THE ELECTROLYTES IN PATHOLOGICAL BODY-FLUIDS

By OSKAR C. GRUNER, M.B. LOND., *Clinical Pathologist, Leeds General Infirmary.*

(Received June 13th, 1907)

The chemical study of exudates and transudates has occupied the attention of numerous investigators, mainly during the past forty years. The most interest has been attached to the proteid content, while the other constituents, estimated by Hoppe-Seyler, C. Schmidt, Halliburton and others, have been considered of less importance. In respect of their total quantity these substances are insignificant, but they constitute the bulk of the electrolytes present.

The reflection that some substance or substances might be present in some pathological body-fluids and not in others, consequent on the cause of the effusion, has led to the present research. For instance, when cancer is disseminated over the peritoneum, the cells pour out the products of their metabolism into the peritoneal exudate: in this way certain substances might be present which are absent from other exudates. However, the most important of such substances (in this particular class of case) are likely to be ferments or anti-bodies to the same. The question of the presence of these bodies is not to be dealt with in this account, but I propose to limit myself now to the electrolytes.

Bugarsky and Tangl (1) were the first to make an exhaustive study of the two main groups of electrolytes in the blood-serum of different animals. They used Kohlrausch's method of determining the electro-conductivity of the serum, and from the results of this combined with certain quantitative analysis they made certain deductions. The same method has been employed in the present study of pathological body-fluids. Hamburger (2) has fully criticised the method, but it will be convenient to explain first the various defects of the method, and then show to what extent one may make useful deductions.

I.—The electrolytes of effusions may be classed as (1) chlorides, and (2) electrolytes which are not chlorides (achloride electrolytes). The second group consists of sodium carbonate, sodium sulphate, sodium phosphate, calcium and magnesium phosphates, and the ions into which they may be dissociated. The molecular weight of each of these substances is greater than that of NaCl. One cannot therefore accurately express the second group in terms of NaCl, in representing their molecular or osmotic concentration. The essence of Bugarsky and Tangl's records lies in their calculating all the achlorides in terms of Na_2CO_3 . This electrolyte is present in far preponderant quantity (after NaCl) in serum. In effusions the same holds good, though not constantly. After working out the different figures, I have found that for the present purpose it is not a serious error to follow the lead of the quoted authors. At first the calculations were made as follows:—

A given pleural fluid contained 0.062 gram-molecule per litre of NaCl. Its conductivity¹ was 1068, which, for the temperature, is equivalent to that of a solution of NaCl of 0.123 gram-equivalent per litre. The difference, 0.061, gives the concentration of the achlorides in terms of NaCl. The ratio of chlorides to achlorides is then $0.062 : 0.061 = 1.016$. This is a simple calculation.

The other method gave these results:—

The chlorides amounted to 0.062 gram-molecule per litre. The degree of dissociation of this (calculated by Arrhenius' formula) is 0.861. The number of molecules plus ions (above formula) is 0.1153. The conductivity of such a strength of NaCl subtracted from that of the fluid gave a conductivity which is possessed by a solution of Na_2CO_3 containing 0.062 gram-molecule per litre, with a degree of dissociation of 0.570, and 0.1342 molecules plus ions per litre.

The ratio NaCl : Na_2CO_3 is now 1.16.

This calculation is obviously much more prolonged.

1. Throughout this account, 'conductivity' means 'specific conductivity,' and is expressed in terms of 10^8 .

The error in these calculations may lie in the values used for the conductivity of NaCl and Na₂CO₃ solutions, which have been estimated in *watery* solution, whereas they occur in *albuminous* solution in the body. The degree of dissociation is vastly different. To this we presently return.

