TOTAL ACID-BASE EQUILIBRIUM OF PLASMA IN HEALTH AND DISEASE: *X. The Acidosis of Nephritis*

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TOTAL ACID-BASE EQUILIBRIUM OF PLASMA IN HEALTH AND DISEASE

X. The Acidosis of Nephritis

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The present paper represents an extension of the work outlined in number VII of this series, "Factors causing acidosis in nephritis" (1), with an attempt to explain in part the disturbances of the total acid-base equilibrium of the serum which were there described. The acidosis, a term applied to conditions in which the concentration of bicarbonate of serum is low, appeared to be due to several different types of electrolyte disturbances of which the chief were reduction of total base and increase of undetermined acid (i.e., acids other than bicarbonate, chloride, phosphate and protein). Phosphate increases seemed to play a less important rôle. Variable changes in the level of Cl, usually reductions in its concentration, were observed with great frequency.

To the data then presented many observations have been added, and collateral studies, bearing especially on chloride metabolism, have been made.

EXPERIMENTAL METHODS

Since the appearance of the first paper of this series (2) certain changes in the technique and calculations used in the determination of the total acid-base equilibrium of the serum have ben adopted to increase accuracy. Although these changes in no way alter the conclusions reached in previous articles, they have necessitated a redetermination and restatement of normal values and recalculations of earlier data.

The method, in brief, consists of the determination of total base, CO_2, Cl, inorganic phosphate and protein of serum. The serum was obtained from arterial blood or venous blood (without stasis) which had been secured and treated, by techniques already described, in such a manner as to prevent all air contact.

The procedures for determining CO_2 and Cl have not been changed and the values for these factors previously given need no revision. For total base a modification of Stadie's (3) adaptation of Fiske's method has been employed in the recent studies. We have isolated and analyzed the benzidine sulfate instead of titrating the benzidine filtrate as Stadie recommended. Previously reported base determinations were made by a technique in which phosphates were not removed, but were, supposedly converted to a form in which they combined

TABLE 1

Total base concentration in normal serum

Subject	Sex	Age	Total base
			m.-eq.
D. M.	Male	29	154.4
			157.2
			155.7
			156.3
H. O.	Male	27	153.0
F. B.	Male	30	153.6
L. D.	Male	27	152.5
M. W.	Male	30	155.0
E. D.	Male	26	153.0
J. P.	Male	40	154.0
A. J.	Female	28	153.0
R. I.	Female	31	152.5
H. D.	Female	15	158.0
A. A.	Female	16	152.0

with a definite equivalent of base. Subsequent investigation showed that it was impossible to insure conversion of phosphates to such a stable form with any regularity.

Earlier base determinations were subject to an error, the magnitude of which depended upon the amount of inorganic phosphate in the serum, varying from +1 to −1 equivalent of base for every equivalent of P in serum. As the serum of normal resting adults contains only from 1 to 3 milliequivalents of inorganic P, the error is of little significance. It may, however, attain a considerable magnitude in subjects with advanced chronic nephritis with high serum phosphates.

Fifteen analyses of the sera of 11 normal young adults (medical students, physicians and laboratory workers) carried out by the new technique in this laboratory by Oard and Lee reveal a greater constancy in the concentration of total base than did the determinations reported earlier. See table 1.

Since the earlier papers Van Slyke and his associates (5) have established more accurately the base combining powers of the total proteins of human serum and the albumin and globulin fractions respectively. The equation originally used for converting protein concentrations to equivalents of base combined with protein derived from data published by Van Slyke, Wu and McLean (4) from the blood of a Manchurian pony, was:

$$BP = 0.68\ P\ (pH - 4.8)$$

The new equations are:

$$\text{for albumin } BP_{(alb.)} = 1.248\ P_{(alb.)}\ (pH - 5.16)$$

$$\text{for globulin } BP_{(glob.)} = 0.742\ P_{(glob.)}\ (pH - 4.82)$$

TABLE 2

Protein concentration in normal serum

Subject	Sex	Age	Albumin		Globulin		Total protein		A:G	Calculated total protein
			per cent	*m.-eq.*	*per cent*	*m.-eq.*	*per cent*	*m.-eq.*	*ratio*	*m.-eq. if A:G = 1.8*
A. E.	Female	28	5.21	14.2	3.00	5.6	8.21	19.9	1.74	20.3
H. O.	Male	27	5.31	14.5	1.32	2.5	6.63	17.0	4.02	16.4
			5.49	15.0	1.95	3.6	7.44	18.6	2.82	18.4
F. B.	Male	29	5.65	15.4	1.58	3.0	7.23	18.4	3.58	17.9
E. D.	Male	26	5.37	14.7	1.95	3.6	7.32	18.3	2.75	18.1
H. D.	Female	15	5.17	14.1	3.22	6.0	8.39	20.1	1.61	20.8
M. W.	Male		5.29	14.5	2.31	4.3	7.60	18.8	2.25	18.8
H.	Male		5.31	14.5	2.11	4.0	7.42	18.5	2.52	18.4
R. I.	Female	31	4.83	13.2	2.39	4.5	7.22	17.7	2.02	17.9
F.	Female		4.98	13.6	2.44	4.6	7.42	18.2	2.04	18.4
R.	Male		4.74	13.0	2.91	5.4	7.65	18.4	1.63	18.9
J. P.	Male	40	4.69	12.8	1.84	3.4	6.53	16.2	2.55	16.2
D. M.	Male	29	5.20	14.2	1.59	3.0	6.79	17.2	3.27	16.8
			5.24	14.3	1.61	3.0	6.85	17.3	3.26	17.0
			5.19	14.2	1.90	3.6	7.09	17.8	2.73	17.5
			5.49	15.0	1.51	2.8	7.00	17.8	3.64	17.3

and (assuming an average albumin : globulin ratio of 1.8:1) for total protein, $BP = 1.072\ (pH - 5.04)$. It is evident at once that the new factors indicate more base combined with protein and that albumin binds considerably more base than globulin. It follows that values for the amount of base combined with undetermined acids (sulfate and organic acids), are not as great as had been supposed because the difference,

$$B - (HCO_3 + Cl + H_2PO_4 + HPO_4 + \text{protein}) = \text{undetermined acid},$$

must diminish if protein increases. In the second place variations in the relative proportions of albumin and globulin in serum have an unexpectedly large effect on the combining power of proteins. Therefore, in cases in which the A:G

ratio is abnormal, calculations based on determinations of total protein only and assumption of an average ratio may be subject to significant errors. Such errors are of little importance in dealing with normal blood as can be seen in table 2. They might attain a considerable importance in pathologic conditions associated with abnormal serum albumin : globulin ratios. Fortunately in these conditions the total protein concentration is usually low and the error correspondingly diminished.

The present work has included determination of serum pH only in rare instances. For the purposes of calculating base combined with protein an average pH value of 7.35 has been assumed. The equations given above are, therefore, simplified to:

$$BP_{(alb.)} = 2.733\ P$$
$$BP_{(glob.)} = 1.869\ P$$
$$BP_{(prot.)} = 2.476\ P\ (A/G = 1.8)$$

Such simplification, although obviously necessary if the total procedure is to be made generally applicable to the study of clinical problems, introduces into the calculations another error.

Phosphate combining equivalents are also calculated with the assumption of a constant pH of 7.35. At this pH 80 per cent of the phosphate exists in the dibasic form. pH and the ratio $\frac{HPO_4}{H_2PO_4}$ vary in the same direction, as the reaction of the blood changes.

The total errors entailed in the assumption of a constant pH are seldom of important magnitude. If inorganic P were as high as 19 mgm. per 100 cc. and pH as low as 7.00, phosphate equivalents calculated by the formula that has been employed would give a value only 1 m. eq. too high. If in the same serum the total protein concentration were 7.00 per cent, the value obtained for BP would be 2.5 m. eq. too great. If the A : G ratio were only 1.0, a further positive error of 1.5 m. eq. would be introduced. The total error in this extreme case in the estimation of base combined with protein and phosphate would be +5.0 m. eq. with a negative error of the same magnitude in the undetermined acid value. In the actual analyses presented errors never attained such magnitude because high phosphorus and low pH were usually associated with reduced proteins.

The new "total base" method was introduced in November, 1925. In the tables, then, base values of earlier dates may be in error by as much as the equivalents of inorganic P found in the serum. If proteins were fractionated it is indicated in the tables. When non-protein nitrogen of serum has been determined it is indicated in the tables by the letter *s* after the non-protein nitrogen value. In all other instances whole blood non-protein nitrogen has been used for correction of the serum protein values.

