CLXIII. THE ELECTROLYTE DISTRIBUTION AND THE ACID-BASE EQUILIBRIUM IN THE SERUM IN CASES OF NEPHRITIS AND NEPHRITIC ACIDOSIS¹.

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WE are presenting data obtained by the determination of the principal electrolytes of the blood in a series of cases of renal insufficiency with and without so-called renal acidosis. Various investigators, following Sellards [1914], have shown that if renal insufficiency is advanced the excretion in the urine of acid salts, particularly of phosphates and sulphates, is decreased. Marriott and Howland [1916] demonstrated the increase of phosphates in the blood in such cases. Denis [1921] was the first to show that inorganic sulphates might be increased in the serum in cases of renal insufficiency. Loeb and Benedict [1927] later observed a few cases of renal insufficiency in which the sulphate content of the serum was increased. More detailed studies of the inorganic sulphates in the serum in renal insufficiency have been reported by Wakefield [1929] and by Wakefield and Power [1930], Wakefield and Keith [1930], Wakefield *et al.* [1931]. Atchley and Benedict [1930] and Briggs [1932] recently have summarised the literature dealing with the acid-base equilibrium in nephritis. In their studies they reported values for the total base and for the anion distribution (chloride, carbonate, phosphate, protein, sulphate and ketone).

Our chief concern in this study was to establish the relation of inorganic sulphates to the various anions and cations in renal insufficiency and renal acidosis. Atchley and Benedict [1930] and Briggs [1932] determined sulphates but did not determine the various cations.

Methods of study.

The methods used for determination of sodium, potassium, calcium, magnesium, chloride, bicarbonate and phosphate were those described by Greene and Power [1931]. Sulphates were determined by the method of Wakefield and Power [1930], and lactic acid in tungstic acid filtrates by the method of

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Friedemann, Cotonio and Shaffer [1927]. In the present series we have determined the total base by summation of the values for the individual bases. Atchley and Benedict [1930] pointed out that the method of Stadie and Ross [1925] for the determination of total base "is a treacherous method, requiring constant use...to prevent errors. No method requires more vigilance to make it acceptable." We have found that with care the two methods give identical results, but in the present series the method of summation was used. Previous workers have used the formula of Van Slyke *et al.* [1928] for calculating the total base bound by protein. Greene and Power [1931] obtained a slightly larger value for the base bound by protein from their study of the equilibrium between serum and the *in vivo* dialysate. Both values are included in the accompanying tables.

Results.

The composition of the blood and serum in the ten cases studied is given in Table I. The electrolyte distribution and the acid-base equilibrium are shown in Table II.

The normal range for the total base in the serum is assumed to be 150 to 160 milliequiv./litre of serum. Atchley and Benedict [1930] reported 148 to 155 milliequiv.; we found 144 to 157 in a series of cases of ascites or hydrothorax of non-nephritic origin [Greene *et al.*, 1931]. Briggs [1932] reported values of 145 to 152 in cases of nephritis. In the present series the value for the total base ranged from 144.1 milliequiv. in case 9 to 167.5 milliequiv. in case 2 (Table II), with an average of 150.4 milliequiv. The difference between the total base contents of different samples of serum, as was to be expected, was due almost entirely to variations in the sodium. The changes in the potassium and magnesium were minimal, the calcium was less than 10 mg. in all cases and was reduced below 8 in cases 1, 3 and 5. A minimal value of 4.9 mg. was observed in case 3. In the majority of these cases the change was no greater than could be accounted for by either the increase in phosphates or the reduction in proteins, and there was fair agreement between the calcium actually determined and that calculated by the nomogram of Peters and Eiserson [1929]. Greenwald [1931] has pointed out the difficulties inherent in a mathematical formulation of the relationship between either the serum-protein or serum-phosphate and the calcium. Nevertheless, it may be accepted that in nephritis there is a tendency for the calcium content of the serum to vary directly with the proteins and inversely with the phosphates [Albright *et al.*, 1931; Farquharson and Tibbets, 1931; Peters and Van Slyke, 1931].

