XXX. THE BALANCE OF ANIONS AND KATIONS IN THE PLASMA IN NEPHRITIS.

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THIS work was begun with the intention of finding what anions, accumulated in the plasma, were responsible for the occurrence of acidosis, as shown by diminution of plasma $[\text{HCO}_3^-]$, in patients with nephritis. Such an accumulation of anions might be due either to a general impairment of excretion resulting in the retention to a greater or less degree of all the anions which should be excreted in the urine, or to a specific inability to excrete some particular anion resulting in the retention of this anion alone.

In order to decide to what degree any particular anion is responsible for a diminution of plasma $[\text{HCO}_3^-]$ it is necessary to know the concentrations of all the anions and kations in the plasma; for an increase of one anion will not cause an acidosis if accompanied by a corresponding increase of kation or diminution of some other anion. This explains the lack of correspondence found for example by Denis and Minot [1920] between accumulation of phosphate in the plasma and diminution of plasma bicarbonate.

It is therefore necessary to calculate the balance between the anions and kations in the plasma of patients with acidosis, and for purposes of comparison in that of other patients.

In making this balance other points with regard to individual constituents of plasma and the balance between them have arisen and I will consider these besides the original question of the cause of acidosis.

Table I. *Balance of anions and kations in plasma of control cases.*

<i>Anions.</i>					
Average of control cases	[HCO ₃ ⁻]	—cc. of CO ₂ per 100 cc.	61.0	0.0277	g. equivalents per litre
	[Cl ⁻]	—g. NaCl	0.600	0.1026	” ”
	[HPO ₄ ⁻⁻]	—g. P ₂ O ₅	0.0066	0.00165	” ”
Denis [1921]	[SO ₄ ⁻⁻]	—g. S	0.0008	0.0005	” ”
	Protein	—and organic acids		0.0105	” ”
				Total	0.143
<i>Kations.</i>					
Average of control cases	[Na ⁺]	—g. Na	per 100 cc.	0.030	0.1305 g. equivalents per litre
Myers and Short [1921]	[K ⁺]	—g. K	”	0.020	0.005 ” ”
	[Ca ⁺⁺]	—g. Ca	”	0.010	0.005 ” ”
	[Mg ⁺⁺]	—g. Mg	”	0.003	0.0025 ” ”
				Total	0.143

Table II. *Balance of anions and kations in cerebrospinal fluids from patients with no evidence of nephritis. These fluids contained only minute traces of protein.*

<i>Anions.</i>					
Average of these cases	[HCO ₃ ⁻]	—cc. of CO ₂ per 100 cc.	62.0	0.028 g. equivalents per litre	
	[Cl ⁻]	—g. NaCl	0.735	0.126	" "
	[HPO ₄ ⁻⁻]	—g. P ₂ O ₅	0.004	0.001	" "
			Total	0.155	
<i>Kations.</i>					
Average of these cases	[Na ⁺]	—g. Na	per 100 cc.	0.337	0.147 g. equivalents per litre
Myers [1917]	[K ⁺]	—g. K	"	0.022	0.005 " "
Halverson and	[Ca ⁺⁺]	—g. Ca	"	0.005	0.0025 " "
Bergeim [1917]	[Mg ⁺⁺]	—g. Mg	"	0.003	0.0025 " "
			Total	0.157	

The figure given for Mg in cerebrospinal fluid is that for plasma as I can find no estimate of magnesium in cerebrospinal fluid.

BALANCE OF ANIONS AND KATIONS IN NORMAL PLASMA.

The balance of the average values of anions and kations in my control cases is shown in Table I. There is an excess of kations unaccounted for by Cl⁻, HCO₃⁻ and HPO₄⁻⁻ equal to about 0.010 g. equivalents per litre. This is combined with protein and anions of organic acids. Probably organic acids only account for a small fraction of these kations. In cerebrospinal fluid which contains practically no protein, the excess of kations does not occur, as shown in Table II. Also Greenwald and Lewman [1922] have recently published a method by which they estimate the amount of kations in plasma combined with HCO₃⁻ and with protein together. In the normal cases in which the bicarbonate is given, the kations combined with protein are equivalent to 0.0097 and 0.0136 g. equivalents per litre, and are therefore about equivalent to the amount of base in plasma unaccounted for by HCO₃⁻, Cl⁻ and HPO₄⁻⁻.

Kramer and Tisdall [1922] have published a table of average values of the anions and kations in plasma showing the excess of bases unaccounted for as 0.025 g. equivalents per litre. I think it probable that the "average" value taken by them for plasma [Na⁺] is high in proportion to their "averages" for [Cl⁻] and [HCO₃⁻].

I have estimated only the [HCO₃⁻], [Cl⁻], [HPO₄⁻⁻] and [Na⁺]. Calcium may vary between 0.006 and 0.011 %, or between 0.003 and 0.0055 g. equivalents per litre, potassium between 0.010 and 0.020 % or between 0.0025 and 0.005 g. equivalents per litre. Variations of magnesium are negligible as the amount is so small. If, therefore, we add to the [Na⁺] 0.0125 g. equivalents we shall obtain an estimate of the total kations with a maximum error of 0.0045 g. equivalents per litre, not more than 3.5 % of the total kations, and little more than the errors in sodium estimation.

As normally the principal anions, HCO₃⁻, Cl⁻ and HPO₄⁻⁻, are about equivalent to the Na⁺, and therefore the other kations to the normal protein, it is possible to omit these last items in balancing the anions and kations.

Taking them into account merely involves adding two equal amounts to both sides of the equation.

In such a balance an accumulation of Cl^- or HPO_4^{--} in the blood, causing a diminution of plasma bicarbonate, is shown directly; while, if an accumulation of another acid ion, such as SO_4^{--} , occurs, its presence is shown by an excess of Na^+ unaccounted for by the anions estimated. Such an accumulation is illustrated in Table III; the excess of Na^+ is equivalent to the keto-acids within the limits of error of the method.

As I originally intended to consider acidosis only, the patients in this series have been selected mainly from severe cases of nephritis, who might be expected to have some disturbance of their acid base regulation.

Table III.

Excess of Na^+ unaccounted for by HCO_3^- , Cl^- , and HPO_4^{--} in plasma in ketosis.

