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THE EFFECT OF PITRESSIN AND WATER INTAKE ON THE CEREBROSPINAL FLUID

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FREMONT SMITH *et alia* (1930) have shown that dilution of the blood and of the cerebrospinal fluid (C.S.F.) occurs on giving subjects large quantities of water by mouth after a preliminary subcutaneous injection of extract of the posterior lobe of the pituitary (vasopressin). In their experiments sodium, chlorides, protein, non-protein nitrogen, total solids, and freezing-point estimations were made. The few figures shown do not suggest an even alteration of blood and C.S.F. In a later paper (1931) they again measured the depression of the freezing-point of blood and C.S.F. in patients subjected to similar experiments as before. They showed in these later experiments that in seven out of nine cases depression of the freezing-point of both blood and C.S.F. occurred, but in two cases there was an elevation of the freezing-point of the C.S.F. with a lowering of that of the blood.

We have conducted experiments of a similar character, but have estimated different constituents of the blood and C.S.F. Our results and the interpretation of these are recorded below.

Methods

After blood and C.S.F. had been obtained from patients who had, with only the few exceptions stated in the tables, fasted for some hours, 0.5 c.c. of pitressin was administered subcutaneously. During the next 4 hours 6 pints of water were drunk, as large a quantity as possible being taken within the first 2 hours. At the end of the 4 hours blood and C.S.F. were again withdrawn.

There were four groups of male patients. The first consisted of seven normal subjects from whom lumbar C.S.F. was obtained ; the second of two subjects from whom ventricular fluid was taken, the third of patients who had spinal lesions producing a spinal block and from whom C.S.F. from below the block was withdrawn ; and, lastly, a group of two subjects from whom hydrocele fluid and blood were taken for examination.

The following constituents in these fluids were estimated : hæmoglobin, blood only, by Haldane's method ; sugar by Folin and Wu's method ; urea by Archer's modification of Folin and Wu's method ; calcium by Kramer and Tisdall's method ; inorganic phosphorus by Brigg's method (Harrison, 1937) ; magnesium and chlorides (McCance and Shipp, 1933). Duplicate samples in every case of all four specimens (two of blood and two of C.S.F.) were estimated together for each of these substances. If any variation occurred between the duplicates, further samples were estimated.

Results

The full list of results in all 14 cases is recorded at the end of the paper. There was a gain in weight in the patients which, in every case, corresponded with the weight of water drunk, when the weight of the urine passed was taken into consideration. The amount of urine passed in most cases was not more than a few fluid ounces.

In general the blood diluted in every case ; however, the individual constituents did not dilute evenly. The C.S.F. behaved differently in the different groups of patients. In group I (lumbar fluid from normal patients) there was not only an irregular dilution of the C.S.F. but in certain instances some of the constituents increased in concentration. For example, urea increased in subjects S and L, calcium in subject S, phosphorus in subject M, magnesium in subject L, and chlorides in subjects K and S. This was also true for group II (ventricular fluid), and the similarity of these results suggests that changes found in the lumbar C.S.F. may be taken as a true reflection of the changes taking place in the ventricular fluid. It is seen that in group III (lumbar fluid from below a spinal block) there is much less dilution of the C.S.F. and in many instances there is practically none at all. Group IV (those from whom hydrocele fluid was examined) shows that hydrocele fluid diluted in every instance, and as will be seen later, in a very similar ratio to the dilution occurring in the blood.

If the Donnan theory for the formation of the C.S.F. were true, the ratio of the concentration of the same substance in the C.S.F. to that in the blood should remain the same before and after dilution, or at least the variation between the ratios should be slight. Further, if in one subject the ratio for one substance did vary, then the ratios for the other substances should vary in a corresponding manner. Accordingly the results have been expressed in terms of this ratio in the following tables.

