TOTAL ACID-BASE EQUILIBRIUM OF PLASMA IN HEALTH AND DISEASE

XII. A Study of Renal Edema

By JOHN P. PETERS, A. MAURICE WAKEMAN, ANNA J. EISENMAN and CARTER LEE

(From the Department of Internal Medicine of Yale University and the Medical Service of the New Haven Hospital, New Haven, Connecticut)

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In a study of the metabolism of patients with nephrosis and the nephrotic type of glomerular nephritis, the total acid-base equilibrium in the serum has been determined by a procedure described in previous papers of this series (1, 2). Briefly, this consists of the determination of the concentration of base and of most of the important acids of the serum: protein, bicarbonate, chloride and inorganic phosphate. It was hoped that such studies might throw some light on the pathogenesis of edema and especially on the relative influence of individual electrolytic components in the production of edema.

NATURE OF THE CLINICAL MATERIAL

A brief description of the chief characteristics of each patient will suffice for the purposes of the present discussion. It may be assumed that the patients were subjected to careful routine examinations and that relevant findings, when not mentioned, were negative.

Case no. 29122. A Greek, aged 30, in the four months before admission developed generalized subcutaneous edema, ascites and right sided hydrothorax. There was no history of antecedent infection; his blood pressure was moderately elevated, 154/85 on admission, but rapidly fell to normal. The urine always contained large amounts of albumin and casts, but no red blood cells.

Case no. 31190. An Italian male, aged 52, in the three weeks before admission developed moderate pitting edema of the lower extremities and back. There was no history of antecedent infection. His blood pressure on admission was 145/80, but rapidly fell to normal. His urine contained much albumin and many casts, but

few leucocytes or red blood cells. A year after discharge albuminuria persisted; but edema had not returned as long as he continued treatment. His blood pressure was 164/88 on one occasion, at other times normal. In 1924 he had become infected with syphilis and his Wassermann was found to be strongly positive.

Case no. 35628. (Protocol given at length in a previous paper (3)), a Polish male, aged 43, four months before admission, after tonsillitis, developed generalized subcutaneous edema, double hydrothorax and ascites. His blood pressure was normal. The urine contained much albumin, many casts, moderate numbers of leucocytes and variable numbers of red blood cells. Early in his course in the hospital he had two attacks of sore throat with fever. His edema did not subside until after tonsillectomy, March 17th.

Case no. 34854. (Protocol of first admission given at length in a previous paper (3)), a Polish male, aged 29, was admitted with generalized subcutaneous edema, double hydrothorax, ascites and splenic enlargement, which had first appeared two years earlier after an attack of polyarthritis and had been aggravated by frequent sore throats which had continued even after tonsillectomy. His blood pressure was 155/95 on admission, but soon fell to normal. His urine contained much albumin, many casts and leucocytes and variable numbers of red blood cells (sometimes gross blood). His course was marked by attacks of sore throat associated with fever and exaggeration of the hematuria. He was discharged in August, but returned the next June, after a prolonged stay in another hospital, temporarily free from edema, but sick and emaciated. After July 10th, symptoms and signs suggesting embolic phenomena appeared with increasing frequency. September 19th and October 8th he had typical apopletic seizures and died shortly after the second.

Autopsy revealed a massive cerebral hemorrhage; evidences of old and recent infarcts in several organs; a single, small fresh vegetation on the mitral valve; and large, swollen, kidneys that presented evidences of focal embolic lesions, diffuse glomerular nephritis and tubular degenerative changes.

Case 56883. An American male, aged 21, was admitted because of a profuse albuminuria that had developed after a severe attack of "grippe" five years earlier. His blood pressure was normal. The urine contained much albumin and moderate numbers of casts and leucocytes.

Case no. 50265. A Swiss male, aged 36, with tuberculosis of the upper lobe of the left lung and a chronic discharging right ear, developed edema of the lower extremities six months earlier. His blood pressure was normal. The urine contained large amounts of albumin and many casts, but no red blood cells nor leucocytes.

Case no. 61711. A boy of five, developed edema and pallor ten months before admission, after a sore throat. Five months before admission a normal appendix was removed because of an attack of abdominal pain associated with fever. He presented massive subcutaneous edema, ascites and hydrothorax. His blood pressure was normal. He had striking anemia. The urine contained much albumin and many casts throughout, but red blood cells were found only after December 27th. The edema was quite unresponsive to treatment. His course was punctuated by infections of the upper respiratory tract, culminating in mastoiditis from which he was just recovering (after mastoidectomy), when he developed fatal streptococcus peritonitis and septicemia. Autopsy revealed acute and chronic diffuse glomerular nephritis.

Case no. 56577. An American girl, aged 19, with a long history of multiple bone abscesses, developed general anasarca while she was under treatment for pelvic osteomyelitis with psoas abscess. Her blood pressure was normal. Her urine contained much albumin and some leucocytes. The blood examination was made after the abscess had healed and when she was almost free from edema. The urine remained unchanged.