The following analysis of pus-serum by Hammarsten (3) :—

NaCl	...	...	5·39%	or,	Chlorides	...	...	5·39%
Na ₂ SO ₄	...	...	0·31		Carbonates	...	...	1·13
Na ₂ HPO ₄	...	...	0·46		Sulphates	...	...	0·31
Na ₂ CO ₃	...	...	1·13		Total phosphates	...	...	0·94
Ca ₃ (PO ₄) ₂	...	...	0·31					
Mg ₃ (PO ₄) ₂	...	...	0·12					
PO ₄ (in excess)	...	...	0·05					

shows the preponderance of carbonates over phosphates and sulphates. It must be admitted that this is not invariable, but it has been found that even if the phosphates be in excess and the mode of expression of chlorides be altered accordingly, the ratio still remains similar. It is obvious that the only way of avoiding errors at all would be by complete chemical analysis. The present method is an attempt to obtain useful results by the simple method of conductivity determination.

II.—*The presence of non-electrolytes.* Those which are present in exudates and transudates are sugar, urea, cholesterin (sometimes), creatin (sometimes), lecithin (ascitic fluid); but their actual amount compared with *albumen* is quite negligible, so that any correction which has to be made for the latter body will cover that needed for the other non-electrolytes.

The retarding influence of albumen on the conductivity of a fluid is 2·5 per cent. for every 1 per cent. of albumen. The formula

$$\text{Corrected conductivity} = \frac{\text{Original conductivity} \times 100}{100 - (\text{percentage of albumen} \times 2\cdot5)}$$

has been used in the results which follow (1).

III.—*The temperature at which the observations are made.* All that need be said on this point is that I have found 18° C. the most convenient to use for the following reasons :—

The low temperature is easily maintained without rapid evaporation of the water in the thermostat; the fluid will not so readily putrefy if the determination should happen to be delayed and the containing vessel remain in the thermostat longer than really necessary; thirdly, the temperature of the fluid comes level with that in the thermostat within ten minutes; and lastly, all the standard observations of conductivity of salt solutions have been made at 18° C., and thus correction formulae for temperature are avoided.¹

It may be of use to say that if the temperature be other than 18° C., the value for the conductivity can be corrected to 18° C. by this formula:—

$$k_1 = k_{18} \pm \frac{k_1 \times (t_1 - 18) \times 2.21}{100}$$

IV.—*The estimation of Albumen.* In all the earlier cases (some of which are recorded below) the albumen was estimated with Esbach's instrument, after diluting 1 in 10, in spite of the reputed inaccuracy of the method. The sole reason was the saving of time. Most of the measurements were, however, made by weighing after coagulating the fluid (slightly acid) and drying the coagulum in vacuo over sulphuric acid. The objection was that one had to wait some days before one's analysis was available for the clinician. But it was finally decided to be more important to sacrifice this desire to the need for more accurate figures, since the electrolyte content of fluids is dispensable as an aid to diagnosis, and is of use solely because of the insight into the constitution of these fluids which it affords.

Determination of the weight of albumen by Kjeldahlising was found to be no gain in point of time over simple weighing.

V.—*The estimation of Chlorides.*—With this question is bound up that of the affinity of albumen for Cl. Albumen is well known to combine with Cl if presented to it in the form of acid, but whether it will do so when in combination with Na does not seem to have been discussed. But if albumen be bound up with Cl as a 'solution-

1. For convenience, I have made determination of many strengths of NaCl and Na₂CO₃ myself, so as to obtain more intermediate values than are obtainable in Kohlrausch's tables. The values for fractions of a degree were calculated from their determinations by Newton's interpolation formula.

aggregate' (4), then when the albumen is coagulated the Cl will presumably go down with it, and not appear in the filtrate which was tested for chlorides by Volhardt's method. More than that, in the coagulum there may be some 'free' chloride entangled which may escape analysis in the same way. The only solution to this difficulty would be to analyse the ash, but this method was cast aside because of necessity for economy in analysing the fluids,¹ and it became necessary to find by experiment whether there be any relation between albumen and Cl which might lead to error in analysis. If there were it would be possible to devise a formula by which the error could be corrected for within reasonable limits.²

Solutions of egg-white of various strengths (8, 4, 2 and 1 per cent.) such as would be equivalent to the strength of the albuminous fluids under consideration were made up, and NaCl was added in varying proportions (8, 5, 2, 1 gramme per litre) to each of the albuminous solutions. The fluids were well shaken, allowed to stand overnight, and the chlorides estimated in the usual way. It was then found that if there were only 2 per cent. of albumen, and less than 5 grammes per litre of NaCl, the latter could be recovered from the filtrate after boiling, while if the NaCl amounted to 1 per cent. in such a weak solution, there was distinct loss of chlorine, though only slight even then. With higher strengths of albumen the loss of NaCl was greater, but not proportionately. The error was slight even at the worst.