In three cases (1, 3 and 5) the calcium content of the serum was less than could be accounted for by the changes in protein or phosphates. The occurrence of renal rickets has been accepted by some as evidence of a primary disturbance in calcium metabolism associated with renal insufficiency. Greenwald [1918] found that intravenous injection of solutions of sodium sulphate will produce marked reduction in serum-calcium. The amounts of sulphates in the serum in nephritis are in no way comparable with those

Table I. *Composition of blood and serum in nephritis.*

Age years and sex	Urea mg./ 100 cc. whole blood	Crea- tinine mg./ 100 cc. whole blood	Protein g./ 100 cc. serum	Sodium mg./ 100 cc. serum	Potas- sium mg./ 100 cc. serum	Cal- cium mg./ 100 cc. serum	Mag- nesium mg./ 100 cc. serum	Chlo- rides NaCl mg./ 100 cc. serum	Carbo- n dioxide content volumes/ 100 cc. serum	Phos- phates P mg./ 100 cc. serum	Sul- phates SO ₄ mg./ 100 cc. serum	Lactic acid mg./ 100 cc. serum	Diagnosis
38 F.	415	15.0	6.80	322	23.3	6.2	2.8	560	26.2	12.0	77.6	5.2	Hypertension, grade 4; renal arteriosclerosis; uraemia
35 M.	339	18.8	6.12	353	28.5	8.0	3.4	621	40.3	12.6	28.4	10.4	Renal arteriosclerosis; uraemia
19 M.	315	11.0	6.05	327	24.2	4.9	2.2	625	21.5	9.5	39.3	3.4	Chronic glomerulonephritis; renal dwarfism
22 M.	271	12.0	6.35	304	23.7	8.0	2.4	475	67.7	10.5	25.3	5.0	Chronic glomerulonephritis; uraemia
60 M.	219	7.0	6.35	325	22.0	6.5	2.4	638	36.7	8.3	24.6	6.1	Hyperostate uremia; pyelonephritis
54 M.	151	8.1	5.45	308	25.2	8.3	3.1	582	50.9	5.3	19.6	6.1	Renal arteriosclerosis; uraemia
58 F.	115	5.0	6.85	316	21.9	9.6	3.0	637	41.7	5.4	12.0	4.5	Renal arteriosclerosis; uraemia
36 F.	95	8.1	6.95	305	22.9	9.1	3.0	608	43.8	5.3	16.2	6.3	Chronic glomerulonephritis
30 M.	10	1.0	4.54	309	19.3	8.2	2.8	581	58.3	3.8	6.5	12.8	Chronic glomerulonephritis with oedema
24 M.	23	1.3	4.80	317	20.3	8.4	2.0	596	64.2	3.9	3.5	4.3	Chronic lipoid nephrosis with oedema

Table II. *Electrolyte distribution of serum in nephritis: milliequiv./litre of serum.*