Case no. 34753. A male, aged 19, developed general anasarca in the course of a chronic diarrhea. Both conditions persisted remittently until his death which was immediately due to acute peritonitis. Autopsy revealed: chronic proliferative tuberculous enteritis; tuberculous infection of the lymph nodes of the mesentery and the hilus of the lungs; chronic proliferative and exudative tuberculosis of the upper lobe of the right lung; acute tuberculous peritonitis; amyloidosis, involving particularly the kidneys.

Case no. 61090. A single, Irish female, aged 29, in the four months preceding admission, gradually developed massive generalized subcutaneous edema, ascites and double hydrothorax. There was no history of antecedent infection. Her blood pressure on admission was 160/108, but gradually returned to normal. Her urine throughout contained much albumin and many casts, but no red blood cells. She was discharged from the hospital October 31st and subsequent studies were made in the dispensary. After discharge she remained free from edema, although her urine continued to show much albumin and casts and her blood pressure rose as high as 195/110.

Case no. 62246. A married Italian female, aged 30, developed edema of the lower extremities five months before admission, without any recognized antecedent infection. In the latter part of pregnancy, in 1924, edema had also appeared. Her blood pressure was constantly normal. The urine contained much albumin, occasional casts and rare red cells. The edema, although not extensive, responded with difficulty to treatment and, up to September, 1928, recurred as soon as dietary therapy was relaxed.

Bacteriological studies of the urine, blood and throat or other possible foci of infection were made in most cases. Cultures of the urine proved sterile in cases 29122, 50265, 56883, 56577, 61090, 62246, 61711 and 34753. The urines of 50256, 56577 and 34753 were also repeatedly examined for tubercle bacilli but none were found; cultures and guinea pig inoculations were also negative. Blood cultures from 34854 were repeatedly negative, although the urine cultures on several occasions yielded non-hemolytic streptococci. Urine cultures from 35628, on two occasions recovered a Gram-negative, non-motile bacillus which produced no acid on most sugars and was not agglutinated by the patient's serum. Cultures from the abscess of 56577 yielded staphylococci. Throat cultures from 61090 revealed chiefly non-hemolytic, but some hemolytic streptococci. In the case of 61711, hemolytic streptococci were obtained repeatedly from the throat during the acute infections; the same organisms were later recovered from the mastoid, and finally from the blood and the peritoneal cavity.

Besides the examinations of the blood which are presented in the table, studies of nitrogen and chloride in food and urine were made on cases 35628, 34854 and 50265. Stools and vomitus of cases 61090, 62246, 61711 and 34753 were also examined for the same constituents. The notes on chloride balance in the table are derived from these data, which will be presented in more detail in another paper.

As a matter of routine all patients, as long as edema was evident, received diets which contained not more than 2 grams of Cl (as NaCl) daily. Limitation of fluid was purposely practised only while edema was extreme. Fluid intakes were, however, seldom large because, deprived of salt, patients lost their desire for water. When edema could no longer be detected increasing measured amounts of salt were given; these were discontinued if evident retention of fluid ensued. If rest, diet and salt regulation were not followed by diuresis, ammonium chloride, urea and sometimes other diuretic drugs were given.

ANALYSIS OF RESULTS

The results of electrolyte studies with weights of patients and notes on edema and salt balance are presented in table 1.

No attempt will be made in this discussion to differentiate the nephroses from the glomerular nephritides. In the authors' opinion such a differentiation on a functional basis is impossible and on a clinical basis extremely difficult. Only a classification on etiological grounds can be of great value. At certain stages of the disease 29122, 31190, 50265, 56883, 56577, 61090, 62246, 61711 and 34753 presented the characteristics of nephrosis. Of these 34753 proved to have a true amyloid nephrosis. Case nos. 50265 and 56577, with pulmonary tuberculosis and chronic osteomyelitis respectively, may well have the

same condition. Case no. 56883, with a definite infectious etiology probably has a chronic glomerular nephritis; 61711 certainly had such a condition. Case no. 61090, in the course of her disease, developed signs,—notably hypertension,—that exclude her from the nephrosis class. Case nos. 29122 and 31190 also had mild hypertension on admission to the hospital. Only 62246 presents neither history suggesting an infectious etiology nor findings incompatible with the diagnosis of nephrosis and the course of her disease has been characterized by bouts of irregular low-grade fever.

There is nothing in the data to distinguish the definite or presumable cases of nephrosis from those with clear cut glomerular nephritis.

Proteins. The only consistent finding in all cases, at times when clinical evidence of the disease was present, is reduction of the concentration of serum proteins. When these were fractionated (and presumably in other cases) this reduction was found to take place chiefly at the expense of the albumin fraction.

Expressing the concentration of serum proteins in terms of combining equivalents does not give an entirely correct impression of the actual amount of protein in the serum. When the proteins were not fractionated their combining powers have been estimated with the assumption of a normal average albumin : globulin ratio of 1.8:1. It is reasonably certain, however, that the true A:G ratios were much lower than this. As albumin binds far more base than globulin (7), failure to determine the two fractions separately and the assumption of a normal A:G ratio tend to exaggerate the protein figures. Allowance must be made for this fact in analysis of the data.