Case	p_{H}	$[\text{HCO}_3^-]$	$[\text{Cl}^-]$	$[\text{HPO}_4^{--}]$	Sum of three anions	$[\text{Na}^+]$	Excess Na^+	β -Hydroxy- butyric acid and aceto-acetic acid	
					Gram equivalents per litre				
60	7.0	0.0055	0.112	0.002	0.1195	0.144	0.0245	0.0215	Diabetic coma; Moderate hyperpnoea. Blood sugar 0.44 %. Died next day.
61	7.4	0.0215	0.099	0.002	0.1225	0.1305	0.008	0.0065	Diabetes; prolonged ketosis without coma. Blood sugar 0.26 %.

Total acetone bodies were estimated by the method of Van Slyke; 20 % was assumed to be present as acetone.

Some cases of heart failure have been included to illustrate the changes that may be found in this condition.

METHODS.

For plasma bicarbonate when determined without p_{H} Van Slyke's [1919] titration method was used. When p_{H} and plasma bicarbonate were determined, methods of Van Slyke [1922] and Cullen [1922].

The blood was obtained through a needle with a short piece of rubber tubing attached; a piece of rubber tubing was fixed tightly round the patient's upper arm. After the needle was inserted the blood was allowed to flow, to allow all congestion from the constriction of the arm to pass off, and the tubing was then connected to the entry tube of a 25 cc. centrifuge tube as shown in Fig. 1. By withdrawing the wide part of this entry tube a short distance from the hole in the stopper, air was allowed to escape as the blood flowed in. The centrifuge tube had previously been filled with alveolar air in order that the CO_2 tension of the oil and any air with which the blood came in contact might approximate as nearly as possible with that of the blood taken. When the oil began to overflow the entry tube was removed, a glass plug inserted,

and the tube inverted three or four times. The effect of the small bubble of air left in the tube would be negligible. The blood was then rapidly centrifuged and the plasma thus obtained was removed with a pipette through the hole in the stopper for p_H , bicarbonate, Cl and P_2O_5 determinations. These therefore were determined at the CO_2 tension of the patient's venous blood.

The solutions of known p_H used for p_H determinations were made according to the formula in Cullen's paper, from pure salts recrystallised. These solutions contained the theoretical amount of phosphorus determined gravimetrically. The p_H is given to the nearest 0.05 as it was occasionally difficult to get a more exact match.

Chlorides were estimated by the Volhard method on filtrates after precipitation of protein by trichloroacetic acid. Precipitation with trichloroacetic acid is less complete than with picric and tungstic acids, and in some cases some difficulty was experienced in getting the silver chloride to flocculate satisfactorily, probably owing to proteoses left unprecipitated. In two cases, in one of which the flocculation did not take place readily and in the other the chloride value was very low, the result was checked by an incineration method.

In some cases, when sufficient blood was not available for estimation of chlorides in whole blood, the corpuscles separated from the plasma as above were used for chloride determination. As the separation was done rapidly it is probable that the corpuscles were not completely separated from plasma and that the Cl values found are too high; this would occur especially in the more normal cases in which the corpuscles sink slowly. These figures therefore are upper limiting values only.

Inorganic phosphates. The figures given in brackets were estimated by the original method of Bell and Doisy [1920] before the effect of oxalate was realised. The amount of oxalate used was minimal, and the figures are therefore probably a little too low. Later the modification given by Denis and Meysenbug [1922] and the method of Briggs [1922] were used.

Sodium was estimated by the method of Kramer and Tisdall [1921]. This method gave theoretical results with pure solutions of sodium chloride, duplicates agreed and added sodium chloride was satisfactorily recovered from plasma or serum.

Determinations were mainly made on plasma as more can be obtained from a given amount of blood, and the delay and risk of haemolysis during the separation of serum is avoided by using plasma.

Determinations on plasma and serum from the same blood agreed.

This method is liable to an error of $\pm 3\%$ which is of importance in considering the balance of acids and bases.

Calcium was determined in a few cases by the method of Clark [1921].

Fig. 1.

Plasma proteins were determined in some of the cases by Dr Villett by the method of Wu [1922, 2]. He has kindly permitted me to use his figures.

Blood urea was estimated by the urease method.

In Table V [HCO_3^-], [Cl^-], [HPO_4^{--}], and [Na^+] are given in g. equivalents per litre; "Sum" represents the sum of the g. equivalents per litre of the anions.

Chlorides in plasma.

The concentration of Cl^- in plasma is affected by changes of the tension of CO_2 which cause a migration of Cl^- between the red corpuscles and plasma, but the changes produced thus are much less than the variations found in these cases. Thus Doisy, Eaton and Chouke [1922] found the plasma [Cl^-] fall from 0.65 to 0.61 % NaCl (0.111 to 0.104 g. equivalents per litre), in human blood with an increase of CO_2 tension from 23.3 to 72.5 mm. These values for CO_2 tension are extreme; such deviations from normal CO_2 tensions do not occur in normal persons, and were only found in the extreme cases in this series. In normal persons, also, variations of plasma [Cl^-] occur much greater than those caused by variations of CO_2 tension. Thus in the series given by Wu [1922, 1] the values ranged from 0.56 to 0.67 % NaCl—0.096 to 0.1145 g. equivalents per litre. His figures for the Cl in the corpuscles also show that the variations in plasma were not due to migration of Cl^- in and out of the corpuscles, as high concentrations in plasma were usually associated with high values in corpuscles and *vice versa*.

The variations found by Wu are greater than those usually found, *e.g.* by Norgaard and Gram [1921], although Wu and Norgaard and Gram are in fair agreement as to the average value, about 0.62 % or 0.104 g. equivalents per litre.

The plasma Cl in this series was on the whole low. Out of 98 determinations 27 were under 0.096 g. equivalents per litre.

In another series of 100 patients taken without selection of the more severe cases the plasma [Cl^-] was under 0.096 g. equivalents per litre in 7.

All patients with plasma [Cl^-] under 0.092 g. equivalents per litre were severely ill, and those with values under 0.0855 still more so. In cases such as (31), (32), (38) and (39) which steadily became worse the plasma [Cl^-] steadily fell; this did not always occur however, as for example in case (33). Cases (6) and (37) had very low figures when at their worst with an increase on improvement.

There is no relation between the type of nephritis and the plasma [Cl^-]. Oedema occurred both with normal and low values.