Case	Sodium	Potas- sium	Cal- cium	Mag- nesium	Total base	Chlo- rides	Bicar- bonate	Phos- phates	Sul- phates	Lactic acid	Deter- mined acids	Base proteinate		Total acids		Total base less total acids as	
												Calcu- lated by formula		Deter- mined B pro- teinate formula		Calcu- lated by formula	
												I*		II		I*	
1	140.0	6.0	3.1	2.3	151.4	95.7	11.2	6.9	16.2	0.6	130.6	15.7	21.8	146.3	152.4	+ 5.1	- 1.0
2	153.4	7.3	4.0	2.8	167.5	106.1	17.0	7.3	5.9	1.1	137.4	14.4	19.3	151.8	156.7	+ 15.7	+ 10.8
3	142.1	6.4	2.5	1.8	152.8	117.1	9.1	5.5	8.2	0.4	140.3	12.5	14.3	154.6	159.4	- 1.8	- 6.6
4	132.2	6.1	4.0	2.5	144.8	81.4	29.0	6.1	5.2	0.6	122.3	22.5	15.7	138.0	143.3	+ 6.8	+ 1.5
5	141.3	5.6	3.3	2.0	152.2	109.1	15.5	4.8	5.1	0.6	135.1	17.1	15.0	150.1	155.2	+ 3.0	- 1.4
6	133.9	6.4	4.2	2.5	147.0	101.4	21.7	3.1	4.1	0.7	131.0	16.0	13.0	144.0	148.4	+ 3.0	- 2.6
7	137.3	5.6	4.8	2.5	150.2	108.8	17.3	3.1	2.5	0.5	132.2	18.0	16.2	148.4	153.8	+ 1.8	- 6.0
8	132.6	6.0	4.5	2.5	145.6	103.9	18.5	3.1	3.6	0.6	129.7	15.9	16.4	146.1	151.6	- 0.5	- 2.6
9	132.7	5.0	4.1	2.3	144.1	99.9	21.5	2.0	1.3	1.4	126.1	18.0	10.7	136.8	140.4	+ 7.3	+ 3.7
10	137.8	5.2	4.2	1.6	148.8	101.9	27.5	2.0	0.7	0.5	132.6	16.2	11.3	143.9	147.7	+ 4.9	+ 1.1

* Base bound by proteins as calculated by formula I [Van Slyke *et al.*, 1928].† Base bound by proteins as calculated by formula II [Greene *et al.*, 1931].

+ Represents excess of base.

- Represents excess of acid.

present in the experiments of Greenwald, but it is possible that retention of sulphates is one factor in the reduction of the serum-calcium in these cases.

The changes in the various anions are more striking than those in the various bases. Atchley and Benedict [1930] point out the difficulty of explaining the apparent loss of chlorides in many cases of nephritic acidosis. The chlorides were essentially normal in the majority of these cases. There was marked reduction in case 4 in which the chlorides fell to a level of 81.4 milliequiv. in consequence of prolonged vomiting. This case is of interest in that there was a compensatory increase in the bicarbonate to make up for the low values for chloride. Briggs [1932] likewise minimises the extent of the change in chlorides produced solely by impaired renal function. There was retention of sulphates and of phosphates to the extent of 10 milliequiv. or more in the first five cases (Table I). Phosphates and sulphates tend to be retained in the same cases, but apparently there is no necessary relationship between the degree of retention of either. The maximal value for the two was 23.1 milliequiv. (15 % of the total base). Under these conditions the part played by retention of phosphates and sulphates in the production of acidosis is manifest.

The data given in Table I for the lactic acid content of the serum indicate that there was no retention of this substance in the cases studied. On the contrary, the values seem to be somewhat lower than usual. According to Noshi [1929], the concentration of lactic acid in the serum is only slightly higher than that in whole blood. Recent determinations of the lactic acid in whole blood, by the same methods as were used in the present study, have been made by Campbell and Maltby [1928] in a series of thirty-five cases, in which metabolic abnormalities were not present. The lactic acid content of the blood of these fasting subjects averaged 14.1 mg./100 cc.; in thirty-one cases (88.5 %) it fell within the range 10–17 mg./100 cc. In a less extensive series of determinations on fourteen adult subjects without diabetes, Koster *et al.* [1930] obtained somewhat higher values, averaging 21.3 mg./100 cc. Bishop [1931] determined the lactic acid in the blood of five normal subjects by means of a slight modification of the Friedemann, Cotonio and Shaffer [1927] method, with results ranging from 10.6 to 16.0 mg. and averaging 13.2 mg./100 cc. Wakefield and Greene [1930] found values of 7–26 mg. in a series of cases of various types of hepatic disease.