If the newer factors and methods are employed for the estimation of the acid-base equilibrium of serum the concentration of the base combined with "undetermined acids" (sulfate + organic acids) seldom exceeds and is usually considerably less than 10 milliequivalents.

EXPERIMENTAL RESULTS AND DISCUSSION

Nature of clinical material

Altogether 161 serum electrolyte studies have been made on 51 patients with chronic diffuse glomerular nephritis, arteriosclerotic renal disease and a group of conditions which, for want of a better inclusive term, might be called "suppurative nephritis:" bilateral tubercular or pyogenic infections of the kidney, either hematogenous or ascending in origin, with or without obstruction of the lower urinary tract, which have caused sufficient destruction of kidney substance to produce striking evidence of renal insufficiency. All but two of the patients in the three groups had well marked hypertension. In 84 instances complete analyses (total base and all the acids) were made. In table 3 are presented the serum electrolyte data from 8 of the 51 cases. These have been chosen, either because they have been subjected to more prolonged and intensive study than the others or because they serve to illustrate specific points to which reference is made in the discussion. Similar data from 11 other cases were published in the preliminary report (1). Short descriptions of the same cases are given in the preliminary report and at the end of this paper. It may be assumed that all patients were subjected to the usual routine questions and procedures.

The inclusion in a single group of patients with such varied conditions is justified by the fact that they possess certain important common characteristics, regardless of the causes of the diseases from which they suffer or the names by which they may be called. In Table 3 the first 3 subjects had chronic glomerular nephritis, the next 2 had arteriosclerotic renal disease, the last 3 suppurative nephritis. Although, as one might expect, certain differences characterize the three groups, the recurrence of similar electrolyte patterns in all three indicates that the disturbances encountered are the results, not so much of a given type of renal disease as of the advanced destruction of kidney substance in general or of some of the functional disturbances that regularly attend such destruction. At first an attempt was made to secure blood from all patients in the terminal stage of nephritis with uremia. Later many patients in earlier stages were included in order to gain some idea of the mechanisms responsible for the dis-

TABLE 3

Data in nephritic patients

Number	Date	Weight	Edema	Vomiting	O_2 capacity	Cell volume	1 Serum total protein	2 HCO_3	3 Cl	4 Inorganic P	5 Acid 1+2+3+4	6 Base	Undetermined acid 6−5	Non-protein nitrogen	Phthalein per cent in 2 hrs.	Treatment and remarks
	1924	*kgm.*			*volumes per cent*	*per cent*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*mgm. per 100 cc.*		
29267	February 19	67.8	0	0	14.8	29.4	16.5	19.0	102.7	3.1	141.3			85	18	
	February 25	66.4	0	0	15.0	32.6	17.5	18.1	100.0	2.9	138.5			75		After salt poor diet
	February 29	66.0	0	0	14.3	32.5	16.7	18.8	105.3	3.2	144.0			69		After 2 days of low fluid + 5 grams NaCl
	March 8	68.2	0	0	13.8	31.3	15.5	19.5	104.4	2.2	131.6			44		After 8 days of high fluid + 5 grams NaCl
	1925															
	January 14		0	0	12.7		17.1	16.3	109.0	6.5	148.9	183.7	34.8	75		Ambulatory. Without symptoms
	November 19	59.0	0	+	8.7	23.0	16.4	9.8	105.5	5.5	137.2	173.0	35.8	167	<5	Uremia
	November 27	59.0	0	+	8.4	21.3	15.6	8.2	96.4	5.4	125.6	132.9	7.3	168		
	December 1		0	+	7.3	17.1	12.6	13.3	95.3	5.4	126.6	148.0	21.4	167		Coma. Bicarbonate and saline on November 30
	December 6		0	+	5.9	17.1	15.3	14.2	96.2	7.4	133.1	137.5	4.4	163		Convulsions. Before and after intravenous $MgSO_4$
					6.3	16.3	15.3	12.6	94.3	7.4	129.6	140.6	11.0			
	December 11		0	+	4.9	15.3	13.9							158		Before and after intravenous $MgSO_4$
					5.4	15.4	13.9									
	December 17		0	0	7.4	20.0	14.5	10.5	102.4	4.8	132.2	133.6	1.4	145		Rational. Free from symptoms. After frequent subcutaneous saline
	1926															
	January 2	51.8	0	+	7.1	18.3	16.1	6.8	94.4	5.7	123.0	128.1	5.1	165		Ascending urinary infection. After 10 days of negative Cl balance
	January 9			+	5.1	14.9	11.1	4.5	90.8	5.6	112.0	120.5	8.5	171		Heart failure. Comatose. Has received subcutaneous NaCl. Died January 11
	1927															
60345	April 20	52.7	+	+	7.2	20.5	14.6	17.3	102.4	3.5	137.8	148.2	10.4	117	<5	Heart failure
	April 25	49.1	0	+	8.0	17.7	15.5	16.5	103.2	5.0	140.2	148.0	7.8	122		After diuresis and negative Cl balance
	May 3	49.8	0	+	6.7	17.6	15.8	16.3	105.6	4.2	141.9	145.9	4.0	118		Positive Cl balance
	May 10	51.6	0	0	6.8	17.3	13.4	16.8	106.6	4.2	141.0	149.1	8.1	112		Positive Cl balance
	May 17	51.4	0	0	5.0	16.1	14.9	16.3	110.0	4.9	146.1	154.5	8.4	124		Cl equilibrium
	May 27	51.2	0	+	5.7	17.5	15.4	17.8	103.8	4.7	141.7	150.5	8.8	123		Negative Cl balance
	June 7	51.2	0	0	6.6	19.8	15.7	17.1	107.6	4.7	145.1	153.4	8.3	94		Positive Cl balance
	June 17	53.5	0	0	6.8	19.9	12.7	15.8	107.0	4.7	140.2	148.8	8.6	98		Positive Cl balance. Died some months later
	1926															
56247	December 27	65.7	+	+	10.7	41.8	12.5	25.0	106.8	3.5	147.8	154.3	6.5	85		Heart failure

	1927															
	January 4	61.6	+	(+)	11.2	41.3	16.7	26.5	99.2	4.1	146.5	149.4	2.9	77		After salt poor diet and diuresis
	January 11	59.3	0	(+)	11.1		16.5	23.5	99.0	4.3	143.3	149.2	5.9	98		Negative Cl balance
	January 18	60.4	0	(+)	10.6	27.5	16.0	26.6	94.7	4.2	141.5	144.7	3.2	88		Negative Cl balance
	January 25	60.9	0	(+)	12.4	43.5	15.0	25.0	92.5	4.7	137.2	140.5	3.3	121		Negative Cl balance
	January 26	62.2	+	+												
	February 1		+	+	9.3	23.8	13.7	19.1	87.0	6.5	126.3	130.9	4.6	125		Slight positive Cl balance. Edema has developed
	1924															
33030	April 24		0	0	12.8	29.3	12.7	17.0	101.8	3.9	135.4	154.2	18.8	137	14	During acute attack of gout
	April 29	51.5	0	0	11.8	29.6	12.8	21.7	100.3	2.6	137.4	158.4	21.0	114		Acute attack subsiding
	May 28		0	0	10.4	25.7	12.8	19.5	101.1	3.6	136.0	149.8	13.8	130		During recurrence of arthritis. Discharged improved
	1925															
36041	February 23	64.8	0	0	19.2	45.9	16.2	22.5	116.2	4.4	159.3	199.2	39.9	54	62	No symptoms. On high fluids and unrestricted salt
	March 2	63.5	0	0	20.5	48.3	17.9*	19.2	107.0	2.1	146.2	168.0	21.8	51		Improved, on same regime
	1926															
	October 15	72.3	0	0	17.8	39.3	15.0	23.5	108.5			151.7		55		Headache and nervousness only. On same regime
	November 12	72.3	0	0	19.5	43.8	16.0	24.8	102.6	7.6	151.0	155.2	4.2	58		After short period of moderate salt restriction
	1927															
	December 13		0	0					104.0							Died less restricted. Condition not yet serious
	1928															
	May 6		0	±		35.5	12.8*	28.8	96.8	3.1	141.3	152.5	11.2	90		
	May 14		0	±		34.7	13.2*	20.4	100.4	3.6	137.6	146.2	8.6	106		5 grams NaCl added to diet } Vomited at intervals throughout
	May 22	69.0	+	±		33.9	12.7*	17.2	99.1	4.2	133.2	140.0	6.8	92		No salt restriction
523	May 31		+	±		34.2	12.7*	19.3	103.0	2.7	137.7	147.5	9.8	103		No salt restriction
	June 19		+	±		33.8	13.7*	20.5	104.3	2.8	141.3	143.2	1.9	104		No salt restriction
	1924															
33247	May 15											182.0		43		Polycystic kidneys. No serious symptoms
	May 21									2.4		158.4		43	25	After forcing fluids. Discharged improved
36048	March 8		0		15.5		16.9	2.5	104.1	2.1	125.6	139.0	13.4	175		Urethral fistula. Ascending urinary infection. No fluids nor salt
	March 10		0		12.3		14.8	4.9	118.1	2.3	140.1	148.5	8.4	164		After subcutaneous glucose and salt
	March 13		0		9.4		13.9	21.4	106.8	2.1	143.2	154.0	10.8	83		After saline, glucose and bicarbonate
	March 19		0		11.0		14.6	15.5	107.8	1.2	139.1	145.4	6.3	79		Taking food and fluids by mouth. Died shortly after leaving hospital
20921	March 1		0	+	13.5	32.9	14.8	21.0	101.5	2.7	140.0	155.5	15.5	53	15	Recurrent pyelonephritis. Convulsions
	March 29	51.3	0	0	14.7	29.9	12.0	22.2	106.8	2.8	143.8	160.0	17.2	51		Greatly improved after forcing fluids and salt
	December 24		0	+	11.1	31.1	16.1	17.8	105.8	3.5	143.2	140.7	−2.5	72		Acute exacerbation of pyelitis
	1926															
	March 29		0	+	7.5	16.4	15.1	16.4	100.5	6.7	138.7	142.2	3.5	136		Slight negative Cl balance
	April 7		0	0	7.3	18.5	14.8	16.2	106.6	3.0	140.6	150.2	9.6	115		Positive Cl balance
	April 19		0	0	7.1	19.1	15.1	14.2	109.5	4.6	143.4	154.5	11.1	111		Positive Cl balance
	May 11	49.8	0	(+)	11.2	29.8	16.8	7.2	105.6	4.1	133.7	151.2	17.5	121		In convulsions. Before and after intravenous $MgSO_4$
					10.5	28.7	14.8	6.8	102.5	4.2	128.3	147.7	19.4	116		
	May 20		+	+	7.3	20.7	13.6	12.8	91.6	6.7	124.7	149.6	24.9	151		Receiving bicarbonate and subcutaneous saline. Died 2 weeks later

