VIII. THE CHLORIDES AND INORGANIC CONSTITUENTS OF THE SERUM AND CEREBROSPINAL FLUID IN MENINGITIS.

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INTRODUCTION.

It has been established for many years that in meningitis and especially in tuberculous meningitis the concentration of chloride in the cerebrospinal fluid falls, and this fact has become of considerable value in diagnosis. Mestrezat [1912] was one of the first to note that the chloride concentration of the cerebrospinal fluid was higher than that of the serum, and he further reported its decrease in meningitis.

In health the concentration of chloride in serum is 0.58 % (100 millimoles per litre) and in the cerebrospinal fluid 0.73 % (125 *mM.*). Attempts have been made to explain this difference on physical grounds, by the difference in water content and protein concentration of the two fluids leading to an unequal distribution of ions in accordance with the Donnan law [Hamilton, 1925]. Mestrezat and Lebebt [1921] produced by dialysis *in vitro* and *in vivo* fluids very closely resembling cerebrospinal fluid, and showing a higher chloride content than the serum from which they were formed. Duke-Elder [1927] found a higher chloride content in the aqueous humour than in the corresponding serum; he attributed this to the Donnan effect and found no evidence that the aqueous humour is a secretion. The aqueous humour is very closely related to the cerebrospinal fluid. Fremont-Smith [1927] reviews the evidence for and against the secretion of the cerebrospinal fluid by an essentially vital activity of the choroid, and accepts it as proven that its composition can be explained by the laws of filtration and dialysis.

Against accepting this conclusion too hurriedly it may be observed that the value of the ratio $\text{Cl}_{\text{serum}}/\text{Cl}_{\text{C.S.F.}}$ is always much smaller than the value of R predicted from the formulae of Van Slyke, Wu and McLean [1923], and much less than the ratio for Cl actually found by Hastings, Salvesen, Sendroy and Van Slyke [1927] in a study of the relation of oedema fluid to serum. And further according to Donnan's law

$$R = \frac{\text{Cl}_{\text{serum}}}{\text{Cl}_{\text{C.S.F.}}} = \frac{\text{HCO}_3 \text{ serum}}{\text{HCO}_3 \text{ C.S.F.}} = \frac{\text{A}_{\text{serum}}}{\text{A}_{\text{C.S.F.}}} = \frac{\text{B}_{\text{C.S.F.}}}{\text{B}_{\text{serum}}} = \frac{\text{H}_{\text{C.S.F.}}}{\text{H}_{\text{serum}}}$$

where A = total univalent anions and B = total univalent cations. In the

study of oedema fluid just referred to there was a much closer approximation to the above conditions than has yet been demonstrated for cerebrospinal fluid, but it might be argued that the great stagnation of oedema fluid would allow more complete equilibration to take place. There is yet much to learn as to the properties of the separating membranes of the body. Since the ratio for bicarbonate departs entirely from that predicted, the membranes of the choroid and meninges would appear to be impermeable to this ion, as the membrane of the red blood cell is impermeable to basic ions [Van Slyke, Wu and McLean, 1923].

Recently Cohen [1923, 1927] has attempted to explain the fall in the chlorides of the cerebrospinal fluid in meningitis by attributing it to an increase in permeability of the choroid plexuses so that the chloride concentration approaches more closely to that of the serum. In favour of this hypothesis he brings evidence to show that in meningitis the magnesium and inorganic phosphate concentration of the fluid approach that of the serum; that fibrinogen, bile pigments and "complement" appear in the cerebrospinal fluid; and that certain foreign substances such as nitrates and iodides, which do not normally pass into the cerebrospinal fluid from the blood stream, will then do so.

But the decrease of chlorides in tuberculous meningitis from 0.72 % to as low as 0.55 % is unassociated with a great increase of protein in the cerebrospinal fluid, and therefore such a great fall would not be required to bring the chlorides into equilibrium with the serum if the serum chlorides remained unchanged.

It is the object of this preliminary paper to show that the fall of chlorides in meningitis is due to other causes than increased permeability of the meninges.

EXPERIMENTAL.

Four patients have been studied; two had tuberculous meningitis, one meningococcal meningitis and one streptococcal meningitis. All were proven bacteriologically. Cerebrospinal fluid was withdrawn by cisternal or lumbar puncture into a paraffined syringe without contact with air; 15 to 20 cc. were taken. Immediately afterwards arterial blood was drawn from the femoral artery with similar precautions and the serum was separated as soon as possible.

Chloride was determined by Van Slyke's method [1923], CO_2 by the constant volume apparatus of Van Slyke and Neill [1924], total fixed base by the benzidine method of Stadie and Ross [1925], inorganic phosphate by the method of Benedict and Theis [1924], and p_{H} by the Hastings and Sendroy [1924] colorimetric method. The p_{H} and CO_2 analyses on the cerebrospinal fluid were made without delay. The bicarbonate was calculated from the Hasselbalch equation taking 6.10 as the p_{K} of serum and 6.13 as that of cerebrospinal fluid [Shohl and Karelitz, 1926]. The "undetermined acids" were

determined by subtracting from the total base the sum of the base bound by the chloride, bicarbonate, phosphate and protein; the base bound by the protein was derived from the formula $(BP)_s = 0.097 (P)_s (p_{Hs} - 5.26)$ [Hastings, *et al.*, 1927].