There is no evidence that the variations were due to variations of CO_2 tension or reaction of the plasma or to migration of Cl^- between plasma and corpuscles¹. Thus case (47) with an alkaline plasma had a plasma [Cl^-]

¹ It is not suggested that migration of Cl^- between corpuscles and plasma did not occur, but that it was overshadowed by other changes.

0.093 g. equivalents per litre and the low plasma $[Cl^-]$ of cases (31), (32) and (39) was associated with low values for Cl in the corpuscles.

Phosphates in plasma.

The plasma $[HPO_4^{--}]$ varies in the same sense as the blood urea but not proportionately; which is to be expected from the large and variable excretion of phosphate which takes place in the faeces also. Two cases, (39) and (40), especially have high blood urea with no increase of plasma $[HPO_4^{--}]$. In these cases Cl appears to have been stored in the tissues and it is possible that a similar storage of HPO_4^{--} occurred; but one cannot exclude the possibility that the excretion of HPO_4^{--} may have been performed completely by the intestine, so that there was actually no retention. It is remarkable that in these two cases the kidneys were entirely out of action.

Sodium in plasma.

Two values for normal sodium concentration in plasma are found in the literature. Those of Kramer [1920] 0.28 to 0.31 %, 0.122 to 0.135 g. equivalents per litre, and those of Kramer and Tisdall [1921], 0.326 to 0.350 %, with average of 0.33 %, 0.142 to 0.152, with average 0.144, g. equivalents per litre. My figures for the mild cases of nephritis and cases without evidence of kidney damage agree better with the first.

The values found in this series were on the whole low, but reductions of $[Na^+]$ as great as those of $[Cl^-]$ did not occur. Except in case (37) (10. viii. 22) the reduction of $[Na^+]$ was not more than equivalent to that of $[Cl^-]$ in the same patient.

It is remarkable that, as has long been known for Cl, as is shown by Myers and Short [1921] for K, various workers for Ca and by these results for Na, no accumulation of these constituents occurs in the plasma in nephritis, even with extreme degrees of renal inefficiency, which are accompanied by great increase of plasma urea and HPO_4^{--} . This points to methods of regulation of the amounts of the former substances in the plasma other than excretion through the kidneys; which methods may be retention of water, and deposition in the tissues.

In case (39) the water retention must have been inadequate to keep down the Cl concentration; the NaCl retained during 15 days on ordinary diet with no restriction of Cl intake must have been at least 45 g., which would require 11 litres of water to dilute it to the concentration of the plasma at death; an amount which could not have been retained without gross oedema. The second process therefore, deposition in the tissues, must have played a large part. His Na intake was increased by large doses of sodium bicarbonate, the absorption of which is proved by increase of the plasma bicarbonate to normal, and its subsequent maintenance at normal in spite of increasing amounts of undetermined acids in the plasma; but the plasma $[Na^+]$ did not increase,

instead towards the end it fell. Accompanying this there was a steady fall of $[\text{Cl}^-]$. This suggests that Na also was deposited in the tissues so that, instead of the plasma bicarbonate being increased by the absolute increase of $[\text{Na}^+]$ in the plasma, it was increased by removal of Cl^- into the tissues along with the extra base supplied, leaving a relative excess of Na^+ in the plasma.

A similar effect of treatment with bicarbonate is seen in other cases, (13), (26), (30) and (35), although in these we have not such satisfactory evidence that the result is not brought about by water retention; in case (35) especially the output of water during two days of bicarbonate administration fell below the intake by 2 litres, although after the administration was stopped output was equal to intake.

The low values of plasma $[\text{Cl}^-]$, and to a less degree of plasma $[\text{Na}^+]$, point to some disturbance of the mechanisms that regulate these constituents. It is probable that in most of the cases water retention played a large part; such water retention would explain the low values of cell volume and total proteins¹. It is probable, however, that tissue deposition, as in (39), occurs also in other cases; in case (31) for example, in which output equalled intake in spite of profuse sweating until the last three days, water retention alone does not seem adequate to explain the fall in plasma $[\text{Cl}^-]$ which occurred in spite of retention of about 1 g. of NaCl a day.

There is further evidence of such a deposition of chloride in the tissues in the high Cl content of the heart muscle in cases (39) and (33)—0.24 and 0.31 % of sodium chloride as compared with 0.16 and 0.19 in the hearts of two healthy men who were killed suddenly in accidents. Such deposition in the tissues was shown by Wahlgren [1909] to occur in dogs after large doses of sodium chloride; he found however that the percentage increase in muscle was less than in other tissues, so that had some other organ been chosen for analysis in these two cases the increase found might have been greater. In cases (26), (32), (33) there is a striking increase in the $[\text{Cl}^-]$ and $[\text{Na}^+]$ in the cerebrospinal fluid in comparison with that in the plasma.

In cases (3), (6), (31), (32) and (38) the excretion of Cl in the urine was continued although the plasma Cl had fallen well below the recognised threshold.

It is reasonable to suppose that these changes are all due to some alteration of the mechanism which regulates the distribution of sodium chloride between plasma and other body fluids. It is possible that this is the result of changes in the plasma proteins.

The low figures found for $[\text{Cl}^-]$ and $[\text{Na}^+]$ are of great importance in the balance of acids and bases. Such changes make it impossible to calculate what effect accumulation of some acids such as phosphoric will have on the plasma bicarbonate unless these constituents also are estimated.

¹ The change in plasma proteins however is more than a mere reduction of total protein; there is a change in the proportions of the protein fraction and actual increase of fibrinogen.

BALANCE OF ACIDS AND BASES.

In the cases of hyperpiesia the relation between the sum of the anions estimated and the sodium is the same as in the control cases. In the mild cases of nephritis (2), (4), (6), (14) and (15) there is slightly more sodium in relation to anions but not enough to justify any conclusion. Also in several of the more severe cases, (26) (except on 27. iv. 22), (30), (34) and (38) (on 28. vii. 22) the relation differs little from that in the controls.

Table IV.