* Albumin and globulin in these experiments were determined separately.

turbances earlier observed. It is believed that the data presented give a comprehensive view of the types of electrolyte disturbances

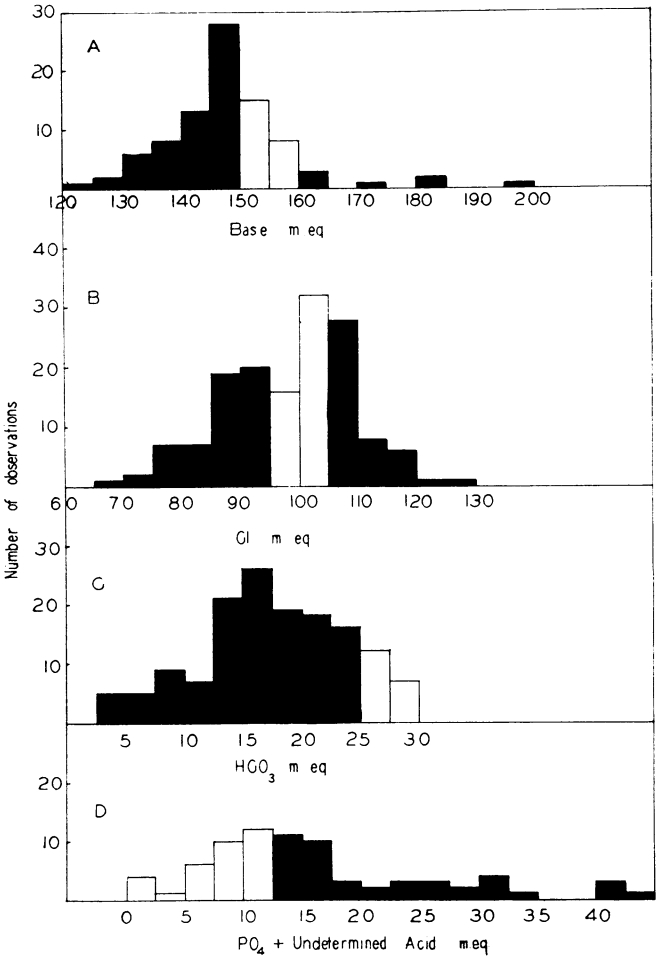

FIG. 1. DISTRIBUTION OF VALUES FOR BASE, Cl, HCO_3 AND PO_4 + UNDETERMINED ACID

White columns indicate normal values, black columns abnormal values

that may be encountered in the blood of patients with conditions that cause subtotal destruction of renal tissue, although they do not

indicate the frequency with which any given type of electrolyte disturbance occurs.

Electrolyte disturbances observed

In all groups the most striking feature was the variability of the concentration of all electrolyte constituents. That this variability is not due to any differences in the character of the disease in different patients is demonstrated by analysis of the studies of case no. 29267 who, at different times, presented almost every combination of electrolyte changes shown by the other patients. It may be inferred from this that the variations of electrolyte patterns exhibited by different patients are referable not to certain types of disease, but to stages in the progress of renal disease in general or to symptoms or functional disturbances that appear in the course of such disease.

In spite of this variability, when one considers the data as a whole, there become evident certain distinct tendencies. These can be appreciated best, perhaps, if they are arranged in statistical form as they are in figure 1.

Bicarbonate deficiency. "Acidosis"

The first and most striking fact brought out by the figure (C) is the frequency of reduction of the bicarbonate concentration. A condition of "acidosis" (according to the generally accepted terminology) was found in 126 out of a total of 145 carbon dioxide determinations. The absolute frequency of the condition is, of course, exaggerated, because patients with acidosis were especially sought. That some degree of acidosis almost always develops in the terminal stages of uremia is quite clear and has been repeatedly pointed out by other observers. That this may be quite slight and is not an important factor in the production of the uremic syndrome or death is evident from case 56247. On the other hand, as in case 36041 acidosis may be found unexpectedly early in the disease, without a symptom to indicate its presence.

One rather surprising fact seems to have been accepted without comment by previous observers; the fact that bicarbonate is never found elevated in a condition in which vomiting is such a prominent symptom. It has been repeatedly shown that pyloric obstruction and

persistent vomiting from other causes (6, 18) result in loss of Cl and compensatory increase of bicarbonate in serum. From the fact that vomiting of nephritis does not cause alkalosis one would be inclined to infer that the vomitus is relatively deficient in free acid.

Phosphate, sulfate and organic acid as causes of acidosis

Figure 1 D shows the frequency with which excessive quantities of PO_4 + undetermined acids are encountered. That PO_4 accumulation alone offers an inadequate explanation of nephritic acidosis has already been mentioned. Denis and associates (8) and others (9) have shown that the inorganic sulfate content of blood is often greatly increased in chronic nephritis with nitrogen retention. More recently Atchley (10) found that, after complete ablation of kidney function, both PO_4 and SO_4 accumulated in the serum and that the increases of these two ions accounted for the reduction of the concentrations of HCO_3 and Cl. In the present work no attempt has been made to estimate SO_4 directly. It is, however, included in the "undetermined acid" fraction. Figure 1 D, while proving that excessive PO_4 + undetermined acid values occur, also shows that the increases are far less frequent and usually of smaller magnitude than CO_2 reductions. This would prove, as far as statistical treatment can prove, that accumulation of inorganic phosphate, sulfur, organic acids or any combination of the three affords an entirely unsatisfactory explanation of nephritic acidosis as a whole, although any one of them exist and act as a contributory factor in individual instances. Figure 2 more specifically demonstrates the absence of any definite relation between PO_4, undetermined acid and HCO_3 in observations in which all were determined.

Analysis of data from individual cases shows that high undetermined acid occurred, with few exceptions, only when vomiting was an important symptom and on this account or another patients had not received adequate carbohydrate and fluids by mouth or by parenteral routes. It was more frequently encountered in the cases observed early in the study when the administration of carbohydrate fluids was not so vigorously pushed; it often failed to appear even in the premortal state when large amounts of carbohydrate and fluid were given; and it often disappeared rapidly after their administration.