GROUP I

Results expressed as the ratio $\frac{\text{concentration of substance in blood}}{\text{concentration of substance in lumbar C.S.F.}}$

NAME		SUGAR	UREA	CALCIUM	INORGANIC PHOS- PHORUS	MAGNESIUM	CHLORIDES
*H	Before experiment.	1.24	1.14	1.66	1.05	0.74	0.84
	After dilution.	1.37	0.94	1.72	1.09	0.72	0.77
M	Before experiment.	1.46	1.10	1.80	1.15	0.80	0.82
	After dilution.	1.42	0.98	1.90	1.08	0.82	0.79
K	Before experiment.	1.20	1.16	2.17	1.09	0.82	0.83
	After dilution.	1.10	1.20	2.27	1.08	0.78	0.80
A	Before experiment.	1.14	1.03	2.10	1.90	0.69	0.79
	After dilution.	1.09	1.02	2.08	1.90	0.61	0.74
*B	Before experiment.	—	0.93	1.60	1.45	0.79	0.83
	After dilution.	—	0.94	1.57	1.25	0.75	0.74
L	Before experiment.	1.30	1.26	1.74	1.87	1.14	0.82
	After dilution.	1.29	1.09	1.78	1.83	1.00	0.82
S	Before experiment.	1.30	1.08	1.90	1.60	—	0.84
	After dilution.	1.15	0.83	1.86	1.60	—	0.77

GROUP II

Results expressed as the ratio $\frac{\text{concentration in blood}}{\text{concentration in ventricular C.S.F.}}$

NAME		SUGAR	UREA	CALCIUM	INORGANIC PHOS- PHORUS	MAGNESIUM	CHLORIDES
S	Before experiment.	1.20	1.40	2.70	2.00	0.72	0.81
	After dilution.	1.15	1.08	3.00	1.86	0.68	0.70
K	Before experiment.	1.34	1.10	2.30	1.04	0.70	0.80
	After dilution.	1.30	1.14	1.99	1.02	0.70	0.79

GROUP III

Results expressed as the ratio $\frac{\text{concentration in blood}}{\text{concentration in lumbar C.S.F. below block.}}$

NAME		SUGAR	UREA	CALCIUM	INORGANIC PHOS- PHORUS	MAGNESIUM	CHLORIDES
A	Before experiment.	1.30	1.03	1.75	1.55	0.63	0.86
	After dilution.	1.28	0.89	1.70	1.40	0.68	0.78
R	Before experiment.	1.50	1.10	2.08	1.50	1.03	0.79
	After dilution.	1.20	1.09	1.90	1.30	0.87	0.76
B	Before experiment.	1.90	1.00	2.10	1.04	0.94	0.84
	After dilution.	1.60	0.91	2.10	1.10	0.97	0.74

GROUP IV

Results expressed as the ratio $\frac{\text{concentration in blood}}{\text{concentration in hydrocele fluid.}}$

NAME		SUGAR	UREA	CALCIUM	INORGANIC PHOS- PHORUS	MAGNESIUM	CHLORIDES
*H	Before experiment.	0.70	1.09	1.06	1.15	0.97	0.94
	After dilution.	0.77	0.96	1.04	1.17	0.94	0.83
*E	Before experiment.	—	0.95	1.24	1.20	1.19	0.92
	After dilution.	—	0.96	1.30	1.09	1.13	0.88

* Not fasting.

Discussion

It will be seen from these figures that the ratio of blood to hydrocele fluid after dilution of the blood has not appreciably altered. In fact, the constituents of these two fluids have followed each other very closely. The dilution of hydrocele fluid being so regular and retaining so constant a ratio to the blood points to this dilution being the result of dialysis. It may also be assumed that the rate of blood dilution is fairly regular and that other fluids, such as C.S.F., should dilute in a manner similar to hydrocele fluid if the mechanism for their dilution be the same. When consideration is given to the other tables it is seen that the C.S.F. from below a spinal block shows a marked contrast to the hydrocele fluid in that there is a very considerable variation in the ratio before and after dilution. In nearly half of the various substances estimated there is a variation of more than 10 per cent. between the two ratios. An inspection of the tables giving the actual amounts of each substance present shows that this variation in the ratios before and after dilution is due to the fact that the C.S.F. has been only very slightly diluted. This suggests that the spinal subarachnoid space is not similar to any serous surface, in that the alteration of substances across the membranes is not controlled according to the theory of dialysis.