Organic (undetermined) acid. This fraction of the acids, estimated by subtracting from total base the sum of the determined acids, represents sulfates + organic acids. Observers who have studied the sulfate content of blood in patients with nephritis have found it increased only in the types of renal disease associated with hypertension (4, 5, 6). Consequently, if all other analyses and calculations are correct, "undetermined acid" in these studies could be considered as a reasonably exact measure of the amount of base combined with organic acids. Any error in the analysis or calculation of other acid factors or total base will be reflected in the "undetermined acid" value. It has already been pointed out that when protein is not frac-

TABLE 1

Data on patients with renal edema

Case number	Date	Weight	1 Serum total protein*	Albumin	Globulin	2 HCO_3	3 Cl	4 Inorganic P	5 Acid 1+2+3+4	6 Base	Undetermined acid 6-5	Blood non-protein nitrogen	Phenolsulphonephthalein test	Edema	Cl balance	Diet NaCl†	Treatment‡
	1924	*kgm.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m eq.*	*m.eq.*	*m.eq.*	*mgm. per 100 cc.*	*per cent*				
29122	February 2	69.1	10.9			26.1	106.0					33	55	++		0	
	February 14	61.9	11.1			25.2	102.9	3.2	142.4			33		+		0	
	February 23		11.1			25.1	101.3	2.6	140.1			29		0		0	
31190	May 26	71.6	10.0			27.4	100.7	2.6	140.7	156.5	15.8	32	45	++			
	June 4	68.3	(15.9)§			29.6	(118.1)§	2.6	(166.2)	153.5	(−12.7)§	31		+		0	
	June 6	68.4	10.2			29.2	102.6	2.6	144.8	158.5	13.7			+		0	
	June 9	67.2	11.0			21.9	108.9	2.1	143.9	160.2	16.3	42		+		0	NH_4Cl
	1925																
	May 15		12.7			30.3	103.5	2.0	148.5	156.0	7.5	23		±			
35628	January 12	76.4	10.0			20.7	110.8					61		++			
	January 20	75.0	10.2			21.8	114.1	2.8	148.9	171.4	22.5	41		++		0	
	January 23	72.7	10.4			10.8	122.6	2.7	146.5	162.5	16.0	45		+	+	0	NH_4Cl
	February 13	68.6	9.8			17.5	118.6	2.6	148.5	151.3	2.8	45		+	+	0	
	March 3	70.0	10.4			24.3	112.8	2.4	149.9	169.0	19.1	34		+		0	
	April 5	64.6	10.7			23.6	111.5	2.6	148.4	154.4	6.0	30		0		2	
	1924																
34854	October 16	71.5	11.3			15.6	117.9	3.9	148.9	160.5	11.6	43		++			
	October 23	66.8	10.8			20.2	112.9	3.4	147.3	157.7	10.4	35		+			
	October 28	64.8	9.8			22.4	116.2	3.5	151.9	160.8	8.9	51		+		0	
	November 6	66.6	9.0			21.3	110.7	3.3	144.3	156.0	11.7	53		+		0	
	November 13	67.5	10.3			21.0	114.0	3.0	148.3	146.0	−2.3	43		+	+	5	
	November 18	68.2	10.4			4.3	124.2	4.0	144.6	161.7	17.1	43		+		0	

	November 25	62.7	10.1			15.6	114.5	2.7	142.9	149.5	4.6	32		0		0	NH_4Cl
	December 6	63.5	10.4			25.4	106.0	2.8	144.6	140.2	−4.4	33		0		0	
	1925																
	June 24	59.6	11.9			19.9	114.5	3.1	149.4	151.3	1.9	44	43	±			
	July 3	61.0	11.7			22.0	110.3	3.1	147.1	152.2	5.1	34		±		0	
	July 14	63.9	12.2			19.6	111.5	3.5	146.8	155.0	3.2	38		+	+	+	
	July 28	64.9	12.2			22.1	108.9	3.1	146.3	149.5	3.2	45		+		0	
	1927																
56883	March 4	64.3	13.0			27.8	105.4	2.5	148.7	151.3	2.6	36	56	0			
	March 9	64.1	13.7			27.5	103.0	2.2	146.4	148.8	2.4	40		0		2	
	March 15	64.6	13.2			27.5	104.8	2.6	148.1	150.0	1.9	39		0		5	
	March 21	64.2	14.1			28.0	106.3	2.5	150.9	148.7	−2.2	21		0	±	5	
	1926																
50265	April 28	56.7	11.6			25.6	104.6	1.6	143.4	149.5	6.1	30	60	+			
	May 11	53.7	11.7			27.2	105.6	2.4	146.9	164.6	17.7	25		0	+	0	
	May 25	55.9	11.3			30.3	104.0	2.1	147.7	149.0	1.3	29		0	+	5	
	June 5	57.0	10.8			30.4	103.3	2.4	146.9	157.8	10.9	25		0	+	10	
	June 15	58.0	11.7			28.1	102.9	2.4	145.1	180.1	35.0	33		0	+	10	
	1927																
	February 15	60.0	12.6			26.3	101.3	1.9	142.1	148.7	6.6	32		0			
61711	September 29	19.0	5.5	3.2	2.3	14.8	112.2					33		++		+	
	October 4	16.0	7.4	3.9	3.6	5.5	112.8					45		++		+	
		Ascitic fluid					130.7					32					
	October 11	16.2	8.3	4.0	4.4	17.3	113.6					37		++		+	
	October 31	17.4	6.8	3.3	3.5	17.6	109.4					35s††		++	+	1	
	November 23	17.6	8.1				113.0					56		+	±	1	

