain, water exchange, no significant arterial-sagittal sinus D_2O difference could be detected indicating either very slow or very fast water transfer into the brain. Study

on CNS tissue revealed the brain substance to be in equilibrium with blood in one minute and thus exchange is very rapid. Their conclusions are that the water of the CSF is continually exchanging at all surfaces of the brain and spinal cord by free diffusion. The author makes this comment, "It must be kept in mind that water exchange and CSF production are independent phenomena" and the explanation of hydrocephalus and the necessity of CSF circulation require more research into the other components of CSF. In a later paper (8) on hydrocephalus, Bering showed that two hours were required for the tracer to equalize in both ventricles suggesting lack of CSF movement and poor mixing characteristics of the ventricular system. In another two hours, only 82% of the D_2O had been absorbed.

Sweet and Locksley (39) present evidence that the formation and absorption of CSF takes place independently of flow from one area to another. They state that the elements tested, K^{42} and Cl^{38} enter and leave the ventricles and subarachnoid space by direct molecular capillary exchange, and may be considered to be in a state of dynamic equilibrium with the plasma. In their work, they used essentially normal patients with no flow from the lateral and third ventricles except

through plastic tubes. There results were as follows: K^{42}-there is a more rapid rise in isotonic concentration in the lumbar CSF than in the ventricles following intravenous injection. This has also been shown by others (15); Cl^{38}-appeared at the same rate in all three sites after intravenous injection. Electrolytes apparently moved in and out of the CSF independently of each other and at their own characteristic rates. He concludes that water, from previous experiments, and electrolytes of the CSF are in dynamic equilibrium with plasma and that CSF is renewed by local exchange in every region. These authors also used radioiodinated human serum albumin to show that it's reabsorption from the ventricles was slow (half-time 31 hours) and also from the subarachnoid space (two components; half-time 30 hours and 2.6 hours). They reasoned that the site and rate of protein reabsorption is an important determinant of the direction and rate of flow of CSF.

Fishman (16) injected activated protein intravenously and withdrew CSF and plasma at intervals following. Their results showed that no radioactive protein was detected in the cisternal fluid in ten minutes but in the second sample (40 minutes) there was a significant amount. Equilibrium time between CSF and plasma was

17-25 hours. "The fact that the maximal specific activity in cisternal fluid occurs at the time that the CSF specific activity equaled that of plasma, indicates that the plasma is the immediate precursor of the CSF albumin". They also noted that the protein gradient increased in the CSF tract from ventricle to lumbar space. From these experiments it was concluded that the delayed appearance time, equilibrium time, and turnover rate of iodoalbumin in cisternal fluid are functions of the blood-CSF barrier.

SUMMARY AND CONCLUSIONS

The pertinent past work concerning formation, absorption, mechanism, and circulation is reviewed.

The recent studies of formation, as well as absorption, utilizing radioactive ions, deuterium oxide, and protein, are presented.

The recent advancements in the use of radioactive elements have enabled us to present new evidence concerning the formation and absorption of CSF. This new evidence, while not entirely conclusive, advances the idea that CSF is produced throughout the ventricles and subarachnoid spaces. The source of this fluid is primarily the capillaries and small vessels of the linings of the ventricles and subarachnoid spaces and not the

choroid plexuses as previously theorized.

The mechanism for this formation seems to be a combination of two or more theories. Thus, ions and water are produced by a method of selective dialysis while protein seems to be elaborated by both dialysis and secretion. The various experiments seem to indicate that the choroid plexus elaborates a small albumin molecule by secretion plus some small amounts of water and other elements. This is apparently the main function of the choroid plexuses.

The circulation may also be concerned with the production of this small albumin molecule by the choroid plexus. Since it is concentrated in the ventricles, circulation, if any, may be a result of some process of osmosis.

Although we are not immediately concerned with the process of absorption, it appears to be similar to formation and not by way of the arachnoid villi.

It is obvious that more research is needed before any definite conclusions are reached.

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