	Average values in g. equivalents per litre				
	[HCO ₃ ⁻]	[Cl ⁻]	[HPO ₄ ⁻]	Sum	[Na ⁺]
Control	0.0274	0.1026	0.0016	0.1316	0.1305
Hyperpiesia	0.032	0.099	0.002	0.133	0.131
Mild cases	0.029	0.103	0.002	0.134	0.1365

But in 18 cases (1, 9, 12, 13, 18, 23, 25, 26, 28, 29, 31, 32, 33, 35, 39, 40, 41 and 52), the Na exceeded the sum of these three anions by more than 0.0085 g. equivalents per litre, the maximum error to which this method of estimating the total kations is liable. Of these, 16 were frankly severe cases with blood urea raised. Of the remaining two, one case, (52), had severe heart failure, and one case, (18), was an old man with an enlarged prostate and considerable impairment of renal efficiency as tested by phenolsulphone-phthalein excretion and urea concentrating power.

A steady increase of this excess of kations is seen in cases (31), (32) and (39) as the blood urea rose, while in cases (6) and (1) the excess of kations fell as the patient improved and the blood urea fell.

This excess of kations may be combined (1) with protein or (2) with undetermined acid ions.

The changes in plasma proteins that occur in nephritis are reduction in total protein and albumin, increase of fibrin and a relative and sometimes absolute increase of globulin. These changes are seen in cases (7), (9), (11), (31), (32) and (33). It is difficult to see how such changes can result in an increase of kations combined with protein unless we suppose the fibrin has a much greater power of combining with kations than have albumin and globulin. In case (32) the excess of kations was much greater when the total protein was 6.04 % than when it was 7.89 %; in case (33) with high fibrin there was no excess of Na⁺.

In the cerebrospinal fluids of cases (26), (32) and (33) there is no excess of kations, as in the plasma taken before and after, but the difference between the sum of the three anions and the Na⁺ is the same as in normal cerebrospinal fluids. This might be due to the absence of protein, but can be just as well explained by supposing that there is a much lower concentration of the unknown anions in cerebrospinal fluid than in plasma, just as is the case with phosphoric acid, and as found by Berglund [1922] with amino-acids, creatine and uric acid.

It is therefore probable that the excess of kations is not combined with protein but with some anions which have not been determined.

Undetermined acid in the form of keto-acids probably accounts for the excess in case (40) and possibly in the form of lactic acid in cases (26) and (52).

In the other cases it is probable that no one anion is responsible, but a mixture of anions which should be excreted in the urine—among these SO_4^{--} —which has been found by Denis [1921] in nephritic blood in sufficient amount to produce this effect.

In the ascitic fluid of case (39), post mortem there were 12 mgm. S as sulphate per 100 cc., or 0.0075 g. equivalents per litre. Such a concentration would account for part of the excess of kations of 0.021 g. equivalents per litre found in the plasma.

However this sulphate may have been produced by bacterial changes which had taken place in the fluid.

It is hoped to evolve a method of sulphate estimation applicable to the small quantities of plasma available.

Plasma bicarbonate and reaction.

Owing to the migration of Cl^- between red corpuscles and plasma with variations of the CO_2 tension, it is necessary to have some method of distinguishing low plasma bicarbonate due to accumulation of acid in the blood from low plasma bicarbonate due to the exposure of an otherwise normal blood to abnormally low CO_2 tensions with consequent migration of Cl^- into the plasma. Charts I and II serve this purpose. Abscissae represent venous CO_2 tension, ordinates $[\text{HCO}_3^-]$ in g. equivalents per litre. Since the hydrogen ion concentration of plasma is proportional to the ratio of the CO_2 tension to the plasma bicarbonate, the points representing plasmata with the same hydrogen ion concentration and therefore the same p_{H} must all lie on a straight line passing through the origin. Such lines for p_{H} 7.1 to 7.6 are shown; they were calculated by the formula given by Austin *et al.* [1922].

The point representing a plasma can be determined by its $[\text{HCO}_3^-]$, giving the ordinate, and p_{H} , giving the p_{H} line on which it lies, or CO_2 tension, giving the abscissa.

Points for plasmata separated from normal bloods at varying CO_2 tensions may lie within the shaded area. The two curves shown are taken from the paper of Doisy, Eaton and Chouke [1922] and the limits of the normal area are calculated from the limits of the normal dissociation curves given by Peters, Barr and Rule [1921]. If a low $[\text{HCO}_3^-]$ is due to the separation of the plasma from otherwise normal blood at low CO_2 tension, the point for the plasma will still fall inside the normal area, while if it is due to accumulation of anions in the blood (acidosis) the points will fall below the normal area. If there is an excess of kations in the blood (alkalosis) the points will fall above the normal area.

The normal p_H lies between 7.3 and 7.4 the average being nearer 7.4. Normal cases should therefore fall between these two lines.

The plasmata of control cases all fall within the normal area, and with the exception of case (56) have normal p_H . Case (56) is an example of the effects of hyperpnoea reducing the venous CO_2 tension and causing a high p_H and comparatively low plasma $[\text{HCO}_3^-]$. A similar condition has been produced outside the body in case (59) by not taking precautions to avoid loss

of CO_2 . In the balance of acids and bases in these two cases we find evidence of the migration of Cl^- into the plasma in the increase of $[\text{Cl}^-]$ above the average without corresponding increase of $[\text{Na}^+]$. As closely as can be expected with the errors to which the method is liable the fall in $[\text{HCO}_3^-]$ is accounted for by this relative increase of $[\text{Cl}^-]$.

In the cases of heart failure two (48) and (52) (b) and (c) fell at the upper and lower limits of the normal area and three (49), (51) and (52) have high p_H .

This high p_H in heart failure which is consequent on a low venous CO_2 tension was also found by Fraser, Ross and Dreyer [1922]. It may be due either to shortage of oxygen leading to the circulation of some products of incomplete combustion other than acid, which stimulate the respiratory centre with resulting increase of lung ventilation, so that CO_2 which passes out of the blood into the alveolar air more readily than O in the reverse direction is washed out of the blood; or to a local stagnation of the circulation in the respiratory centre leading to local accumulation of CO_2 and stimulation of the respiratory centre although the CO_2 tension in the general circulation is being abnormally reduced.

Chart II. Nephritis.

Case (52) affords an example of the variation of p_H and bicarbonate that may occur in heart failure from interaction of the two factors hyperpnoea and acid accumulation. On 4. xi. 22 hyperpnoea had reduced her CO_2 tension with resulting high p_H . On 10 and 11. xi. 22, when much worse, CO_2 elimination was also impaired with the result that the venous CO_2 tension rose in

spite of increased hyperpnoea, while there was an accumulation of undetermined anions resulting in reduction of the $[\text{HCO}_3^-]$; in consequence of these two changes the plasma p_{H} fell. With great clinical improvement on 14. xi. 22 her $[\text{HCO}_3^-]$ rose above the value on 4. xi. 22 but her CO_2 tension remained still somewhat low although the hyperpnoea was hardly noticeable.