This shows that in exudates, where albumen may be present to the extent of 8 per cent., the NaCl found volumetrically will be less than that actually present, but not so much less as to cause serious error in the subsequent calculations.

The consideration that even if albumen in a fluid do contain Cl bound up with it, the two together will probably influence the conductivity in the same way as albumen alone, shows once more that we are not introducing any important error by our method.

1. A fairly exhaustive analysis has been made of the proteid constituents and their decomposition-products in these particular fluids as well as of their electrolyte content.

2. Prof. Bayliss' paper in the *Bio-Chem. Jour.*, Vol. I, No. 4, refers to the adsorption of electrolytes by colloids, and here would be an explanation of the error to which I refer.

There is, however, another aspect of the case, and that is with reference to the globulins present in these fluids. The proteid present in pathological body-fluids contains varying ratios of globulins and albumen. The ratio has been called the 'proteid quotient' (Halliburton), which varies from 0.6 to 1.5 in different specimens of fluid. In other words, globulin may exceed albumen in actual amount. Now globulin in the presence of electrolytes behaves as an amphoteric electrolyte, whose particles are not true ions but pseudo-ions (5). The affinity of globulins for salts is the explanation of their precipitation in very dilute media. These points have an important bearing on whether the presence of electrolytes in combination with proteid in a fluid introduces error in the method of calculation. Pauli (6) has made researches on the electrical behaviour of albumen when in combination with Cl, but apparently the alteration produced in albumen by the presence of Cl is not as formidable as that produced in globulin. We have to recognise that the influence of globulin on electro-conductivity is less inhibitory than that of albumen. This will be in favour of achloride electrolytes, for the figures obtained in the tables which follow will represent the conductivity lower than the reality, and the corresponding concentration of achlorides will be raised.

TABLE I

i	ii	iii	iv	v	vi	vii	viii	ix	x	xi
No. of case ¹	Nature of case	Fluid contains chlorine g. aeq. in litre	Degree of dissociation 'α'	No. of molecules + ions	Specific conductivity of fluid corrected (x 10 ⁵)	Conductivity of iii	Conductivity of a chlorides (vi - vii)	No. of molecules + ions pro litre of a solution of Na ₂ CO ₃ with conductivity in column viii	Total concentration of electrolytes (v + ix)	ix - v
8337	Pleurisy secondary to pneumonia		'860	'1190	1496	550	946	'1804	'2611	2'23
8338	Tubercular pleurisy		'885	'0639	1169	325	844	'1830	'2469	2'86
7313	Ditto		'901	'0456	825	205	620	'1334	'1790	2'92
7334	Empyema		'901	'0456	616	205	411	'0866	'1342	1'93
7617	Pleurisy secondary to pneumonia		'891	'0586	1071	245	826	'1733	'2319	2'95
6677	Tubercular pleurisy		'861	'1153	1068	550	518	'1146	'2299	0'99
6325	Pleurisy secondary to abdominal cancer		'901	'0456	1096	205	891	'1813	'2269	3'97
6603	Peritoneal cancer (colloid)		'858	'1263	1183	589	594	'1400	'2663	1'10
6712	" sarcoma		'880	'0752	1188	345	843	'1758	'2510	2'33
6838	" cancer (ovary)		'874	'0863	1165	425	740	'1733	'2596	2'00
A	" (ovary)		'876	'0825	900	405	495	'1066	'1891	1'29
b	" (ovary)		'922	'0269	971	145	825	'1813	'2082	6'74
8344	" (?)		'837	'1910	1102	855	247	'0516	'2426	0'27
6417	Tuberculous peritonitis		'866	'1055	1171	505	666	'1599	'2654	1'51
7553	Chronic peritonitis (gastric ulcer)		'877	'0800	1311	425	986	'1875	'2675	2'34
8182	Chronic peritonitis		'852	'1444	1432	720	712	'1663	'3107	1'15
8340	"		'878	'0788	965	380	585	'1330	'2118	1'68