This suggests that starvation may be a factor in the production of the acidosis which may be partly due to ketone acids. It would, at least, be surprising if no ketonuria developed as a result of starvation in human beings. The failure of Atchley to discover any appreciable excess of organic acid in the sera of his dogs with either pyloric obstruction or renal destruction may be due to the fact that these animals

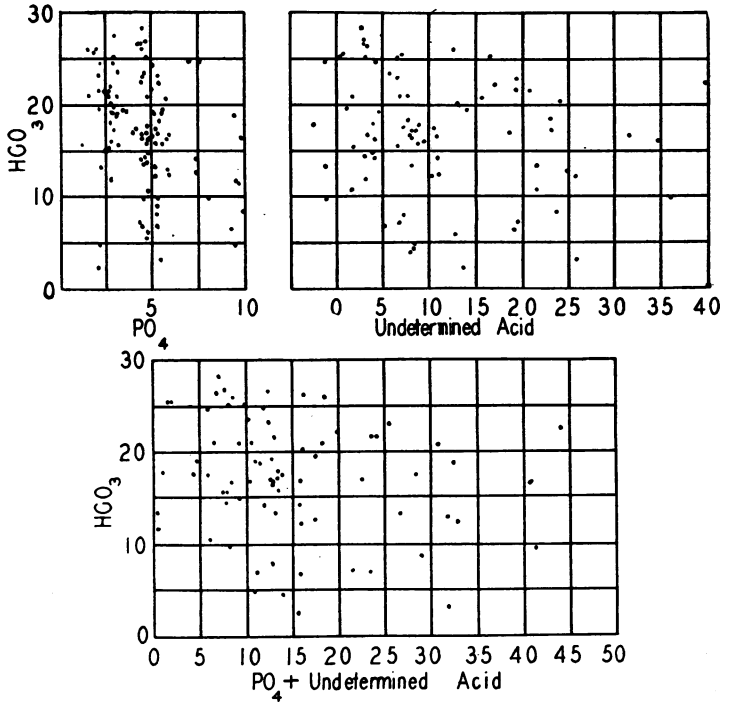

FIG. 2. BICARBONATE PLOTTED AGAINST PHOSPHATE, UNDETERMINED ACID, AND PHOSPHATE + UNDETERMINED ACID

are relatively insusceptible to starvation ketosis. Denis and Reed (11) have recently shown that sulfate accumulations in the blood in nephritis may rapidly disappear as the result of diuresis. If, then, the undetermined acid excess is partly or largely composed of sulfate, its disappearance after the administration of large quantities of fluid may be due to the diuresis which the latter produce.

Even if accumulation of phosphate and sulfate in the blood were responsible for or regularly associated with the observed bicarbonate reductions, it would still be impossible to ascribe the phosphate and sulfate accumulations directly to failure of the renal excretory function. Such an explanation involves certain assumptions: that phosphates and sulfates are obligatory excretory products for the elimination of which the organism is dependent upon the kidney; and that, in advanced renal disease, the urinary excretion of these substances is diminished. As far as phosphate is concerned, neither of these assumptions is supported by experimental work. Phosphate is largely excreted in the feces as well as the urine and its partition between feces and urine seems to be determined chiefly according to the needs of the organism for the elimination of acids or bases. Its level in the blood can be altered without appreciable effect on its excretion in the urine (12) and its elimination by the kidneys can be completely or almost checked by procedures that have no demonstrable injurious effects upon the kidneys (13). Even if it were granted that the phosphate accumulations in the serum of dogs after complete ablation of kidney function demonstrated by Atchley (10) were a direct result of the animals' inability to excrete phosphorus in the urine, it remains doubtful whether such extreme experiments have any important bearing on the problem of clinical nephritis. The deduction that similar accumulations observed in dogs after pyloric obstruction are due to renal injury (14) seems unwarranted.

Boyd (15) found that nephritic children with high serum phosphate showed negative phosphate balances on diets containing small, but adequate amounts of phosphorus. One experiment performed by Fetter (16) has an interesting bearing on the whole problem of the relation of hyperphosphatemia to acidosis and renal function in nephritis. Fetter administered disodium phosphate to a nephritic patient with high serum phosphate and low bicarbonate. As a result serum bicarbonate was restored to the normal level and urinary phosphate increased, but serum phosphate remained unchanged.

Because of the low concentration of sulfate in normal blood and the rapidity with which administered sulfate is excreted in the urine, it is generally assumed with some reason that sulfate is essentially a waste product and an obligatory excretory product for the elimination of

which the organism is dependent on the kidneys. Nevertheless, because of its low concentration in the blood and the consequent difficulties attending its determination, actual analytical data on the level of blood inorganic sulfate under normal and abnormal physiological conditions and its influences on sulfate excretion are scanty. Now that methods for the determination of inorganic sulfate on clinically practicable amounts of blood have become available, it is to be hoped that our knowledge of blood and urine sulfate and hence, the cause of hypersulfatemia in nephritis and its relation to acidosis may be placed on something more than an inferential basis. Meanwhile, it has been established with reasonable certainty by the present studies that sulfate accumulations must play a comparatively minor rôle in the production of the acidosis of nephritis.

Certain exceptions to the general rules concerning the incidence of high undetermined acid values deserve especial mention. Case 33030 had high undetermined acids on three occasions, although he had not vomited, had no symptoms of uremia and only a mild serum bicarbonate reduction. The undetermined acid accumulations may have been associated with acute gout from which he was suffering when the determinations were made. It is not meant to imply that the undetermined acid was uric acid, because the latter was determined by the Benedict direct method, which showed, on each occasion, about 10 mgm. per 100 cc., far too little to account for the excess of undetermined acid.

In three instances (29267, January 14 and November 19, 1925; 36041, February 23, 1925) high undetermined acid was observed with extremely high total base. The first and third of these were attended by no symptoms; but were observed in ambulatory patients during periods of relatively good health.

Total base disturbances

Figure 1 A shows that base itself is more variable in severe renal disease than in any other condition which has yet been investigated. Although, out of a total of 87 observations, 57, or far more than half, lay below the normal limits, 7 lay above and among these 7 are found three of the highest values ever observed, 2 between 183 and 185 and one almost 200 mM. It is unlikely that such figures were due to

analytical errors because excellent duplicate checks were obtained and because similar values have been found in no examinations in the normal series or in non-renal pathological subjects. Furthermore, it is more than a peculiar coincidence that two of the high bases should have been found in one individual, 29267, at an interval of 10 months. In only one instance (29267, November 19, 1925) was high base found at a time when a patient presented serious symptoms or evidences of uremia. In this one exceptional instance base was presumably falling, with the rather acute development of uremic manifestations and vomiting, from a still higher level.

As to the causes for high base concentration the data available are altogether too meager to permit any entirely satisfactory conclusions. High base occurred only when patients were or had recently been outside of the hospital on comparatively unregulated diets. In one case, 33247, administration of large amounts of fluid, with the production of water diuresis without salt restriction, was followed by reduction of the base concentration to the normal level within a week. One gains the impression that the insufficient kidney is unable to excrete large quantities of base unless large amounts of water are simultaneously made available.

Low base is encountered far more frequently than high base and is especially prone to develop in the uremic state. As base may be considered a measure of the total electrolyte concentration of the serum, it is also a measure of the substances normally responsible for the determination and maintenance of the osmotic pressure of the serum. On this account it has been suggested that the total electrolyte (base) deficiency in the serum in nephritis is an adaptive reaction to compensate for the presence of an abnormal excess of organic molecules, such as the end products of nitrogenous metabolism, which accumulate in the blood as the result of renal insufficiency. Gram (17) and others have, in point of fact, demonstrated, in certain cases of nephritis with nitrogen retention, diminished serum conductivity with normal or excessive freezing point depressions. A similar association of high non-protein nitrogen and low base is found in pyloric obstruction. Because, from the nature of the condition, it seems logical to presume that the reduction of base is the primary change, Hartmann, Scott and Moser (18) have sug-

gested that non-protein nitrogen retention is an adaptive reaction to compensate for the diminution of osmotic pressure that results from base deficiency. With the discovery that similar phenomena are frequently encountered in nephritis, Hartmann, Darrow and Morton (23) have more recently suggested that in this condition, also, urea retention is not a direct result of renal insufficiency, but only a reaction to compensate osmotically for serum electrolyte deficit. It is evident that, given an association of phenomena, the argument of cause and effect may serve equally well for the deduction of entirely opposite conclusions. The authors (19) have already shown that in diabetes,