In cases (49) and (52) the migration of Cl^- is not detectable, being obscured by other changes.

The plasmata of two cases, (45) and (46), of the three cases of hyperpiesia in which the p_{H} was determined, fell in the normal area, and of one (47), who had been treated with large doses of sodium bicarbonate, above this area.

Cases (46) and (47) with high p_{H} had disturbances of the central nervous system which may have affected their respiratory centres. Case (47) was also in considerable distress from violent headache, which may also have caused hyperpnoea. In these two cases the excess of plasma $[\text{Cl}^-]$ and low bicarbonate are not seen; in case (47) the absence of high plasma $[\text{Cl}^-]$ is explained by the low $[\text{Cl}^-]$ in the whole blood, so that even with a lower proportion of this Cl^- than usual in the corpuscles that in the plasma would not be high.

In all the mild cases of nephritis (Chart II) the plasma $[\text{HCO}_3^-]$ fell within the normal area. The average $[\text{HCO}_3^-]$ for the five cases (2, 4, 5, 14 and 15) was 0.0287 g. equivalents per litre which agrees closely with that for the controls. In one case (15) (pyelitis of pregnancy) the plasma p_{H} was high. It is not improbable that a slight degree of hyperpnoea and consequent high plasma p_{H} occurs in pregnancy apart from any pathological condition. In this case as in case (47) the $[\text{Cl}^-]$ in the plasma and blood was low.

Of the severe cases also a large number fell in the normal area; among these are cases (26, *b*) (2. v. 22), (33), (34), (39 *d*) (29. vi. 22) with high plasma $[\text{HPO}_4^{--}]$ or undetermined anions showing that in these cases kation had been retained in sufficient amount to neutralise these anions. Cases (3), (22 *a* and *b*) (5. vii. 22 and 13. vii. 22) (38 *b* and *c*) (3. vii. 22 and 28. vii. 22) and (35 *b*) fall above the normal area; cases (9), (13), (32), (35 *a*) (16. xi. 22), (39 *a*) (21. vi. 22) and (40) fall very low, and cases (31), (20 *a*) (23. vi. 22), (26 *a* and *d*) (27. iv. 22 and 17. vii. 22), (36), (37 *b*) (10. viii. 22) and (23 *a*) (28. vi. 22) below the normal area.

In the majority the plasma p_{H} was normal, in (11 *a*) (3. viii. 22), (22 *a*) (5. vii. 22) and (26 *b*) (2. v. 22) slightly raised, and in (3), (35 *b*) (20. xi. 22), and (33 *b*) (26. x. 22) very high. Of these, cases (22 *a*) and (35 *b*) who had received large doses of sodium bicarbonate, had a high plasma $[\text{HCO}_3^-]$ not fully compensated by increased CO_2 tension. Case (3) who had also received large doses of sodium bicarbonate had a temperature of 101° accompanied by definite hyperpnoea.

Case (33 *b*) (26. x. 22) had heart failure with extreme dyspnoea and is therefore comparable to the case (52 *a*). On treatment with morphia, which presumably deadened his respiratory centre, the dyspnoea was much reduced and his plasma p_{H} returned to normal. Other cases of heart failure with

nephritis, cases (21), (23) and (38), do not show a high p_H so that the increased respiratory effort in these cases was ineffective, or had less effect than other changes.

The cases which fell very low in the charts had abnormally low values for plasma p_H —7.1 and 7.2—that is to say their respiratory mechanism failed to reduce their CO_2 tension in proportion to their low plasma $[\text{HCO}_3^-]$.

Returning to the cases which fell outside the normal area. Those, (3), (22 *a* and *b*) (5. vii. 22 and 13. vii. 22) (35 *b*) (20. xi. 22) and (38 *b* and *c*) (3. vii. 22 and 28. vii. 22), falling above the normal area had all received doses of sodium bicarbonate which resulted in high plasma $[\text{HCO}_3^-]$ levels. In all the plasma $[\text{Cl}^-]$ is low and the $[\text{Na}^+]$ not increased, that is the high plasma bicarbonate has been produced not by an actual but by a relative increase of kations in the plasma and a reduction of anions in the shape of Cl^- . Case (38 *b* and *c*) had heart failure and oedema of the lungs with very high CO_2 tension compensating his high plasma $[\text{HCO}_3^-]$.

The cases falling below the normal limit are the true cases of acidosis. With them may be included cases (12) and (24); in their case the plasma p_H has not been estimated but there is no reason to suppose that they were cases with low plasma $[\text{HCO}_3^-]$ consequent upon reduction of the venous CO_2 tension by hyperpnoea. There were, therefore, in this series of 41 cases with definite kidney damage, 14 with acidosis. The large proportion in this series is due to the severity of the cases chosen. In another series of 100 cases which included a larger proportion of mild cases there were 22 with plasma bicarbonate below 55, and these cases may not all have been true cases of acidosis as some of the less low plasma bicarbonates may have been secondary to reduced CO_2 tension only. The severity of the condition is shown by the fact that of these twenty-two, out of five who had plasma bicarbonate between 35 and 44, four died within two weeks, and out of the five who had plasma bicarbonate below 35 all died within a few days. This heavy mortality also occurred among the cases considered in this paper; of the six cases with severe acidosis four died within fourteen days, and one within a month.

By comparison of the anions and kations in the plasmata of these cases with those of the control cases, we find that the diminution of plasma $[\text{HCO}_3^-]$ is due in the majority of cases to excess of HPO_4^{--} and anions of undetermined acids. Only in two cases (24) (on both occasions) and (23) (on one occasion) does excess of Cl^- alone account for this diminution, and in four an absolute or relative excess of Cl^- together with an excess of HPO_4^{--} or undetermined anions. In four, (13), (32 *a*), (35) and (40), out of the six cases in which the $[\text{HCO}_3^-]$ was extremely low the reduction was wholly due to HPO_4^{--} and undetermined anions; of the other two, the reduction was mainly due to undetermined anions in case (9), while no conclusion is possible in case (39) as the analysis was not completed.

