THE INFLUENCE OF PLASMA PROTEIN ON THE CHLORIDE CONTENT OF THE CEREBROSPINAL FLUID

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During the past two decades much attention has been given to the mode of formation of the cerebrospinal fluid. Until recently it was generally considered that the fluid was actually secreted by cells of the choroid plexus. This theory was first suggested 70 years ago by Schmidt (11), Faivre (3), and Luschka, and it was the working basis of almost all of the numerous investigations of this subject until 1912. In that year Mestrezat (10) brought forward the theory that the cerebrospinal fluid is a dialysate in equilibrium with the blood plasma, the choroid plexus acting merely as a simple dialyzing membrane. Since 1912 many investigations have been undertaken to determine the actual mechanism, and the results of most of this work have been reviewed by Fremont-Smith (4) who, from his survey and from the results of his own researches, has been led to think that "there is no good evidence for secretion."

There are other authors, however, who are not in accord with the view of Fremont-Smith, as there are some facts that have not been easily explained by Mestrezat's theory of dialysis. The center of difficulty has chiefly been the marked disparity between the chloride content of the blood and spinal fluid. A very similar disparity has been found in several other fluids of the body, and therefore the difference seems to be a real one, of fundamental importance.

Many of the conflicting results which have been obtained for the blood and other body fluids may be explained by the inherent difficulties of tests, and by the non-specificity of certain analytical and colorimetric methods when applied to various constituents of the above fluids. However, this explanation cannot be used in the case of chlorides which can be estimated with accuracy and certainty. Levinson (8) makes the comment that "there has been greater uniformity in the results of various workers upon the chloride content of the cerebrospinal fluid than upon its other chemical constituents."

Loeb, Atchley, and Palmer (9), in a work of classical importance, showed that the relationships between blood serum and edema fluid seem to result from a simple membrane equilibrium influenced in part by the proteins present. They showed that transudates, occurring with cirrhosis, nephritis, or cardiorenal disease, or exudates of tuberculous pleurisy, contain more chloride than the serum, while the sodium, glucose, non-protein nitrogen, and some other constituents exist in the same concentrations.

Duke-Elder (2), in a detailed piece of work on the chemical constituents of another fluid of the body, the aqueous humour of the eye, reached the conclusion that the ocular fluid is a dialysate from the blood. He, too, found a similar disparity in the chloride content of these two body fluids.

The disparity of chloride content of blood plasma with reference to the spinal fluid has been noted by many observers, and it has been one of the chief difficulties in the acceptance of Mestrezat's theory. Levinson, in reviewing this subject, states that, "the chlorides are the substances normally present in greater quantity in the cerebrospinal fluid than in the blood plasma." He goes on to say that, "the reason for this is unknown. It has been suggested by Mestrezat and also by Depisch and Richter-Quittner that the higher chloride content of the cerebrospinal fluid is associated with its lower protein and colloid content." Loeb and his coworkers leaned to the same explanation, because they found that in general the difference in the chloride content of the blood and edema fluid diminishes as the protein content of the edema fluid rises. After diluting the plasma protein of dogs by the intravenous injection of fluids, Kubie and Schults (7) found evidence which led to the conclusion that less chloride passed into the cerebrospinal fluid when the plasma protein was lowered, the plasma chlorides remaining constant. During routine clinical analyses of blood and spinal fluids, Fremont-Smith found a relationship between the concentration of the plasma protein and the distribution of chlorides. He also found the disparity of chloride of the spinal fluid and of the plasma to be reduced in a few pathological conditions which were accompanied by elevation of protein content of the spinal fluid.

It was thought that considerable light would be thrown on this problem if several simultaneous chloride determinations of the blood and spinal fluid were done on a subject whose plasma protein concentration was varied considerably. This variation in protein concentration of the blood may easily be brought about by plasmapheresis

(Abel, Rowntree, Turner (1)), a method used often in experimental work with animals (Kerr, Hurwitz, and Whipple (6)), and sometimes used as a therapeutic procedure for human beings (Irving (5)).

EXPERIMENTAL

Four large dogs each weighing about 20 kilos were selected as suitable subjects. Preliminary samples of blood and cerebrospinal fluid were obtained. Several times daily during the next 4 or 5 days blood was withdrawn from the heart or a convenient artery, and was delivered into citrate solution, which mixture was centrifuged, and the plasma was discarded. The cells were washed with saline, centrifuged, and were reinjected into one of the veins of the animal. When the plasma protein had become markedly reduced in this manner the animal's protein equilibrium was slowly allowed to come back to normal. The animals were maintained on a low protein diet while analyses were being carried out.