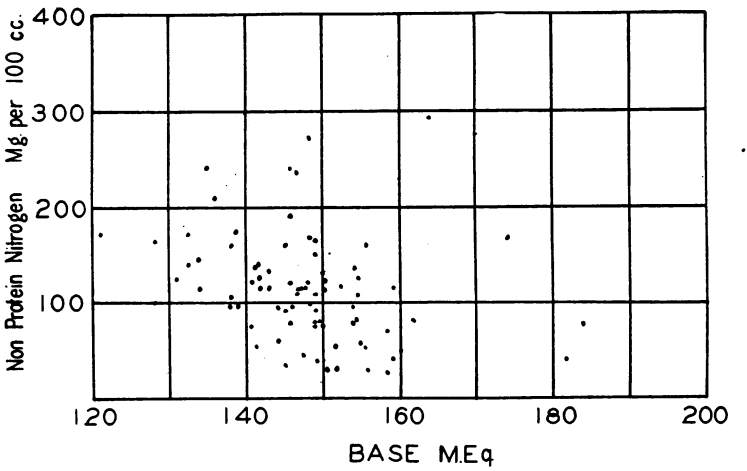

FIG. 3. NON-PROTEIN NITROGEN PLOTTED AGAINST BASE

low total electrolytes may be found in conjunction with high blood sugar without causal connection. In pyloric obstruction Gamble, McIver and Marsh (20) have shown that the electrolyte deficiency is the result of vomiting of Cl and NaCl. The accumulation of non-protein nitrogen in the blood may well be accounted for as the result of toxic destruction of protein, lack of water available for the formation of urine and later secondary circulatory disturbances akin to shock. In nephritis the high non-protein nitrogen seems to be referable directly to impairment of the excretory functions of the kidney; the low base to some tendency to waste salt.

That there is not even a close association between reduction of base and azotemia is clearly indicated in Figure 3. The slight tendency for high non-protein nitrogen and low electrolytes to coincide is certainly no more than one might expect if electrolyte deficiency and azotemia

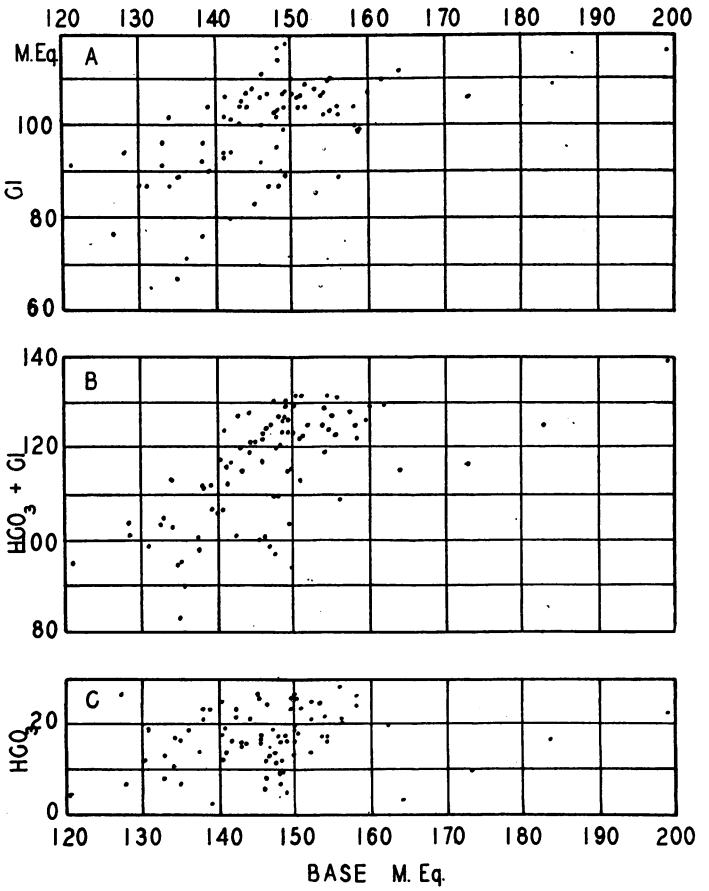

FIG. 4. Cl, HCO_3 + Cl AND HCO_3 PLOTTED AGAINST BASE

were both frequent but unconnected results of the same pathologic condition. Theoretically it is questionable whether a reduction of electrolytes to which body membranes show a peculiarly selective permeability would offer an effective compensation for increased

non-electrolytes toward the greater part of which these same membranes appear to be completely permeable.

Cl disturbances

Figure 1 B shows the level of Cl. Again the most striking thing is the variability of Cl concentration. Out of 148 determinations 56 lay below and 44 above the normal limits.

Of the acids in serum, Cl, which makes up about two-thirds of the total anions in normal serum, plays the chief rôle in the maintenance of osmotic equilibrium and is the only acid which could, without causing excessive disturbances of acid-base equilibrium, compensate for large changes in the concentration of base. Figure 4 A shows, as one would expect, that there is a distinct tendency for base and Cl to vary together. There is, however, considerable scattering in the figure, an indication that other variables influence the level of either base or Cl independently.

Figure 4 B shows the relation of the concentration of base to that of HCO_3 + Cl, the two chief acids of serum. The correlation is slightly, but appreciably, better than that of Figure 4 A. This is because, under certain circumstances, HCO_3 and Cl vary reciprocally. There are cases in which Cl or HCO_3 remains relatively high when base is reduced. In these cases the second of the two acids must yield.

Although, if base is reduced, there must be a proportionate reduction of acids in which, presumably, HCO_3 will share, it is impossible to demonstrate any statistical relationship between base and bicarbonate, as Figure 4 C shows. The failure to demonstrate such a relationship does not mean that reduction of base has no effect on bicarbonate, but that other factors, accumulations of other acids, depress HCO_3 at times when base is normal or elevated.

Total electrolyte disturbances

Comparison of the four figures in Figure 1 permits a certain general analysis of all the factors responsible for reductions of bicarbonate and the other electrolyte disturbances encountered in nephritis. If it is appreciated that base represents the sum of acid components, or the limit beyond which the acids can not increase, it is evident, first of all, that the total acid concentration is seldom greater than normal in

spite of the fact that both Cl and PO_4 + undetermined acid are often elevated. This explains the fact that HCO_3 never exceeds the normal limits.

If the determinations with high base only are considered it appears that the acids that combine with the excess are Cl or undetermined acids. Among the cases with low or normal base one finds a few in which Cl is above the normal level with HCO_3 proportionately reduced. Both these groups conform to the type which Blum, Delaville and Van Caulaert (21) and others have spoken of as "dry chloride retention." Such a term, however, carries the unproved implication that the hyperchloremia is a primary change, the result of inability of the kidney to excrete the chloride ion.

In most cases in which Cl is low, base is also diminished; the converse is not, however, as consistently true. HCO_3, alone may bear the brunt of base reduction.

It is evident that most of the disturbances described can be included under the general term "acidosis," if the latter is used in the sense in which Van Slyke has employed it to describe those conditions in which there is a deficiency of bicarbonate (or base not bound by acids other than carbonic). It is clear, however, that such a simple term hardly does justice to the great variety of electrolyte patterns observed in nephritis. Such reductions of bicarbonate may be associated with total electrolyte deficiency (low total base), high Cl, high phosphate, high undetermined acid, or a combination of two or more of these factors. It is also clear that profound disturbances of electrolyte equilibrium may occur without any serious alteration of bicarbonate, especially if base is high. It would seem obvious that more than one factor must be responsible for the production of so many diverse patterns and that, to be rational, therapy must take these factors into account.

Pathogenesis of electrolyte changes and their therapeutic implications

In discussing the subject of pathogenesis of electrolyte change and their therapeutic implications use will be made of certain metabolism data which are presented in the succeeding paper. In the last column of Table 3 when it is noted that the Cl-balance was negative it means that the Cl in the excreta collected exceeded that in the food and

fluids ingested or injected. There can be no doubt that in these cases the balances were negative. On the other hand, there can not be the same certainty about positive balances unless all excreta are examined and, therefore, no balances have been called positive unless stools and vomitus as well as urine were examined, except when the amount retained was extremely large.

Whether hyperphosphatemia is or is not a condition deleterious to the organism is a question that can not be answered. As a prognostic sign it is important. As an indication for therapy, it can neither be interpreted nor combatted until its cause is understood.