* Protein, grams per cent, is converted to combining equivalents by multiplying by the factor 2.476. If the proteins are fractionated, the factor 2.733 albumin +1.869 globulin has been used.

† 0 = salt poor diet, 2 grams NaCl daily; figures represent grams of added NaCl; blanks indicate that patients were out of hospital; + indicates that salt content of diet is unknown.

‡ The treatment, in each instance, refers to special therapy given during the preceding period.

§ The values in parentheses differ so greatly from the others that they have been omitted from the general discussion on the assumption that there was some analytical error.

†† s after the non-protein nitrogen figures indicates that serum was analyzed.

TABLE 1—*Continued*

Case number	Date	Weight	1 Serum total protein*	Albumin	Globulin	2 HCO_3	3 Cl	4 Inorganic P	5 Acid 1+2+3+4	6 Base	Undetermined acid 6-5	Blood non-protein nitrogen	Phenolsulphonephthalein test	Edema	Cl balance	Diet NaCl†	Treatment‡
	1928	*kgm.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*m.eq.*	*mgm. per 100 cc.*	*per cent*				
56577	March 23		13.5	7.8	5.6	26.3	103.6	2.3	145.7	150.2	4.5	27		±			
	1926																
34753	October 21	66.5	7.4			33.0	100.8	3.0	144.2	142.9	−1.3	31		+			
	October 29	66.5	7.9			30.2	101.2	3.0	142.3	141.1	−1.2	33		+		0	
	November 6	65.2	7.1			29.6	101.0	2.7	140.4	144.8	4.4	35	48	+		0	
	November 16	66.1	7.4			30.5	105.5	8.3**	151.7**	150.9	−0.8**	25		+		0	
	December 2	65.2	9.2			31.1	99.5	2.3	142.1	141.3	−0.8	30		+		0	
	December 9	66.8	8.5			30.9	104.8	3.1	147.3	155.9	8.6	27	50	+		0	
	December 18	64.0	8.5			30.6	102.4	10.0**	151.5**	146.0	−5.5**	10s††		+		0	
	December 23	63.4	8.6			25.2	109.7	2.8	146.3	144.9	−1.4	23		+		0	NH_4Cl
	1927																
	January 7	68.0	10.4			30.2	103.4	2.8	146.8	144.9	−1.9	23		+		0	
	February 16	57.8	8.5			28.9	104.4	2.2	144.0	142.0	−2.0	32		+			
	April 8	71.3	9.0			30.0	105.2	2.5	146.7	149.6	2.9	25		+			
	July 1		8.2	6.0	2.3	29.4	104.4	2.2	144.2	151.9	7.7	29		+			
	July 22	70.6	7.8	4.2	3.5	28.1	105.8					27		+			
	1928																
	January 13		7.2	3.4	3.8	23.1	107.8	2.7	140.8	155.8	15.0	56		+		+	Peritonitis
	February 4‡‡	73.0	7.5	3.7	3.8	16.3	103.4	4.4	131.6	142.3	10.7	85		+		+	
	February 8‡‡		8.8	4.5	4.3	14.7	96.4	6.9	126.8	141.2	14.4	155		0		+	
	February 10‡‡		8.6	5.6	3.1		89.0	11.1				238		0			
	February 12‡‡		5.6	3.7	1.9		88.0	12.2		152.8		301	Post-mortem pleural fluid				