In five cases, (12), (13), (31), (32) and (40) the effect of the increase of these anions was modified by a reduction of $[\text{Cl}^-]$ both absolute and relative to

[Na⁺]. In view of what has been said about the distribution of Cl⁻ it is not justifiable to conclude that there has been no retention of Cl⁻ in these cases, but in view of the high values for HPO₄⁻⁻ and undetermined anions it can be said that there has been no specific retention of Cl⁻ in cases other than (24), and (23) on 28. vi. 22. Even in this last case on the second occasion, 14. vii. 22, there was an increase of undetermined anions and HPO₄⁻⁻ in the plasma and none of Cl⁻.

In all the cases the excess of HPO₄⁻⁻ was less than the excess of undetermined anions or the excess of Cl⁻ relative to Na⁺, so that the reduction of [HCO₃⁻] is much greater than the excess of HPO₄⁻⁻ would account for.

The CO₂ tension of the cerebrospinal fluid must be about the same as that of venous blood, so that in order to maintain the p_H of the fluid the same as that of plasma the [HCO₃⁻] must be the same also. The average values found for the [HCO₃⁻] in cerebrospinal fluid and plasma were about the same 0.0276 and 0.0280 g. equivalents per litre, and in the cases (25), (27), (32) and (33) in which the cerebrospinal fluid was examined at about the same time as the plasma the two agree closely. But in case (32) the low [HCO₃⁻] in the cerebrospinal fluid is accounted for by excess of Cl⁻ instead of high HPO₄⁻⁻ and undetermined anions, as in the plasma. Presumably, as in the process of secretion of cerebrospinal fluid the [HPO₄⁻⁻] and undetermined anions are kept low, the bicarbonate has to be reduced by a relative excess of Cl⁻.

Of the patients with acidosis the only ones with dyspnoea were cases (23), with heart failure, and (37 *b*) (10. viii. 22). On the other hand, dyspnoea occurred in cases such as (22 *a*) (5. vii. 22) with high [HCO₃⁻] and p_H . This dyspnoea therefore, as in the case of heart failure (52), was independent of the reaction and [HCO₃⁻] of the plasma. Dyspnoea appears more as a manifestation of disturbance of the circulatory and respiratory apparatus than of acidosis. Moreover the patients with severe acidosis had little hyperpnoea. It was not noticeable in case (9) when she was sitting in the ward after coming up to hospital and it was not striking in the extreme cases (35 *a*) (16. xi. 22) and (13 *a*) (20. vii. 22). None of the cases had the extraordinary air hunger often seen in diabetic acidosis.

Although acidosis only occurred in severe cases it seemed, like urea retention, to cause little disturbance in itself, even when the p_H of the plasma was reduced. Case (13 *a*) (20. vii. 22) was quite clear-headed and case (35 *a*) (16. xi. 22) was only a little drowsy. Of the more severe cases of acidosis only case (40), who had a ketosis, was comatose; while case (9) was able to go about her work and case (24) (27. ii. 22) was able to get about.

Acidosis was not always present in uraemia, for example it was not present in cases (6), (11) and (29).

Table V.

Case		Plasma					Corpuscles		Blood		Cell volume	
		pH	[HCO ₃ ⁻]	[Cl ⁻]	[HPO ₄ ⁻]	Sum	[Na ⁺]	[Cl ⁻]	[Cl ⁻]	urea		
1	31. v. 22	—	0.030	0.088	(0.0035)	0.121	0.135	—	—	120	40	Acute nephritis.
	8. vi. 22	—	0.023	0.096	0.0025	0.121	0.126	—	—	54	40	Much improved.
2	1. xii. 21	—	0.030	0.102	(0.002)	0.134	—	—	—	25	—	Acute nephritis. Oedema.
	21. xii. 21	—	0.0285	0.1105	(0.002)	0.140	0.139	—	—	24	—	Much improved.
3	22. viii. 22	7.55	0.032	0.090	0.003	0.125	0.133	—	0.0735	141	33	Exacerbation of subacute nephritis. Slight oedema. Sodium bicarbonate given by mouth. Subacute nephritis; no oedema.
4	6. ii. 22	—	0.0295	0.109	(0.0025)	0.141	0.146	—	—	75	40	"
5	11. i. 22	—	0.026	0.102	(0.002)	0.130	0.130	—	—	38	—	"
	6. ii. 22	—	0.030	0.106	(0.002)	0.138	0.144	—	—	19.5	50	Little change.
6	3. vii. 22	7.4	0.027	0.0785	0.003	0.109	0.117	—	—	120	40	Infective endocarditis; uraemia; NaCl in urine 0.05 %.
	13. vii. 22	7.3	0.030	0.102	0.002	0.134	0.1305	—	—	54.5	33	Free diuresis 5. vii. 22 to 7. vii. 22, great clinical improvement at same time.
	26. vii. 22	7.4	0.0265	0.1005	0.002	0.129	0.1305	—	—	31	33	Still better.
7	13. ix. 22	7.4	0.0275	0.1105	0.0025	0.140	0.142	—	—	43	25	Subacute nephritis; oedema. Plasma fibrin 0.31 %, globulin 1.53 %, albumin 2.15 %.
8	28. ii. 22	—	0.033	0.104	(0.002)	0.139	0.139	—	—	18	33	Subacute nephritis; oedema. Fits—probably hysterical.
9	25. i. 22	—	0.024	0.112	(0.0025)	0.138	0.142	—	—	96	50	Congenital cystic kidneys. Able to live moderately active life.
	8. iii. 22	—	0.025	0.114	0.002	0.141	0.142	—	—	102	40	—
	26. x. 22	7.2	0.015	0.117	0.002	0.132	0.142	—	0.1006	141	33	No dyspnoea, nor hypernoea. Plasma fibrin 0.31 %, globulin 0.77 %, albumin 3.38 %.
10	25. i. 22	—	0.027	0.107	(0.002)	0.136	0.139	—	—	47	40	Subacute nephritis; no oedema. Serum Ca 0.010 %.
11	3. viii. 22	7.45	0.025	0.099	0.002	0.126	0.126	—	—	36	—	Pyelonephritis; one kidney removed 7 years ago. Occasional fits.
	10. x. 22	7.40	0.0265	0.101	0.003	0.130	0.133	—	0.0795	41	—	Plasma fibrin 0.31 %, globulin 1.12 %, albumin 2.16 %.
12	29. xii. 21	—	0.028	0.109	(0.003)	0.140	0.144	—	—	109	33	Pyonephrosis.
	12. i. 22	—	0.022	0.078	(0.006)	0.106	0.128	—	—	109	25	Much worse. Died 21. i. 22.
13	20. vii. 22	7.1	0.007	0.092	0.008	0.107	0.126	0.0565	—	320	—	Pyonephrosis; slight oedema. Fully conscious, no fits. Given 30 g. sodium bicarbonate in next 48 hours.
	22. vii. 22	7.2	0.013	0.088	0.009	0.110	0.126	—	—	320	16	Ca in serum 0.006 %. Fits started 8 hours later. Died next day.
14	2. iii. 22	—	0.034	0.102	—	0.136	0.135	—	—	22.5	—	Pyonephrosis.
15	24. viii. 22	7.5	0.029	0.096	0.002	—	0.126	—	0.0742	25	50	Mild pyelitis. Treated with sodium bicarbonate.
16	—	—	0.035	0.097	(0.002)	0.134	0.142	—	—	25	—	Chronic interstitial nephritis.
17	9. i. 22	—	0.030	0.102	(0.002)	0.134	0.128	—	—	41.5	—	Enlarged prostate. Fairly good condition.
	—	—	0.0335	0.096	(0.002)	0.131	0.130	—	—	37.5	—	—