Undetermined acid accumulations are common and sometimes important causes of nephritic acidosis. In part these may be due to sulfate, perhaps a direct result of renal insufficiency. The magnitude of the accumulations, however, often exceeds any inorganic sulfur figures yet reported. The fact that high undetermined acid is usually found in the presence of persistent vomiting or starvation and can often be reduced to normal by the administration of carbohydrate and fluids suggests that the excess foreign acid may be partly ketone bodies, a result of carbohydrate starvation. Certainly an effort should be made in all cases with a tendency to acidosis of any kind to prevent the appearance and to promote the elimination of any further accumulation of acids. If, then, it is impossible to give carbohydrate by mouth because of vomiting or coma, it should be given by parenteral methods. A minor advantage of carbohydrate administration is its effect in reducing nitrogen metabolism. For sulfate retention, also, the promotion of diuresis and reduction of protein metabolism which result from the administration of carbohydrate fluids should prove beneficial.

Both low Cl and low base are found usually, but not invariably, in patients who have been vomiting. The exceptions in general are found among patients who have received diets poor in salt with high fluids. Where vomitus has been collected and analyzed the Cl found has been quite insufficient to account for the serum Cl deficiency. Excessive loss of Cl by other extrarenal channels may occur. Case no. 56247 excreted very large amounts of salt in his feces. In at least one period, this did not represent salt which had escaped absorption in the alimentary canal, because vomiting prevented the administration of fluids by mouth and he received the salt entirely subcutaneously in the form of normal saline.

It has been suggested that the hypochloremia of nephritis is due to transfer of Cl from blood and body fluids to the tissues, where it accumulates in excess. In dogs deprived of kidney function Atchley (10) was unable to detect such accumulations in any tissues which he analyzed. In our own studies, when all excreta were collected and analyzed it proved possible to account for changes in the level of serum Cl from observed salt and water balances. There would seem to be, in the most severe stages of nephritis with uremia, a loss of the ability of the organism to maintain the usual equilibrium between salt and water excretion and to maintain the concentration of these substances in the serum at the normal constant level. Cl continues to appear in the urine in relatively large amounts even when serum Cl has fallen far below the normal level and even below the level which has been called by Ambard the threshold of chloride excretion.

On the other hand, by giving large amounts of salt, it is possible to maintain Cl at the normal level or to restore it if it is reduced. It is even possible to push it above normal, especially if the fluid intake is not increased in proportion to the salt. Apparently the ability to eliminate large amounts of salt, especially in the absence of a proportional amount of water available for urine formation, is impaired.

In general serum base concentration follows that of Cl, although there are distinct exceptions to this rule. From this one can infer that chloride is largely excreted as BCl. Unfortunately, because of technical difficulties, base balances have been determined in no cases. Base is often reduced when Cl is normal or high and is sometimes high in relation to Cl. These exceptions to the general rule of parallelism between these two factors are probably referable to the accumulation of other acids that may specifically depress Cl, on the one hand; and impairment of the mechanism for the formation of ammonia on the other. Because of the latter the organism is forced to employ fixed base to neutralize any acid products of metabolism excreted in the urine.

It has been suggested by de Wesselow (7) that vomiting and reduction of Cl are adaptive reactions to compensate for retention of phosphate. Others have suggested that base and Cl deficiencies are adaptive reactions to compensate for abnormal accumulations of nonelectrolytic substances, presumably chiefly non-protein nitrogen, in

the blood. If these are adaptive mechanisms, which is seriously to be doubted, they would seem to be poorly adapted to their purpose and prone to run to excess. It would seem safer to avoid such teleological conceptions as adaptation, cause and effect, and to assume that departures from the normal pattern, if not in themselves deleterious, are at least evidence of some abnormal and presumably non-beneficial disturbances, and that restoration of the normal pattern is to be desired. On the other hand, it must be recognized that this does not imply that it is necessarily beneficial or even advisable to restore to normal any one component of a system without consideration of the others.

If retention of nitrogen is responsible for reduction of base, urinary nitrogen elimination should be promoted. The only means at our disposal for this purpose are production of polyuria by the administration of large amounts of fluid, and reduction of nitrogen metabolism. The latter can be effected only by reducing activity to the caloric capacity of the individual and feeding generous amounts of food with limited protein. If our conclusion that the nephritic tends to waste salt is correct, such a regime, if successful, will lead to base and chloride depletion if the conventional salt poor diet is given. Case no. 29267, February 25 and March 6, 1924, illustrates this fact. Other illustrations with better and more complete data could have been selected, but this one is chosen because the blood non-protein nitrogen was not greatly elevated and the patient was not vomiting during this period. It has long been recognized that the severe nephritic with hyposthenuria tends to become dehydrated easily. The best example of this tendency may be found in the response of such persons to restriction of fluid intake. Where the normal will rapidly reduce the urine volume in proportion to the fluid intake the nephritic may continue to exhibit polyuria for several days. But even the nephritic has not entirely lost the general tendency to maintain some relation between the salt and water content of the body. Salt is lost with the water during the development of dehydration. When, therefore, fluids are given without a proportionate amount of salt, to combat such dehydration, a salt deficiency which already exists is aggravated.

If, then, the administration of large amounts of fluid (or the elimination of a large volume of urine) is a desideratum in advanced nephritis

with uremia, enough salt must also be given to prevent salt depletion. How much salt should be given is another question. The authors have found that in cases in which there is no tendency to waste salt by extrarenal channels, 7 to 10 grams of NaCl daily (that is, 5–7 grams added to a salt-poor diet) is sufficient, if the urine volume is 2000 to 3000 cc. If because of previous misdirected dietary therapy or restriction of fluids, dehydration or salt depletion or both already exist, larger amounts of salt are required at first to overcome deficiencies and to permit the retention and storage of water without dilution of the electrolytes of serum and tissues.

Undoubtedly such treatment will, at times, result in the production of or aggravate an already existing edema. In this series edema was never observed, even after the subcutaneous administration of large amounts of saline, unless there were present obvious signs or symptoms of heart failure. This is generally recognized to be the rule in these patients, who ordinarily have a definite tendency to diuresis. The aim of forcing fluids and salt is to overcome and prevent dehydration and to promote the elimination of a large urine volume. Obviously, in the presence of heart failure, oliguria and edema, this end can not be effected unless cardiac compensation can be established. However, fluid restriction even in these cases should be moderate and can only be considered as a temporary expedient. Metabolism does not cease and the production of metabolites, the retention of which is the presumable cause of uremia and death in these cases, continues whether urine is excreted or not, with the result that these substances accumulate in excess in the body during periods of oliguria. The only salvation for such patients is the elimination of an adequate urine volume. Unless this can be induced by rest and digitalis a fatal outcome is inevitable.

The large amounts of fluid lost by extrarenal channels are often forgotten in the treatment of these cases. Loss of water by lungs, sweat, vomitus and bowel is of little benefit to the organism in the elimination of metabolic products. That this is becoming more and more generally accepted theory is evidenced by the ever diminishing use of so-called "depleting measures." In nephritis with edema from heart failure dyspnea is a striking feature, often the result of fixed acidosis as well as of the factors active in the production of cardiac

breathlessness. Vomiting is also a common symptom. Both these factors promote loss of water without proportional excretion of nitrogeneous metabolites and, in consequence, tend to cause concentration of the latter in the body. It is logical, then, to permit enough fluid to replace this loss while awaiting the action of diuretic measures.

When diuresis commences the administration of fluids should be increased. The inability to produce a concentrated urine may, otherwise, lead to the elimination of water in excess of solutes with the result that the latter accumulate in the body in increased concentration. It may be neglect of this consideration that has led to the frequently reported instances in which profuse diuresis with the delivery of edema fluid has been attended by increases of blood non-protein nitrogen or even the precipitation of uremia.

Attention has already been called to the fact that, in the types of nephritis under discussion, the usual tendency for water and salt metabolism to parallel one another is lost. Evidence of this is seen in the fact that even extensive edema may be associated with hypochloremia (case no. 56247 and 36041). (A more striking illustration is found in the previous paper (1), case no. 29796.) To what extent this may be due to previous salt restriction without comparable limitation of fluids and how far to specific loss of salt by renal and extrarenal channels has not been certainly determined. It is notable that out of 39 determinations of Cl in the presence of edema 21 were below normal limits and only 3 above; out of 22 base determinations 17 were low and only 1 high.

That by the over-zealous administration of saline solution alone Cl may be driven above the normal level appears from several of the cases in this series. Although hyperchloremia thus produced seemed to have no deleterious effect there is no reason for believing that it is a desirable thing. When it was observed in patients who had been under treatment in the hospital, receiving and eliminating large amounts of fluid, it was never associated with base excess. After the administration of sufficient amounts of carbohydrate and saline to reduce the undetermined acid to normal limits and to raise Cl to or above its proper level, HCO_3 or both base and HCO_3 still remained low. There has developed, in other words, a specific deficiency of bicarbonate, the most direct possible indication for administration of this salt.