	1927																
61090	July 6	95.0	6.8	3.0	4.0	23.3	108.0	4.3	142.4	145.1	2.7	77		+++			
	July 14	94.3	7.9	4.9	3.2	16.6	114.6	2.9	142.0	152.6	10.6	38		+++		0	NH_4Cl
	August 4	92.0					114.5					60		+++		0	NH_4Cl + urea
	August 10	Ascitic fluid					115.2			148.0		74					
	August 11	89.3	7.3			24.4	102.0	4.0		146.5		72		+++		0	Urea
	August 17	Pleural fluid					118.8	4.0		146.2		70					
	September 2	81.5	9.0	5.6	3.5	11.4	122.6	2.4	145.4	148.6	3.2	34		++		0	NH_4Cl + urea
	September 13	55.9	9.6	6.1	3.7	22.7	109.0	2.6	143.9	144.8	0.9	23		+	+	0	NH_4Cl
	September 21	49.6	9.8	5.6	4.4	17.6	113.0	2.2	142.6	141.3	−1.3	42		0		0	NH_4Cl
	October 5	53.0	9.4	6.2	3.3	28.6	105.0	2.4	145.4	149.5	4.1	38		0		0	NH_4Cl
	October 20	56.4	9.7	6.3	3.5	30.1	104.0	2.9	146.7	152.0	5.3	34		0		0	NH_4Cl
	October 25	57.5	10.2	7.1	3.3	28.6	104.4	7.8**	151.0	156.1	5.1	31		0		0	
	October 31	58.3	10.4	6.9	3.7	28.6	105.2	5.1**	149.3	151.5	2.2	29		0		5	
	December 7		11.8	7.6	4.4	19.2	103.2	2.8	137.0	153.0	16.0	43		0		5	
	1928																
	February 6		14.0	9.4	4.6	22.5	111.2	1.8	149.2	150.3	1.1	46		0			
	June 14		14.6	9.8	4.7	25.4	106.4	2.0	148.4	150.4	2.0	48		0			
	1927																
62246	November 2	87.3	9.1	5.6	3.5	27.5	101.2	2.3	140.1	145.6	5.5	32	30	+			
	November 15	79.9	8.2	4.7	3.5	26.0	117.2	3.0	154.4	145.5	−8.9	16s††		+	+	0	NH_4Cl
	November 28	79.8	9.2	5.1	4.1	31.8	98.4	2.5	141.9	147.9	6.0	36		+		0	Urea
	December 5	80.2	8.8	5.4	3.3	31.1	97.6	4.4	141.9	153.2	11.3	29		+	+	0	Urea
	December 14	78.1	8.3	5.1	3.3	25.0	103.0	2.9	139.2	149.8	10.6	22		±		0	NH_4Cl
	1928																
	February 7	78.0	10.1			29.5	103.2	2.3	145.1	(137.2)§	(−7.9)§	26		+		0	
	March 7	74.5	8.7	4.4	4.4	29.0	102.0	2.3	142.0	144.8	2.8	27		0		0	
	April 5	76.4	8.3	4.3	4.0	28.4	104.9		141.9	143.4	1.5	26		±		0	

** If these P values, which have been discussed in the text, are in error, the corresponding acid and undetermined acid values must be incorrect.

‡‡ These determinations are omitted from the general discussion and statistical analysis because they are so largely due to the influence of the peritonitis.

tionated estimation of the base combined with it is too large. In the same studies, then, the estimated value for "undetermined acid" is correspondingly too small. This offers an adequate explanation for most of the negative (base < total determined acid) values recorded. Some of these (34854, December 6 and 34753, December 18), however, are so large that they can hardly be explained on this score. Furthermore, similar negative values were found in two instances when proteins were fractionated, 61090, September 21 and 62246, November 15. (There is some reason to doubt the accuracy of the determinations on 31190, June 4 and 62246, February 7.) It is hard to believe that the sum of acid equivalents in blood serum can ever exceed that of base; it is almost as hard to believe that the estimations of combining equivalents of acids other than protein can be greatly in error. It is also worthy of note that similar negative values have not been found in a large number of observations of normal human subjects, and have been encountered extremely rarely in patients with other pathological conditions.

On the whole organic acid concentration is seldom high and usually quite low. High values seem to appear at certain stages of the disease in individual cases only, and may well be due not to the renal disease itself, but to some concomitant symptoms or conditions such as intercurrent infections or vomiting.

Inorganic phosphate, with few exceptions, lay within the limits of normal variation. It usually fell slightly as edema disappeared and patients improved. Minor fluctuations can be observed following certain therapeutic measures, especially ammonium chloride. The latter will be discussed elsewhere. Occasionally decidedly high figures were obtained without any evident reason, notably in cases 34753, November 16 and December 18, and 61090, October 25 and 31. (The last two values in 34753 must be laid to the effects of peritonitis.) So suddenly and unexpectedly do these high levels appear and disappear that one is inclined to ascribe them to technical errors. Duplicates checked well and normal values were obtained from other patients on the same days. The sera were separated so expeditiously and with such care that there is no reason to believe that phosphorus escaped from cells to serum. In extensive studies of normal and diabetic sera no such high values were ever found. In this series they

appear in only two cases, but in each of these twice. In some instances among the earlier studies separated sera were kept in the refrigerator for some time before analysis. It was feared that this might have afforded opportunity for decomposition of phospholipins (other organic phosphoric acid compounds exist in serum in negligible quantities and are included with the inorganic phosphorus when the Benedict and Theis (8) method is used). Control experiments gave no indication of such decomposition of phospholipins. Moreover, most of the peculiar high values were obtained from sera which had not stood unduly long before analysis.

In general inorganic phosphorus concentrations lie within the normal limits. If the occasional high values are to be accepted at their face value, the rather general conception that hyperphosphatemia is a grave prognostic sign found only in the terminal stages of nephritis with uremia, must be qualified.