Cerebrospinal fluid was obtained from the cisterna magna by cistern puncture with a lumbar puncture needle of fine bore. No anesthetic of any kind was needed for any of the procedures, as the animals were trained to lie quietly. The dogs appeared absolutely normal and were in excellent clinical condition throughout the period of observation.

Methods

For analytical purposes 15 cc. of venous blood were withdrawn and delivered into a centrifuge tube under paraffin oil, and clotting was prevented by admixture with 3 mg. of heparin. The blood was immediately centrifuged, and the analyses were started within 15 minutes after withdrawal of the blood from the animal. About 4 cc. of cisternal cerebrospinal fluid were collected in a centrifuge tube, and this was routinely centrifuged, although no evidence of bloody tap was ever noted in the specimens used for this report. The analyses of cerebrospinal fluids were also carried out immediately after obtaining the specimens.

Chlorides were determined by the method of Wilson and Ball (12). Particular care was taken to obtain closely comparable results. Sodium was estimated by a method, as yet unpublished, devised by Dr. Allan Butler (private communication). This method proved extremely satisfactory, yielding very consistent results. Protein was estimated from nitrogen determinations of the plasma. Water content was found by determining the loss of weight after 24 hours in an oven at 105°C.

Great care was taken to insure accuracy of all the procedures. The same pipette was used throughout for plasma and for cerebrospinal fluid. All analyses were done in duplicate and some of the chloride figures were checked by an unpublished method of Fiske (private communication). Duplicates rarely differed by more than 2 mg. per cent. The solid content of the cerebrospinal fluid was found to be very constant between 1.0 and 1.1 per cent, and since there was no particular

need for accuracy of this figure, 1.1 per cent was accepted for all the calculations, thus sparing the quantity of cerebrospinal fluid needed for the analyses.

RESULTS

The results of two of the four experiments are tabulated, those of the other two experiments being quite similar.

TABLE I

Day	Residue		Water		Plasma protein	Sodium*		Disparity	Chloride*		Disparity
	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid		Plasma	Cerebrospinal fluid		Plasma	Cerebrospinal fluid	
Dog 1											
	gm. per cent	*gm. per cent*	*gm. per cent*	*gm. per cent*	*gm. per cent*	*mg. per cent*	*mg. per cent*	*mg.*	*mg. per cent*	*mg. per cent*	*mg.*
1	8.5	1.1	95.1	98.9	6.6	355	345	10	409	470	61
Plasmapheresis (350 cc. of blood withdrawn, corpuscles washed, resuspended, reinjected 14 times)											
6	4.5	1.1	95.5	98.9	2.9	345	339	6	439	466	27
7	5.5	1.1	94.5	98.9	3.9	352	348	4	436	469	33
8	6.1	1.1	93.9	98.9	4.5	352	346	4	434	468	34
10	8.3	1.1	91.7	98.9	6.6	355	349	6	432	476	44
Dog 2											
1	9.1	1.1	90.9	98.9	7.4	374	357	18	423	486	63
Plasmapheresis (400 cc. of blood withdrawn, corpuscles washed, resuspended, reinjected 7 times)											
3	5.2	1.1	94.8	98.9	3.8	342	338	4	438	468	30
4	6.2	1.1	93.8	98.9	4.7	355	351	4	437	485	48
5	7.0	1.1	93.0	98.9	5.5	361	349	12	426	474	48
7	7.9	1.1	92.1	98.9	6.4	368	353	15	420	484	64

* Corrected for the water content of the plasma and cerebrospinal fluid.

In both experiments it will be seen at once that there is a very striking decrease in the disparity of the chloride concentrations of the plasma and of the cerebrospinal fluid, when the content of the protein in the plasma is reduced. There is also a similar decrease in the disparity of the sodium values.

SUMMARY

1. When the plasma protein of dogs is lowered by plasmapheresis, the concentration of chloride and sodium in the plasma and the cerebrospinal fluid tends to become the same, a diminishing of the usual disparity which exists in the presence of a normal plasma protein.

2. This is in accord with the theory that the cerebrospinal fluid is a dialysate, with the choroid plexus acting as a simple dialyzing membrane.

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