The results are shown in Table I together with the mean of a series of 26 probably normal cerebrospinal fluid and serum analyses published by Hamilton [1925]. He assumed that 1 litre of serum contained 930 g. of water and that 1 litre of cerebrospinal fluid contained 1 kg. of water. This figure for serum agrees with the one we obtained by calculation from the protein content in Cases I and II so we have adopted it throughout, and the results are given as millimoles per litre of water.

Table I.

Case	Diagnosis	Chloride		Cl serum water Cl C.S.F. water	Bicarbonate		B HCO ₃ serum water B HCO ₃ C.S.F. water	Total base		B C.S.F. water B serum water
		Serum water mM per litre	C.S.F. water mM per litre		Serum water mM per litre	C.S.F. water mM per litre		Serum water mM per litre	C.S.F. water mM per litre	
	Normal	111	124	0.895	25	21	1.19	164	156	0.95
I	Tuberculous meningitis	90	105	0.86	47	32	1.47	172	151	0.88
II	Tuberculous meningitis	97	108	0.90	33	28	1.18	172	144	0.84
		91	102	0.89	31	25	1.24	162	138	0.85
III	Meningococcal meningitis	77	89	0.87	44	40.5	1.09	—	144	
IV	Streptococcal meningitis	86	96	0.90	24	14	1.71	146	124	0.85

Case	Diagnosis	Inorganic phosphorus		Other acids		pH		Protein		Remarks
		Serum water mM per litre	C.S.F. water mM per litre	Serum water mM per litre	C.S.F. water mM per litre	Serum	C.S.F.	Serum %	C.S.F. %	
	Normal	1.2	0.6	10	10	—	—	—	—	Mean of 26 analyses of epileptics 13. iii. 27
I	Tuberculous meningitis	1.8	1.0	15	12	7.60	7.42	6.5	0.09	
II	Tuberculous meningitis	1.4	0.8	26	7	7.48	7.36	6.2	0.14	6. x. 27
		1.4	0.9	24	9	7.48	7.31	6.3	0.14	18. x. 27. Death on 24. x. 27
III	Meningococcal meningitis	—	—	—	14	7.48	7.40	—	0.4	6. iv. 27. Venous serum
IV	Streptococcal meningitis	—	—	20	13	7.20	7.0	—	—	Death next day

Chloride. In all the cerebrospinal fluids a marked decrease in chloride concentration had occurred; the lowest was found in the case of chronic meningococcal meningitis in which it was 0.52 %. On examination of the figures for serum chloride it was at once apparent that there had been a corresponding decrease in these. It was found that the ratio $Cl_s/Cl_{C.S.F.}$ was remarkably constant and agreed well with that calculated from Hamilton's series. The constancy of this ratio excludes the possibility that a change of permeability was the cause of the fall of cerebrospinal fluid chlorides, and is an additional fact supporting the view that the Donnan law has an important rôle in determining the composition of the fluid.

Since the serum and cerebrospinal fluid remain almost neutral in reaction, such a decrease in chlorides must be accompanied by an increase in the other anions, bicarbonate, phosphate, protein or other acids, or by a decrease in the cations. The changes in bicarbonate, total base and "undetermined acids" were therefore studied.

Bicarbonate and p_H . In Cases I and II there was a great increase in bicarbonate, but in Case I a small amount of alkali had been given by mouth during the week preceding our observations; both showed a high p_H in the serum with lower figures for the cerebrospinal fluid. In Case II the bicarbonate was moderately high; the reaction of the serum was normal and the cerebrospinal fluid was slightly more acid. In Case IV there was a marked fall in serum p_H with normal bicarbonate, a state of "uncompensated CO_2 excess," possibly due to insensitiveness of the respiratory centre. The cerebrospinal fluid showed a great fall of bicarbonate and an extremely low p_H . That the cerebrospinal fluids were regularly so much more acid than the sera was attributed to the presence of infection within the meninges.

Total base. The total base in the cerebrospinal fluid was rather less than was found in Hamilton's cases, and this was more marked in Case IV in which the serum base was also definitely reduced. The ratio $B_{C.S.F.}/B_S$ was fairly constant in our cases but considerably lower than the ratio found by Hamilton; they agreed better with, but are lower than, the corresponding values for the chloride ratio. The amount of bivalent base is so small that we have neglected it.

Undetermined acids. There was much less undetermined acid in the cerebrospinal fluid than in the serum and no significant change took place. The increase of lactic acid in meningitis reported by Glaser [1926] to about 10 millimoles per litre of cerebrospinal fluid was not suggested by our figures.

SUMMARY.

1. It seems evident that the fall of chloride concentration in the cerebrospinal fluid in meningitis is dependent on a similar fall in the chloride concentration of the serum. The relative concentrations in cerebrospinal fluid and serum remain the same.

2. The associated disturbances are an increase, sometimes large, of the bicarbonate in both fluids and a small decrease in total base in the cerebrospinal fluid. Sometimes a greater depletion of base occurs in cerebrospinal fluid and in serum, and in such cases the bicarbonate does not rise and may be low.

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