In comparison with these data, it is evident that the values for the lactic acid content of the serum are markedly lower in the present series of cases. The lactic acid in the blood tends to be low in conditions of experimental acidosis [Anrep and Cannan, 1923] and conversely to increase in alkalosis [Frank, Leiser and Weisz, 1930]. In the cases studied, however, there was no apparent relationship between the amount of lactic acid present and the degree of acidosis, as indicated by the carbon dioxide content of the serum. It may be therefore that the low values for the lactic acid are consequent on the prolonged rest in bed undergone by these patients rather than on other factors.

Jervell [1929] studied the lactic acid content of the blood in a series of cases of acute nephritis by means of a method apparently much less specific than the one we used, but found no evidence for retention of lactic acid. Neither did he find the decreased values such as we have encountered in most of the cases under consideration here. In the latter, lactic acid plays a negligible part so far as the acid-base balance is concerned. Atchley and Benedict [1930] have shown the same to be true of the different ketone substances.

When the sum of the determined acids is subtracted from the value for total base, there is an undetermined fraction of 12.5–30.1 milliequiv. Almost all, if not the entire amount, of this undetermined fraction represents base bound by protein. If the formula of Van Slyke *et al.* [1928], which was determined by the titration of the purified proteins of horse-serum, is used for calculation of the latter, and this value is then added to the sum of the determined acids, there remain, on the average, 4.4 milliequiv. of base unaccounted for, and which presumably indicate the presence of undetermined organic acids. If the figures of Greene and Power [1931], which were calculated from the composition of the dialysate of dog's blood obtained *in vivo*, and from the comparative composition of serum and transudates of patients in hospital, are used for the calculation of the base bound by protein, and this value is added to the sum of the determined acids, the resulting figures for the total anions, on the average, are larger by 0.4 milliequiv. than the values for total base. The differences between the values for the total base and the sum of the acids in either case are within the analytical error of the method for determination of total base.

The values for the base-binding power of the serum-proteins were determined by Van Slyke *et al.* [1928] by the titration of dialysed protein solutions with sodium bicarbonate. The values which they obtained agree well with the values found by Greene and Power [1931] for the sodium bound to protein. Greene and Power also found that in the serum *in vivo*, potassium, calcium and magnesium combine with small amounts of protein and so increase the value for the total base bound by protein. In the present instance the base bound by protein was calculated on the assumption that the serum contained a normal albumin-globulin ratio and that the p_H was 7.35. Disturbances in both p_H and in the albumin-globulin ratio are to be expected in nephritis with consequent shifts in the amount of base bound by protein, although these changes presumably are slight. Regardless of the particular figures chosen, the fact remains that when the chlorides, bicarbonate, phosphate, sulphate and lactate in serum are determined, protein will account for practically all the remaining base. A small amount of unidentified organic acids may be present, but, if so, they are apparently negligible in quantity.

Discussion.

The literature dealing with changes in individual electrolytes in the serum in cases of nephritis and nephritic acidosis has been reviewed in detail by

Peters and Van Slyke [1931], and need not be discussed again here. In general, the changes observed in the present series of cases accord with previous observations. In some cases there was reduction in total base, but this change was neither as uniformly observed nor as marked in degree as suggested by previous investigators. When the total base was reduced, the change was due almost entirely to changes in the amount of sodium. Calcium was reduced in several cases, the reduction being associated in part with reduction in the serum-proteins, and perhaps in part with the retention of phosphates and sulphates. There was no evidence for the accumulation in the blood of significant amounts of undetermined organic acids. In the majority of instances, the chlorides were normal, but the importance of vomiting in causing a reduction in the serum-chloride should be emphasised. There is an accumulation of phosphates and sulphates due presumably to renal insufficiency. This retention of inorganic acids plays an appreciable part in the production of acidosis. The changes in bicarbonate depend on the balance between the opposing effects of loss of chloride on the one hand and the loss of base and retention of phosphates and sulphates on the other. Usually, the bicarbonate is decreased.

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