It is possible to consider groups I and II together. In both there is an irregular variation in the ratios, about one-third varying by more than 10 per cent. As examples of this variation the following may be quoted: urea in subject H, phosphorus and chlorides in subject B, urea and magnesium in subject L, sugar and urea in subject S, and calcium in subject K. In each of these specific cases the C.S.F. has diluted less than the blood. If there was any lag, due to the time factor, in the balancing mechanism between blood and C.S.F. in these experiments, then all constituents of the C.S.F. should be equally affected. Thus, if one ratio varied by as much as 10 per cent., then the ratio for the other constituents should have varied similarly. This would be the case if the assumption were true that dialysis was the only mechanism involved. Further, if in these experiments water only passes from the blood to dilute the C.S.F. there should be relatively little lag. It has also been shown that in the case of hydrocele fluid there is no such lag at the end of 4 hours. It is not reasonable to suggest that tissue fluid from the perivascular spaces plays any part as there was no increase of cells between the two C.S.F. specimens taken before and after dilution. It is difficult to believe that fluid from the perivascular spaces should pass into the C.S.F. without a certain number of cells coming into it and being found in the C.S.F.

It is possible that pitressin may act on the choroid plexus and so account for the irregularity of dilution. Pitressin has been shown to act on glandular organs (Dodds and Noble (1937), Dodds (1937)), but the choroid plexus is not morphologically similar to other glandular structures. If, however, pitressin does affect the choroid plexus, the theory that the C.S.F. is formed across a passive dialysing membrane is difficult to uphold.

The results appear to be capable of explanation if it be admitted that the choroid plexus takes an active part in the control of the C.S.F. formation and that following dilution of the blood the choroid plexus either by a secretory

process or by means of selective filtration lets through substances in varying concentrations. However, there is another possibility that has to be considered. As well as some activity on the part of the choroid plexus, it is possible that absorption of individual constituents takes place in the C.S.F. If this were so it would appear that the rate of absorption varies not only from one constituent to another, but also that the same constituent is absorbed at different rates by different individuals. It is only possible to explain the variation of the ratios on such an assumption. In view of the results recorded here the assumption of Fremont-Smith that the alteration of the freezing-point in his experiments was evidence of dialysis in the formation of the C.S.F. would not be correct. Therefore from our experimental results recorded in this paper it must be assumed that either the choroid plexus performs an active function in the production of the C.S.F., or that the varying rate and selectivity of absorption is responsible, or, and this is more probable, that both are concerned. The rate of absorption may also be an individual characteristic. If the choroid plexus is accepted as playing an active part in the formation of the C.S.F. as in one suggestion from the above, then support is given to the contention of Flexner (1934), who showed that a definite amount of energy (13 calories) was produced during the formation of 1 litre of C.S.F. He stated that the C.S.F. could not be a dialysate nor could it be an ultrafiltrate, because ultrafiltration would only account for 0.9 calories. He therefore maintained that the C.S.F. was a secretion, using this in the sense that work was done during its formation and not in the sense that the choroid plexus was a glandular structure.

Summary

Investigations have been conducted by which the blood has been diluted and the behaviour of the C.S.F. in relation to this has been subsequently studied.

It has been found that the C.S.F., both ventricular and lumbar, does not dilute equally with the blood in such constituents as have been examined. Hydrocele fluid, however, does follow blood dilution closely.

C.S.F. from below a spinal block shows extremely little dilution.

These findings have been discussed in relation to the mechanism for the formation and absorption of the C.S.F.

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GROUP I. Normal subjects from whom lumbar C.S.F. was withdrawn.