Chloride. If chloride concentrations are to be studied in relation to the pathogenesis and course of the renal diseases themselves, those observations must be omitted in which hyperchloremia has resulted from ammonium chloride administration. The last 2 observations on 34753, when peritonitis had caused persistent vomiting, must also be omitted. Hyperchloremia, often of a surprising degree, was encountered in a third of the remaining blood examinations, while abnormally low Cl was never found. This tendency for chloride to accumulate in the serum was more striking in some cases than in others and responded tardily, if at all, to chloride deprivation. Sometimes it persisted after edema had been absent for some time (35628, April 5). Usually Cl returned to normal when patients improved and became edema-free on salt-poor diets.

Even when there was no preexisting hyperchloremia, administration of ammonium chloride caused a greater rise of serum chloride than can be produced in normal human subjects by far larger doses of the drug than these patients received, and the resulting acidosis (bicarbonate reduction) was correspondingly exaggerated. Furthermore diuresis often failed to appear, large positive chloride balances were observed while the drug was being given, and excretion of the retained chloride was greatly delayed, often for several days after the drug was withdrawn.

Bicarbonate. Reduction of bicarbonate, when it occurs, does not seem to be due to accumulation in the blood of abnormal acids. Organic acid and phosphate are seldom elevated. Bicarbonate deficit (acidosis) is usually associated with hyperchloremia, low base or both. Because protein is low, bicarbonate is forced to yield less than it otherwise would to these factors and serious bicarbonate deficits are seldom observed except after ammonium chloride. When Cl remains normal as in 34753 and 62246, bicarbonate is often high in spite of base deficiency, by virtue of the small base combining powers of the diminished protein.

Base. The outstanding feature of the total base values is their variability. This is illustrated in figure 1. Of the 59 base determinations 35 lie either above or below the normal limits. The distribution of these abnormal values is illuminating: 29, or almost half of the total number of observations are low, while only 6 are high. Certainly, in this series of cases, base deficiency is far more common than base excess. The proportions of water to solids in several instances was directly determined. The weight of solids, as was expected, tended to parallel the protein concentration[1] and was therefore, low. This would seem to establish the fact that the total concentration of electrolytes per unit of water in the sera of these subjects was low, a condition which should cause the osmotic pressure to fall below the usual level (hypotonicity). Often enough this condition may have been produced or favored by the treatment, restriction of salt without purposeful restriction of fluids. It was, however, found (in case 34753 for example) before treatment.

The level of base bore no direct relation to that of any other serum component studied, nor was it associated with the concentration of non-protein nitrogen in the blood.

DISCUSSION

Only one abnormal feature is characteristically and consistently encountered in the electrolyte picture in the sera of patients with the hydropigenous nephritides: this is reduction of the concentration of protein, and especially the albumin fraction. Furthermore, this is

[1] Presumably because of their large lipoid content, sera from these patients contained a larger quantity of solids in proportion to protein than was found in the sera of other patients.

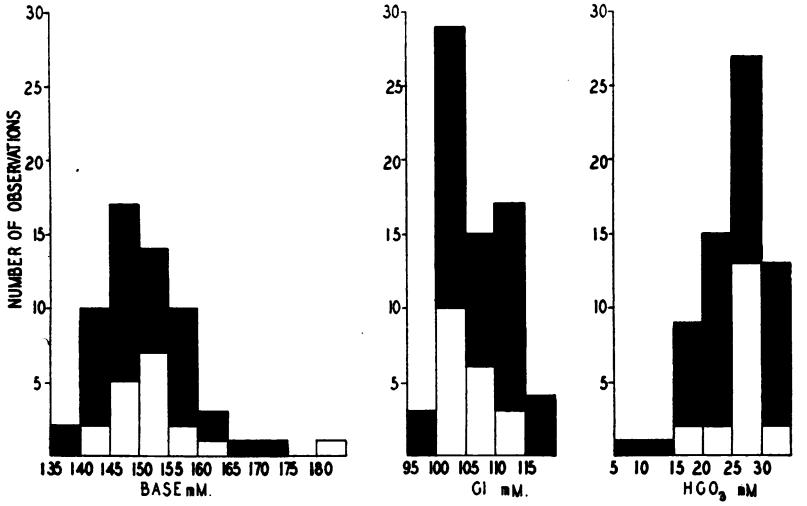

FIG. 1

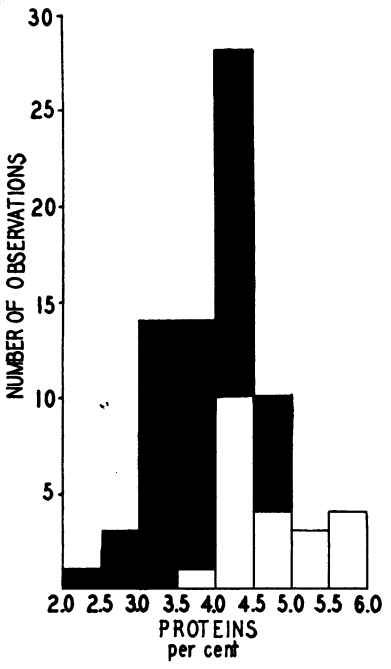

FIG. 2

FIGS. 1 AND 2

Columns represent number of times in which the constituent of the serum under discussion was found in a given concentration. Black portions of columns indicate the number of instances in which edema was present.