18	16. xii. 21	—	0.0265	0.1105	—	0.137	0.148	—	—	47	—	Enlarged prostate. Not considered fit for operation.
19	—, viii. 22	7.4	0.0295	0.099	0.002	0.1305	0.124	—	—	26	40	Chronic interstitial nephritis.
20	23. vi. 22	7.3	0.019	0.107	0.002	0.128	0.135	—	—	43	50	Chronic interstitial nephritis. Just recovering from fit, cyanosed.
21	28. vii. 22	7.4	0.0285	0.104	0.003	0.135	0.130	—	—	40	40	Much better.
	—	7.4	0.0245	0.109	0.002	0.135	0.133	—	—	63	30	Chronic interstitial nephritis. Heart failure. Dyspnoea.
22	5. vii. 22	7.45	0.0365	0.092	0.0025	—	—	—	—	58	40	Chronic interstitial nephritis. Moderate dyspnoea. Given 60 grains each of sodium bicarbonate and potassium citrate 3 times a day from 24. vi. 22.
	13. vii. 22	7.4	0.035	0.096	0.002	0.133	0.130	—	—	70	40	Chronic interstitial nephritis. Heart failure, slight oedema. Dyspnoea.
23	28. vi. 22	7.35	0.022	0.113	0.002	0.137	0.135	—	—	83	40	No oedema.
	14. vii. 22	7.4	0.023	0.097	0.003	0.123	0.133	0.048	—	100	33	Chronic interstitial nephritis. Ascites; no oedema.
24	16. i. 22	—	0.018	0.1145	0.002	0.1345	0.135	—	—	126	40	Globulin 0.3 %, albumin 1.2 %.
Ascitic fluid		—	0.015	0.1215	0.002	0.1385	0.139	—	—	—	—	Able to get about; no dyspnoea, slight hyperpnoea.
		27. ii. 22	0.014	0.1215	0.003	0.1385	0.139	—	—	120	40	Chronic interstitial nephritis. Coma. No dyspnoea.
25	21. xii. 21	—	0.032	0.090	0.002	0.124	0.135	—	—	75	—	Chronic interstitial nephritis. Comatose. Serum Ca 0.010 %.
26	27. iv. 22	7.4	0.021	0.108	0.002	0.131	0.144	—	—	106	50	{ Given sodium bicarbonate 30 grains every two hours from 27. iv. 22 to 2. v. 22.
Spinal fluid		27. iv. 22	0.022	0.135	0.001	0.158	0.146	—	—	—	—	Much better.
		2. v. 22	0.030	0.100	0.002	0.132	—	—	—	75	40	Blood equilibrated with 6 % CO ₂ before separation of plasma.
		26. v. 22	0.022	0.100	—	—	—	—	—	92	50	—
		23. vi. 22	0.025	0.101	0.0025	0.128	0.126	—	—	105	33	Coma and convulsions again; blood taken just after a convulsion.
	17. vii. 22	7.4	0.020	0.106	0.005	0.131	0.128	—	—	105	33	Chronic interstitial nephritis.
27	9. x. 22	7.4	0.030	0.102	0.0015	0.133	0.130	0.060	—	50	—	—
Spinal fluid		—	0.032	0.124	0.001	0.157	0.142	—	—	—	—	—
		27. iv. 22	0.30	0.093	0.0025	0.125	0.148	—	—	120	25	Chronic interstitial nephritis. Drowsy; no dyspnoea.
29	31. vii. 21	—	0.031	0.082	(0.0075)	0.1205	0.135	—	—	152	—	Probably pyonephrosis. Unconscious; muscular twitching. Died 2. viii. 2.
30	16. vi. 21	—	0.0275	0.1105	(0.003)	0.140	—	—	—	131	—	Chronic interstitial nephritis.
	12. vii. 21	—	0.042	0.092	(0.004)	0.138	0.141	—	—	150	—	Given large doses of sodium bicarbonate from 7. vii. 21 to 14. vii. 21 then smaller doses.
	21. vii. 21	—	0.039	0.092	(0.0045)	0.135	—	—	—	138	—	—
	2. viii. 21	—	0.0305	0.099	(0.004)	0.134	—	—	—	155	—	—
	1. ix. 21	—	0.035	0.096	(0.0045)	0.135	0.139	—	—	172	—	Died 26. ix. 21 of bronchopneumonia.
31	21. viii. 22	7.3	0.0185	0.093	0.008	0.119	0.124	0.058	—	300	33	Chronic interstitial nephritis. No oedema, nor dyspnoea.

Table V continued.