NAME	TIME, IN HOURS	SUGAR		UREA		CALCIUM		INORGANIC PHOSPHORUS		MAGNESIUM		CHLORIDES		HÆMO-GLOBIN
		BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	
*H ..	0	64.5	52.0	31.5	27.5	10.0	6.0	4.75	4.5	2.46	3.41	616.6	736.4	111
	4	64.5	46.5	23.5	25.0	9.7	5.6	4.65	4.25	2.36	3.28	531.6	674.4	101
M ..	0	87.0	59.5	28.0	24.75	10.0	5.4	2.53	2.12	2.27	2.82	598.04	723.0	120
	4	84.5	59.5	20.75	21.5	9.8	5.1	2.40	2.225	2.21	2.7	552.2	698.5	113
K ..	0	67.0	55.7	25.5	22.0	10.2	4.66	4.21	3.87	4.3	5.24	554.6	659.88	105
	4	60.0	55.0	22.5	18.5	10.0	4.4	4.0	3.7	3.91	5.01	530.5	662.2	94
A ..	0	74.0	64.5	46.5	45.0	11.0	5.2	5.1	2.58	2.4	3.48	599.0	750.0	—
	4	65.0	59.0	45.0	44.0	10.4	5.0	4.9	2.54	2.12	3.45	526.5	706.7	—
*B ..	0	—	65.0	26.5	28.5	12.0	7.5	2.9	2.0	3.85	4.85	575.0	688.5	106
	4	—	60.0	25.0	26.5	10.7	6.8	2.5	2.0	3.45	4.6	480.2	650.8	102
L ..	0	72.0	55.5	19.0	15.0	12.4	7.1	4.6	2.45	4.9	4.3	603.7	738.3	105
	4	61.0	48.5	17.0	15.5	11.6	6.5	4.16	2.28	4.4	4.42	575.6	716.0	100
S ..	0	78.0	61.0	31.5	29.0	10.9	5.7	2.75	1.8	—	—	606.1	719.5	107
	4	70.0	61.0	24.5	29.25	10.7	5.8	2.6	1.6	—	—	563.9	725.4	101

GROUP II. Normal subjects from whom ventricular C.S.F. was withdrawn.

S ..	0	0.19	0.15	11.3	15.0	11.2	4.1	3.37	1.64	2.89	4.03	570.9	699.7	105
	4	54.0	47.0	15.5	14.7	10.8	3.6	2.68	1.44	2.62	3.81	468.0	664.56	102
K ..	0	65.0	48.5	25.0	22.5	10.6	5.0	3.5	3.34	2.71	3.9	542.9	678.6	109
	4	63.0	48.0	23.5	20.5	10.1	5.1	3.0	2.94	2.52	3.29	508.4	641.7	100

All results are expressed in mgms. per cent.
* Not fasting.

GROUP III. Subjects with a spinal block from whom lumbar C.S.F. was withdrawn below the block.

NAME	TIME IN HOURS	SUGAR		UREA		CALCIUM		INORGANIC PHOSPHORUS		MAGNESIUM		CHLORIDES		HÆMO- GLOBIN
		BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	BLOOD	C.S.F.	
A ..	0	89.0	67.0	29.9	29.0	9.8	5.6	3.87	2.5	2.8	4.4	601.4	699.7	104
	4	87.0	68.0	26.7	30.0	9.1	5.4	3.37	2.37	2.73	4.0	547.6	697.3	
R ..	0	68.0	46.2	19.7	18.0	10.4	5.0	4.5	3.0	3.29	3.2	578.0	730.1	99
	4	61.0	46.5	18.5	17.0	9.4	5.0	4.03	3.0	2.92	3.32	551.1	725.4	
B ..	0	122.0	62.5	25.7	25.5	10.1	4.8	1.53	1.47	3.08	3.28	594.4	704.3	88
	4	98.0	61.5	21.2	23.5	10.0	4.7	1.35	1.18	2.87	2.96	526.5	706.7	

Subjects A and R both had a complete spinal block, but that of subject B was only partial.

GROUP IV. Subjects from whom hydrocele fluid was withdrawn.

*H ..	0	64.5	92.0	31.5	29.2	10.0	9.4	4.75	4.13	2.46	2.52	616.6	650.3	111
	4	64.5	83.0	23.5	24.7	9.7	9.3	4.65	3.95	2.36	2.49	531.6	643.5	101
*E ..	0	—	—	19.0	19.9	11.9	9.6	3.22	2.7	2.54	2.13	552.2	599.0	101
	4	—	—	16.3	16.7	11.7	9.0	2.84	2.6	2.17	1.91	512.4	574.5	89

All results expressed in mgms. per cent.

* Not fasting.