The clearest illustration of this condition is found in Case 36048. When first seen by us this patient was in coma, extremely dehydrated, with blood non-protein nitrogen high, undetermined acid slightly elevated and base and bicarbonate greatly reduced. Two days later, after vigorous intravenous and subcutaneous administration of normal saline and isotonic glucose he was conscious and greatly improved. Base had risen almost to the normal level, the undetermined acid excess had disappeared and Cl had reached the abnormally high concentration of 118 m. eq. Bicarbonate, however, was still extremely low. For the next three days moderate amounts of bicarbonate were given daily, while the administration of salt and carbohydrate was continued. At the end of this time he presented a practically normal electrolyte pattern and was so much improved that he was able to sit up in bed and eat his own meals, making the further parenteral administration of fluids unnecessary.

In certain instances, then, base reductions develop in excess of Cl deficit, perhaps because base is wasted in the urine for the neutralization of foreign acids, since ammonia is unavailable. Under these circumstances bicarbonate administration is indicated. It is not, however, rational to attempt to restore base deficiency in general, or low CO_2 capacity due to other causes, by bicarbonate therapy. Ellis (22) has pointed out the tendency of nephritic patients to develop alkalosis and tetany, if they are given bicarbonate when it is not clearly indicated.

A word should, perhaps, be said about the serum proteins in relation to acid-base equilibrium, although the general subject of the proteins in renal disease will be treated in a separate publication. The concentration of serum proteins is extremely variable, but more often low than high and, therefore, can not be held responsible for reductions of HCO_3 or Cl. The rapid variability of the proteins suggests changes in the water content of the blood.

SUMMARY

Studies of the total electrolyte equilibrium of the serum have been made on a large series of patients with serious renal damage due to nephritis, vascular disease and "surgical" kidney conditions.

The most prominent feature of the data is the extreme variability of almost every electrolyte component.

Bicarbonate is usually below and never above normal. Phosphate increases are relatively insignificant factors in determining acidosis; and sulfate and organic acids are less important than had been supposed.

Undetermined (organic + sulfate) acid is usually found high only in the presence of carbohydrate starvation and is usually reduced when carbohydrate and fluids are given. It is suggested that the acids concerned may be partly ketones.

Base and Cl are extremely variable, but more often low than high. From evidence obtained from studies of Cl balances, examination of vomitus and other excreta, and the effects of therapy, it appears that fluctuations of these elements are due to inability of the kidney, and possibly other excretory organs, to maintain the usual balance between metabolism of salt and water.

In some cases true bicarbonate deficiency (i.e. reduction of base without reduction of acids other than bicarbonate) is observed.

The pathogenesis and therapeutic implications of these electrolyte disturbances are discussed.

PROTOCOLS

Case no. 29267. An American carpenter, aged 45, was admitted to the hospital February 18, 1924. Symptoms of headache, increasing weakness and failing eyesight had developed during the preceding two years, following a severe respiratory infection. Dyspnea on exertion and palpitation began in January 1924.

On admission his systolic blood pressure was 220, diastolic 100. He appeared somewhat pale; his heart was slightly enlarged; there was a systolic murmur at the apex and the aortic second sound was accentuated. There was some sclerosis of the retinal vessels.

He was discharged from the hospital March 8th, feeling much improved, with his blood pressure only 138/86.

His urine had shown a specific gravity of 1.002 to 1.010, a moderate amount of albumin and a few casts.

January 14, 1925, when he returned to the dispensary, he had been pursuing his occupation as a carpenter with no symptoms other than frequent morning headache.

He was readmitted to the hospital November 18, 1925. A few weeks earlier he developed another severe cold and somewhat later began to vomit. The vomiting increased in frequency and severity until he became unable to retain any food. He became increasingly somnolent and, shortly before admission, twitching of the face and extremities appeared.

On admission he appeared pale, wasted, dehydrated, somewhat stuporous, breathing rapidly and heavily, with face and extremities twitching. His heart was enlarged; his systolic blood pressure 180, diastolic 115. He had advanced albuminuric retinitis.

Administration of adequate calories and fluids by mouth failed because of continuous vomiting. His stupor deepened to coma and he finally developed convulsions.

At the time of the 14th study, December 17th, he was much improved, rational, and taking food and fluids by mouth without vomiting. December 22nd, he was able to sit up in a chair.

December 24th he was seized with pain in the flanks, urgency and dysuria, and pus was found in his urine. After this he became rapidly worse.

At the time of the last examination, January 9th, he was again stuporous and vomiting. His breathing was labored and stertorous and profuse râles were heard over both lungs. He died January 11th.

The urine showed a specific gravity constantly low, 1.002 – 1.010, a variable amount of albumin, casts and red cells. After December 24th, 1925 it became frankly purulent.

He had a progressive anemia, his red blood cells and hemoglobin falling from 4.7 million and 80 per cent, respectively, to 1.5 million and 45 per cent in the course of his disease.

Autopsy revealed: Scars of kidney with glomerular adhesions and atrophy and hypertrophy of tubules. Subsidiary: Cardiac hypertrophy. Fibrosis of myocardium. Focal pneumonia. Arteriosclerosis. Acute cystitis.

Case no. 60345. A married American woman, aged 21, was admitted to the hospital April 16, 1927.

During the preceding year she had developed increasingly frequent headaches, dyspnea on exertion, cardiac palpitation, polyuria and nocturia. Very recently puffiness of the face, swelling of her legs, pain and swelling of her throat had appeared, attended by a racking non-productive cough, diffuse backache and dull headache, and later vomiting. As the vomiting increased the edema diminished, but other symptoms, including dyspnea, became aggravated.

She appeared acutely ill, anxious and distressed, pale, cyanotic, with marked dyspnea and orthopnea, tachycardia and a blood pressure of 180/120. There was some puffiness about the eyes, extremities and trunk, but no definite edema. The heart was much enlarged, with a rough systolic murmur at the apex and accentuation of the aortic second sound. Over the bases of both lungs there were dullness and numerous râles, especially on the left side where the breath sounds were somewhat suppressed. The liver was large and tender. There were no significant retinal changes.

With rest, digitalis, and dietetic treatment she improved greatly and was discharged on June 26th. She was readmitted August 31st, in a stuporous condition

after recurrence of heart failure and vomiting. This time she did not respond to treatment, oliguria persisted, edema increased, and she died September 11th in coma.

Autopsy was not obtained.

At the time of her first admission to the hospital her urine showed a specific gravity of 1.017, much albumin, few red blood cells and leucocytes. Subsequent urines were essentially similar.

Blood count: 2.5 million red blood cells, 45 per cent hemoglobin, 8,200 leucocytes.

Blood Wassermann: Alcoholic antigen 0, cholesterol 4+, Kahn test 4+.

Blood culture proved sterile; no hemolytic streptococci were recovered from a throat culture.

Case no. 56247. A married Italian male, aged 39, was admitted to the hospital December 25, 1926.

During the preceding six months he had developed increasing frontal headaches, nocturia, dyspnea on exertion and fatiguability, with occasional dizziness and diplopia. In the middle of November, after a severe cold attended by a productive cough, he noticed increasing weakness, transient edema of the feet, puffiness about the eyes and anorexia. December 24th he vomited six times.

On admission the systolic blood pressure was 180, diastolic 105. He appeared chronically ill, his face pale and puffy, and had a dry cough. His neck veins were distended, the heart enlarged and there was a rough systolic murmur over the base of the heart. Many fine and coarse râles were heard throughout both lungs. There was well marked edema of the feet and legs.

February 1st, he was drowsy and twitching. Vomiting and hiccough were continuous. Dehydration had been prevented and a positive Cl balance established by the subcutaneous administration of normal saline and 5 per cent glucose solution. There was slight dependent edema. He died a few days later.

Autopsy was not obtained.

His urine showed a specific gravity of 1.005 to 1.010, much albumin, granular casts, and occasional red blood cells and leucocytes. He had a moderate anemia.

Case no. 33030. A single male, aged 31, was admitted to the hospital, April 22, 1924.

Since 1915 he had suffered from gout. Since November 1923 he had been troubled by attacks of vomiting and severe headaches. April 8th, 1924 he noticed bleeding from the urinary meatus and dysuria.

On admission he appeared pale and thin, with tophi in his ears, albuminuric retinitis, an enlarged heart, a blood pressure of 178/106, acute arthritis of both knees, ankles and the small joints of his feet and a temperature of 100°.

The first blood examination was made April 24th, two days after admission, during the acute attack of gout.