1. In Register of Clinical Laboratory.

TABLE II

i	ii	iii	iv	v	vi	vii	viii	ix	x	xi
No. of case	Nature of case	Fluid contains chlorine g. aeq. in litre	Degree of dissociation 'α'	No. of molecules + ions.	Specific conductivity of fluid corrected (x 10 ⁵)	Conductivity of iii	Conductivity of a solution of Na ₂ CO ₃ with conductivity in column viii	No. of molecules + ions	Total concentration of electrolytes (v + ix)	ix — v

6196	Pleural fluid (cardiac) ...	... '107	'837	'1965	1065	875	190	'0424	'2460	0'21
6261	Peritoneal fluid (cardiac) ...	... '100	'838	'1838	1281	840	441	'0990	'3194	0'53
6425	" " (renal) ...	... '113	'834	'2035	1326	915	311	'0658	'2847	0'31
5903	" " (cirrhotic liver) ...	... '094	'842	'1731	1187	802	385	'0868	'2763	0'50
5710	" " (thrombosis of portal vein) ...	... '111	'834	'2035	1283	900	383	'0851	'3047	0'41
7191	" " (multiple effusions) ...	... '111	'834	'2035	1215	900	315	'0658	'2848	0'32
7381	" " (cirrhosis of liver) ...	... '113	'834	'2035	993	915	78	'0140	'2224	0'59
7559	" " (") ...	... '088	'845	'1623	974	780	194	'0426	'2121	0'26

TABLE III

7196	Fluid from leg (cardiac) ...	... '128	'827	'2338	1420	1100	320	'0658	'2078	0'28
e	" " (cardiac) ...	... '124	'837	'1910	893	855	38	'0990	'2900	0'51
6668	Cerebro-spinal fluid (tumour) ...	... '161	'814	'2920	1294	1260	34	'0990	'2284	0'33
6658	" " (syphilis) ...	... '157	'814	'2847	1259	1240	19	'0990	'2249	0'34
6643	Ovarian cyst ...	... '001	'970	'0019	1042	20	1022	'1442	'2484	6'01
6151	" " ...	... '040	'880	'0752	1075	360	715	'1680	'2755	2'23
7618	" " ...	... '145	'821	'2640	1080	1080	0	0	'2640	0'00
6178	" " (peritoneal) ...	... '001	'970	'0019	1104	20	1084	'1442	'2546	6'01

Study of the headings in the tables of results will render the meaning of the figures obvious, with the exception of those in the last column, which are obtained by dividing the osmotic concentration of the achlorides by that of the chlorides. Table I contains those fluids which may be classed as exudates (the result of definite inflammatory processes in the serous membranes); the second table shows the transudatory fluids (back-pressure effects, or renal dropsical fluids), and the third table shows the values for a few other fluids taken for comparison¹ with those of I and II. The last column is the one which is of chief interest. It reveals a very striking uniformity in the different classes of fluid. The fraction is seen to be greater than one in nearly all exudates, and to be invariably less than one in all fluids which are not associated with active inflammatory processes in the serous membranes. This shows that the osmotic concentration of the achlorides is preponderant in the former case. An examination of the first column will, however, show the almost constant deficiency of exudates in chlorides as shown by quantitative analysis: transudations contain a very considerable proportion of NaCl. The high chloride content of transudates is naturally associated with a low achloride content. The fact that the conductivity of the two sets of fluids is practically constant is of interest as showing that even in the presence of much albumen the conductivity will be the same as that of a fluid containing less albumen because of difference in electrolyte content. This indicates that in the exudates the low content of NaCl (which is more completely dissociated) counterbalances the retarding influence of the albumen on the conductivity.