Case		Plasma					Corpuscles		Blood		Cell volume
		pH	[HCO ₃ ⁻]	[Cl ⁻]	[HPO ₄ ⁻]	Sum	[Na ⁺]	[Cl ⁻]	[Cl ⁻]	urea	
31	26. viii. 22	7.35	0.020	0.090	0.008	0.118	0.124	—	0.0735	480	30
	30. viii. 22	7.35	0.0195	0.083	0.0080	0.110	0.124	—	0.0725	600	24
	4. ix. 22	7.4	0.021	0.085	0.007	0.113	0.137	—	0.0735	600	23
	11. ix. 22	7.4	0.0165	0.077	0.011	0.104	0.128	—	0.0666	640	20
32	6. ix. 22	7.2	0.0125	0.096	0.011	0.119	0.133	0.0633	—	436	27
Spinal fluid	7. ix. 22	—	0.017	0.135	0.002	0.154	0.144	—	—	456	—
	8. ix. 22	7.4	0.016	0.087	0.01	0.115	0.131	—	0.077	564	27
	13. ix. 22	7.35	0.0185	0.074	0.018	0.110	0.142	0.050	—	600	20
33	8. vii. 22	7.4	0.027	0.096	0.003	0.126	0.130	—	—	57	—
	26. x. 22	7.6	0.0215	0.106	0.004	0.131	0.135	—	0.0923	171	25
	31. x. 22	7.4	0.0245	0.104	0.0055	0.134	0.144	—	0.0915	240	23
Spinal fluid	6. xi. 22	—	0.0245	0.1455	0.002	0.172	0.165	—	—	—	—
	31. x. 22	7.4	0.028	0.096	0.004	0.128	0.133	—	0.0725	171	40
35	16. xi. 22	7.2	0.006	0.1025	0.005	0.1135	0.135	—	0.098	343	20
	20. xi. 22	7.55	0.0335	0.084	0.005	0.1225	0.139	—	0.0785	400	20
36	1. v. 22	7.4	0.020	0.116	(0.003)	0.139	0.146	—	—	68	33
37	6. vii. 22	7.4	0.0275	0.106	0.004	0.137	0.137	—	—	70	—
	21. vii. 22	—	0.015	0.104	0.0035	0.122	0.119	—	—	71	—
	10. vii. 22	7.4	0.0195	0.094	0.0055	0.119	0.119	—	0.083	111	30

Given 20 grains sodium bicarbonate and 10 grains potassium citrate 3 times a day throughout; sweated much in hot packs. Plasma fibrin 0.53 %, globulin 2.41 %, albumin 3.02 %.

Appears better. Plasma fibrin 0.59 %, globulin 2.18 %, albumin 3.43 %.

Worse, comatose. Plasma fibrin 0.61 %, globulin 1.37 %, albumin 2.72 %. Slight oedema of ankles at end. Died 13. ix. 22.

Chronic interstitial nephritis.

{ Given 30 grains acid sodium phosphate every 4 hours from 2. ix. 22 to 7. ix. 22, then large doses of sodium bicarbonate.

Plasma fibrin 0.36 %, globulin 4.02 %, albumin 3.5 %.

{ Possible loss of CO₂ in taking this blood. Urine NaCl 0.12 %.

Rapid shallow breathing. Plasma fibrin 0.51 %, globulin 2.78 %, albumin 2.75 %.

Moderate oedema. Died 16. ix. 22.

Infective endocarditis. Moderate fibrosis of kidneys. Slight oedema. No dyspnoea.

Much worse; oedema; hyperpnoea. Plasma fibrin 0.50 %, globulin 0.49 %, albumin 3.39 %.

Morphia given from 27. x. 22. Hyperpnoea much less; twitching.

Died 6. xi. 22. Taken 10 minutes after death.

Chronic interstitial nephritis. Had one fit and died 6. xii. 22.

Extensive fibrosis of kidneys. Conscious but drowsy. Ca in serum 0.010 %.

About 100 g. sodium bicarbonate on 18 and 19. xi. 22. Ca in serum 0.008 %. Died 8. xii. 22.

Chronic parenchymatous nephritis. General oedema.

Chronic parenchymatous nephritis. General oedema.

Much worse; more oedema; dyspnoea.

Condition unchanged.

SUMMARY AND CONCLUSIONS.

1. $[\text{HCO}_3^-]$, $[\text{Cl}^-]$, $[\text{HPO}_4^{--}]$ and $[\text{Na}^+]$ were determined in plasmata and in a few cerebrospinal fluids of patients with nephritis, also in plasmata and cerebrospinal fluids of control cases.

2. The plasma $[\text{HPO}_4^{--}]$ was increased in the majority of cases with high blood urea.

3. $[\text{Na}^+]$ was not increased in the plasma even in extreme degree of renal inefficiency, on the other hand low values were found in several such cases.

4. Evidence is given of disturbance of the distribution of chlorides between the plasma on the one hand and cerebrospinal fluid and tissues on the other.

5. Very low figures for plasma $[\text{Cl}^-]$ were found in some severe cases of nephritis.

6. The excess of kation in normal plasma unaccounted for by $[\text{HCO}_3^-]$, $[\text{Cl}^-]$, and $[\text{HPO}_4^{--}]$ is combined mainly with protein; a little may be combined with organic anions.

7. In many cases of nephritis with much urea retention an excess of kation over and above that combined with HCO_3^- , Cl^- , HPO_4^{--} and protein was found. This was combined with anions, sulphation among others, classed as undetermined anions. Such undetermined anions were found in cases with and without acidosis.

8. The p_{H} of the majority of cases lay within normal limits, especially about 7.40. High values up to 7.6 were found, these were caused by disturbances of the respiratory centre and by treatment with sodium bicarbonate.

9. In most cases of acidosis in nephritis, the reduction of plasma $[\text{HCO}_3^-]$ was due to accumulated HPO_4^{--} and undetermined anions; of these, undetermined anions were the more important factor. In several cases the effect of these anions was much reduced by a coincident fall of $[\text{Cl}^-]$. In only one case was there evidence of a specific retention of Cl^- as the cause of the acidosis.

10. Dyspnoea in nephritis is not caused by acidosis but by disturbances of the circulation and respiration. Hyperpnoea in acidosis in nephritis is not striking even in severe cases.

11. Acidosis in nephritis is evidence of a very severe condition but is not harmful in itself. It does not cause any of the symptoms of uraemia.

12. The $[\text{HCO}_3^-]$ of the cerebrospinal fluid is the same as that of the plasma. Reduction of $[\text{HCO}_3^-]$ in cerebrospinal fluid is caused by excess of $[\text{Cl}^-]$.

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