At the time of the second study the arthritis was subsiding. By May 6th, when he was free from arthritis, the blood non-protein nitrogen had fallen to 58 mgm. per 100 cc. He was discharged in this condition, greatly improved.

The third examination was made May 28th, when he returned to the dispensary in another acute attack of arthritis. He did not return again.

His urine showed a specific gravity of 1.005 to 1.012. At first there was much albumin and many red blood cells, but these diminished as the acute attack of gout subsided.

Blood counts: 4.1 to 3.6 million red blood cells, 85 to 60 per cent hemoglobin, 17,200 to 4,900 leucocytes.

Case no. 36041. A single male, aged 29, was admitted to the hospital February 23, 1925.

He was reported to have had acute nephritis in 1909, and after 1918 albumin and casts were repeatedly found in his urine. February 23, 1925, his blood pressure was 172/115, but it fell to 142/110 by March 4th when he was discharged. Physical examination was otherwise negative except for a small tophus on the right ear, and the patient was free from all symptoms.

In August 1925, he had an acute attack of gout lasting four or five days and relieved by cinchophen.

From April 1925 on he complained of more and more persistent suboccipital headaches, which continued in spite of medication. His systolic blood pressure also remained more consistently high and the diastolic pressure rose.

October 15th, 1926 the blood was examined again because of the persistent headache and he was ordered a diet restricted in both protein and salt. The fourth blood study was made November 12th, after he had been on this diet for almost a month. The fifth examination was made a month later when he had relaxed his diet. The third, fourth and fifth were all made while the patient was out of the hospital and the diets were never strictly controlled. The changes in dietary salt did not influence his symptoms.

His condition continued with little change until May 1927, when he began to complain of occasional cardiac palpitation. During the succeeding summer he went away for a month's vacation and, during this, was somewhat relieved of his headaches and other symptoms. However, they recurred as soon as he resumed his normal life.

After the latter part of December 1927, he had increasingly frequent attacks of cardiac palpitation and dyspnea. In March 1928, he also developed anorexia and nausea, with occasional vomiting.

April 7th he began to vomit at frequent intervals and the following day developed arthritis of the left great toe. His breathlessness and headache had, meanwhile, improved. The arthritic pain was rapidly relieved by cinchophen, but vomiting continued. About two weeks later he developed a cough and his dyspnea returned.

May 6th he was admitted to the hospital. He appeared anxious and distressed, rather wasted and dehydrated, breathing rapidly. The systolic blood pressure was 200, diastolic 150. The breath sounds in the interscapular regions were harsh. His heart was rapid, but not enlarged; the liver just palpable.

The x-ray revealed patchy broncho-pneumonia extending from the hilus regions of both lungs. There was still some swelling and redness of the left great toe.

From the sputum a few hemolytic streptococci were recovered as well as group IV pneumococci and staphylococci.

His condition changed little. He had an irregular low grade temperature, reaching from 100° to 101°. Attacks of breathlessness, anorexia, sour eructations and vomiting were, however, his chief complaints. His cough continued, with variable physical signs and continuous evidences in the x-ray of patchy broncho-pneumonia of both lower lobes. May 21st he showed definite, soft, pitting edema of the feet and ankles, although his heart action and fluid balance remained practically unaltered. He appeared at this time much more emaciated than he had on admission.

August 11th he began to vomit continuously and soon became comatose, dying August 14th. Autopsy was not obtained.

The blood pressure remained continuously elevated. The urine showed a low specific gravity, variable amounts of albumin and casts and occasional leucocytes. He developed no significant anemia.

Case no. 33247. A married woman, aged 50, was admitted to the hospital May 14, 1924.

She proved to have polycystic kidneys, a blood pressure of 204/146 and some sclerosis of the retinal arteries. Her only symptoms were blurring of vision, frontal headaches, dizziness and hot flashes.

The first blood examination was made the morning after she entered the hospital, when her condition was unchanged. The second examination was made six days later, May 21st, when she was subjectively greatly improved. Meanwhile she had received large amounts of fluids daily.

Her urine showed a specific gravity of 1.010 to 1.015, a trace of albumin and occasional red blood cells. A concentration test showed little variation of specific gravity: 1.013 to 1.015.

Case no. 36048. A married male, aged 58, was admitted to the hospital February 24, 1925.

At the age of 32 he had fractured his lower spine and since that time had suffered from incontinence of urine.

February 1st the patient developed a periurethral abscess and suppurative epididymitis that ruptured after about 5 days, leaving a urethral fistula. From the onset he was troubled also with constipation, anorexia and occasional vomiting.

On admission he was thin, drowsy, and appeared chronically ill. There was a

sharp kyphosis of the lower dorsal and upper lumbar spine, knee jerks and ankle jerks were absent and both legs were definitely atrophied, though not paralyzed. A periurethral abscess was found, discharging pus, blood and urine. The next day this was opened wide and was found to extend into the ischiorectal fossa and to the epididymis. March 5th some abscessed teeth and roots were removed under gas and oxygen.

After this he was unable to take fluids, became more and more stuporous and, by March 8th, when the first blood examination was done, was in coma, with deep, labored respirations.

Intravenous glucose was given with some benefit on this day and on the next intravenous glucose and subcutaneous salt and glucose. The second study was made on March 10th, after this treatment. The treatment was repeated on the 10th, and on the 11th and 12th intravenous sodium bicarbonate was given as well. By March 11th he was much improved, conscious and able to take fluids by mouth. The third study was made on the 13th, after this treatment. After this, intravenous and subcutaneous treatments were stopped because he was able to take food by mouth. His salt and fluid intake fell somewhat lower, but he seemed relatively well when the last study was made, on March 19th and when he was discharged on March 21st. However, he died about three weeks later at home.

Autopsy was not obtained.

Case no. 20921. A married woman, aged 35, was admitted to the hospital February 26th, 1925.

In 1914, 1919 and 1922, the last time following a pregnancy, she had had cystis and bilateral pyelitis.

February 22nd, 1925 she developed dizziness and blurring of vision, vomited, and felt feverish and weak. Three days later she "fainted" several times. February 28th severe headaches, dyspnea and palpitation began with extreme frequency of urination, thirst and vomiting. The next morning she had two convulsions for which she was sent to the hospital. On admission she appeared sick, anxious and restless and complained of severe occipital headache. Both optic discs were swollen and there were hemorrhages in both retinae. The heart was not enlaged, the blood pressure was 200/150.

Her urine showed a specific gravity of 1.010, heavy albumin, numerous casts and leucocytes.

The first blood examination was done when she entered the hospital. She was given large amounts of carbohydrate-containing fluids and salt for the first day and then a diet somewhat restricted in protein, but high in fluids and salt. She improved rapidly and by the time of the second study, March 9th, was eating her diet well and feeling quite fit. She was discharged on March 15th. After this she was followed in the Dispensary.

She was again in the hospital for vomiting and convulsions, October 12th to

26th. December 23rd to 27th and February 2nd to 16th she was in the hospital with symptoms and signs of acute pyelitis.

After this she was completely incapacitated, extremely weak, short of breath on the least exertion, with pains in the back, headaches, orthopnea, blurring of vision and cramps in the extremities.

March 19th she returned to the hospital after a severe epistaxis, emaciated, pale, with severe dyspnea and orthopnea, scattered râles at the bases of both lungs, right hydrothorax, enlarged overacting heart, enlarged liver, and slight pitting edema over the shins. She vomited after oral digitalis and developed massive inflammatory reactions about the sites of subcutaneous injections and was unable to take adequate fluids by mouth. However, she did retain a moderate amount of carbohydrate. At the time of the fourth blood study, March 29th, she had not vomited for two days, but had been in slight negative Cl balance since admission. By the time of the fifth study, April 7th, she was greatly improved, taking her diet without vomiting and had been in positive Cl balance. Improvement continued through the sixth study, April 19th, and until April 26th when she had another attack of heart failure that required digitalis. May 5th she was discharged improved.

She returned May 11th after repeated convulsions and vomiting, in coma, with a blood pressure of 288/130. Blood examinations were made before and after intravenous $MgSO_4$, which reduced the blood pressure to 174/110 and restored consciousness. However, she did not improve otherwise, vomiting continued, and fluids had to be administered subcutaneously. The urine volume remained small. May 14th pericardial friction appeared and by the 17th there was considerable edema of the ankles and evident hyperpnea. Bicarbonate was given but, by the time of the last blood study, May 20th, air hunger was severe. The edema had increased with the bicarbonate. She became steadily worse and died June 8th.

Autopsy was not obtained.

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