In Table III the most striking feature is the usual preponderance of achlorides in ovarian cyst fluids. In fluid taken from the leg in cases of cardiac dropsy the achlorides are deficient, as one might expect.

To return again to Table I. The conductivity of the fluid in three cases of peritoneal malignant disease (6603, 6712, and 6838) will be seen to be practically the same, and these three cases are very

1. A full account of these is reserved: many other specimens have been examined.

like No. 6417, one of tuberculous peritonitis, as regards their conductivity. As regards degree of dissociation these fluids are practically identical, which shows that one cannot hope to diagnose the nature of the fluid by mere determination of the electro-conductivity. On the other hand, one might reasonably expect the products of metabolism in the case of cancer to be different from those of tuberculous masses, and therefore expect a difference in the constitution of the two classes of fluid. It becomes evident that, if this deduction be reasonable, the difference must be one concerned with non-electrolytes.

The next question is as to the reason for the different ratios ($C_{NaCl} : C_{achlor.}$) in the different fluids. The reason must be sought for in a difference in permeability of serous membranes to various ions under different circumstances. As regards inorganic salts the permeability seems to be only limited by the rate of migration of the ions of which the salts are composed. Cl passes through most readily, then NO_3 , and SO_4 ; Na passes more quickly than Mg (Höber 7). Another part of the explanation lies in the power which albumen has of attracting water to itself. Starling showed the effect of having a strong solution of albumen on one side of a serous membrane, and a weak solution containing salts on the other. Moreover, the laws of osmosis are different for watery solutions to what they are for albuminous solutions, and in the case of peritoneal fluids we have to deal with fluids which are frequently hypertonic. If there be as much albumen on one side as there is on the other there will be no movement of water from one side to the other.

It is easy to explain the characters of transudates. In renal disease there is decided inadequacy on the part of the kidney to get rid of NaCl, which consequently becomes more concentrated in the tissues and lymph spaces, &c. Water is necessary for its solution, and hence the effusions. This accounts for the excess of chlorides in these fluids.

Lastly, attention must be drawn to three of the cases. In one case (of peritoneal cancer) (8344) the ratio (last column) is less than one. In the second case (6677) the ratio is again less than one. The explanation for the former cannot be found at present, and it must

be left as an exception to the general rule. In the other case it becomes a question whether the fluid was really of inflammatory origin. The case was one of 'pleural effusion,' cause not stated. The third case is in Table II, No. 7191. There was thickening of all the serous membranes with effusions into them :—'polyorrhomenitis.' In the light of the facts made out one would say that in this case the fluid passes out for similar reasons to that which holds in the case of transudates in general. The nature of the disease is not yet fully established.

I am indebted to Prof. Moore for the suggestion that the characters of exudates depend on the cellular elements which occur in them. The presence, in cells, of more phosphates than chlorides, would explain the preponderance of achlorides in the fluid. This consideration would give an explanation for the finding in No. 7191, for with thickened peritoneum there would be very few cellular elements present.

The conclusions are :—

1. The method adopted is a convenient one, but requires cautious interpretation.
2. Transudates invariably contain an excess of NaCl over achloride electrolytes.
3. Exudates contain a relatively smaller number of chlorides. Whether they contain an absolutely greater number of achloride molecules per litre is not beyond dispute.
4. Ovarian cyst fluids usually contain more achlorides than chlorides.
5. It is substances other than electrolytes which are mainly of importance in the study of exudates.

In conclusion, I should like to express my indebtedness to many of the Honorary Staff of this Hospital for permission to record these observations on their cases.

LITERATURE

1. Bugarsky and Tangl, *Pflüger's Archiv.*, 72, 1898.
2. Ionenlehre, I, 500 et seq.
3. Physiological Chemistry. 4th ed.
4. See Moore and Roaf, *Bio-Chemical Jour.*, Vol. II, No. 1.
5. Hardy, *Journ. of Physiology*, Vol. XXXIII, 251.
6. *Naturwissenschaftliche Rundschau*, 1906.
7. *Pflüger's Archiv.*, 70, 74, 86.