the only change that can be related with any consistency to the occurrence of or tendency to edema. Figure 2 shows that edema was almost invariably found when the total serum proteins were less than 4 per cent and never occurred when they exceeded 5 per cent. Linder, Lundsgaard and Van Slyke (9) found a similar relation between tendency to edema and protein concentration. This lends considerable support to the theory of Govaerts (10) and Schade and Claussen (11). They believe that protein deficiency, by reducing the colloid osmotic pressure of the serum, diminishes the force which ordinarily resists the tendency of hydrostatic pressure (blood pressure) to force fluid through the capillary walls into the tissues. In the edematous nephritides the colloid osmotic pressure is reduced even more than the total serum protein concentration would indicate, because the osmotic pressure of a gram of albumin is, as Govaerts (12) has shown, much greater than that of a gram of globulin.

Alterations of organic acid and phorphorus are rare and must play an unimportat part in the pathogenesis of edema and other symptoms.

Bicarbonate also appears to occupy a rather insignificant, if helpful position. Its behavior seems to illustrate beautifully what Gamble (13) has called its "mendicant position." It effaces itself as far as possible when there is too little base to completely satisfy inflated Cl; thankfully accepts what base the weakened proteins can no longer hold. It is hard to believe that it is acting more than a helpful secondary rôle, fitting in where it may prove useful.

Base has been found to be quite variable, sometimes above and sometimes below the normal limits. In this series it was low in about one-half the determinations, high in only about one-tenth. With the reasonable assumption that base is distributed in approximately uniform concentration throughout the fluids of the body, the frequent occurrence of base deficit is a cogent argument against the generally accepted theory that water accumulations in nephritic edema are entirely secondary to retention of sodium. Reductions of serum base are, perhaps, more frequent in the studies here reported because a more purposeful effort was made to restrict salt in the diet than to limit the fluid intake. However, low base concentrations were found in the sera of some patients before treatment was instituted.

Serum base excess was observed especially during the earlier part of the hospital course of patients 35628 and 34854. At these times both

patients had low-grade irregular fever and night sweats. High base was also encountered in the second blood examination made on case 61090. During the preceding period she had received ammonium chloride, which had caused nausea and vomiting, but little diuresis. Case 50265 developed extremely high base without the appearance of edema when (June 15), during a period of improvement, he was given 10 grams of NaCl daily with only 2000 cc. of fluid.

It seems difficult to avoid the conclusion that patients with hydropigenous nephritis have a tendency to retain both base and water. The fact that high base values were encountered with frequency in only certain cases might suggest that certain individuals, perhaps patients with special types of nephritis, had a greater predisposition to retain one or other component in excess. The rapid shift from base excess to base deficiency in 34854 indicates that, at most, such selective excretory defects can be characteristic only of stages and not types of the disease. It seems more likely that the concentration of base in the serum depends upon the nature of the salt and water metabolism. If salt is given with an inadequate amount of water, if water is restricted further than salt, or if the urine volume is small in proportion to the total fluid lost by the body (that is, when large quantities of fluid are lost by the sweat glands, as vomitus, or in the respiration) base excess should be expected. When no special attempt is made to limit fluids to an uncomfortabe extent and when loss of fluid by extrarenal channels is small, base deficiency is more likely to appear.

One may protest that studies of the serum alone do not offer a satisfactory view of the body as a whole, implying that base may accumulate in excess in other repositories. An adequate reply to such protests requires a knowledge of the nature of the base which is lacking in the serum, something which our observations do not offer. All investigators are agreed that the concentration of potassium in the sera of patients with the diseases under discussion is seldom, if ever, appreciably altered from the normal. Such changes as have been reported in individual instances do not exceed 1 mM. Calcium, on the other hand, is almost always low, the reduction being roughly proportional to and probably connected with the low serum protein concentration (14). This calcium deficit almost never amounts to as much as 2 mM. It can, then, be of little importance in the determination of

the base changes here reported. For the latter, alterations of sodium concentration must be chiefly responsible. In this case repositories in which it may be retained are presumably extracellular,—i.e., the edema transudates themselves. Examinations of such transudates by others (15) and in case 61090 have invariably failed to reveal base concentrations higher in relation to those of the serum than would be anticipated on the basis of current theories of osmotic equilibrium. Cl distribution is not so uniform (16); in two instances in the present investigation (61711 and 61090) the chloride concentration of transudates proved far higher than that of serum.

In about one-third of the determinations the concentration of Cl was distinctly above the normal limits of variation, while hypochloremia was never observed. This again is hard to explain on the theory that it is the basic ion Na^+ and not the acid Cl^- which is chiefly retained by patients with nephritic edema. The chloride excess can not be looked upon merely as a compensatory reaction against protein deficit because it is sometimes so large (35628, January 13; 34854, October 16, 23, 28, November 6) that, with base normal or high, it makes up for the protein deficit and forces a recession of bicarbonate as well. This would indicate that in the hydropigenous nephritides the Cl^- ion is usually excreted with the greatest difficulty.[2] Nor is there any direct or indirect evidence of importance to prove that this is not the case. Hyperchloremia has been found frequently by other observers (16, 17); high base rarely (14, 16, 17).

Changes in the concentration of the inorganic electrolytes can not be directly connected with the presence or absence or degree of edema. This is clearly shown in figures 1 and 2. Extremely distorted electrolyte patterns are less often noted in the absence of edema; but the number of blood studies on non-edematous patients are, for obvious reasons, too few to permit valid comparison. Distinctly abnormal electrolyte pictures involving disturbances of base, Cl and HCO_3 were certainly encountered when no edema could be detected. Due consideration must, of course, be given to the fact that absence of edema was produced and maintained in most instances only by contin-

[2] The authors do not mean to imply that the faulty excretion is necessarily due to abnormalities in the renal mechanism.

uous dieting and other therapeutic measures. The predisposition to edema remained and it is highly probable that it is this predisposition rather than abnormal accumulations of fluid in the body which is responsible for the disturbances of the serum electrolytes.

These conclusions do not agree with the current theory of the relative rôles of inorganic ions and water in the production of edema. They also appear, at first sight, to be contradicted by all recent therapeutic discoveries. It is, therefore, essential to investigate the arguments on which the theory of primary sodium retention rests. These can be briefly stated: 1. If dietary salt is restricted while water is given in comparatively large quantities, the water exchange of the nephritic patient will soon come into equilibrium at the required higher level. If, however, additional salt is given water will almost invariably be retained (18, 19). 2. Alkalinizing sodium salts, such as the bicarbonate, tend to exaggerate edema (23, 19). 3. Acidifying chloride salts (17, 20, 21, 22) and sometimes even potassium chloride (21, 22) (all of which can contribute only the Cl ion to serum), have a diuretic effect. 4. Finally, certain observers have reported abnormally high concentrations of Na in the serum of some patients with nephritic edema.

The last point has been already discussed. It remains to be seen whether the others really support the base retention theory or whether they can be as well or better explained by some other theory. It may be assumed that in either case the mechanism for salt and water excretion in the edematous nephritides responds to stimili of the usual nature, but with less facility. It follows that the presence of an excess of one component in the system will favor the elimination of this component or the retention of other components which will tend to restore the normal pattern of equilibrium. Excess of Cl in the body causes striking diuresis in the normal animal. The most outstanding fact in other studies and our own data is the absence of diuresis in the presence of serum Cl excess. When ammonium chloride produced diuresis it secured its effect only by raising serum Cl to a far higher level than that required for the same result in normal individuals. Chloride metabolism studies also revealed large retentions of Cl after ammonium chloride was given and delay in the excretion of the retained ion after its administration was ended. When the hydropige-

nous tendency was at its worst, the production of extreme hyperchloremia and consequent acidosis was entirely ineffectual as a diuretic measure (34854, November 13 to 18; 34753, December 18 to 23; 61090, July 6 to 14). Salt poor diets in which both base and Cl were presumably low were more often followed by a fall of serum base than reduction of serum chloride. All these results indicate that the Cl ion is excreted with extreme difficulty.

Gamble (17) has suggested that the hyperchloremia is a reaction which promotes diuresis in these cases. With this point of view the authors agree, but not with the apparent implication that it is a favorable adaptive reaction. It is merely the direct result of failure to excrete Cl. When this failure produces a sufficiently unbalanced electrolyte pattern diuresis results. Diuresis may be induced by exaggerating the imbalance by giving ammonia chloride.

By the same reasoning one would expect bicarbonate to favor retention of water. If there is a specific excess of Cl or any other acid ion in the blood the administration of bicarbonate is equivalent to giving so much base. The bicarbonate ion is excreted by the lungs, leaving the base to combine with the Cl. This is, of course, a step towards the restoration of a normal electrolyte picture and must, therefore, remove the stress which was forcing diuresis.

Transferring emphasis from sodium to chloride and water alters current therapy but little. Restriction of salt remains the most practical routine procedure. Diets poor in Cl are also poor in base. Without salt the desire to take fluids diminishes; therefore the restriction of salt results in fluid limitation without distressing the patient.

SUMMARY

1. The concentration of base and the most important acids (protein, bicarbonate, chloride and inorganic phosphate) in the serum, together with the nitrogen and chloride metabolism of patients with nephrosis and nephrotic types of chronic glomerular nephritis have been determined.

2. Neither the level of proteins in the serum nor the electrolyte pattern permits differentiation between nephrosis and the nephrotic type of chronic glomerular nephritis.

3. The only consistent and characteristic finding in all observations were serum protein deficiency.

4. This is also the only abnormality that can be related definitely to the presence or absence of edema. The latter was observed regularly when the total protein concentration was below 4 per cent and was observed in no instance when the proteins exceeded 5 per cent.

5. Organic acids and inorganic phosphate usually remain unaltered.

6. Bicarbonate changes appear to be merely secondary responses to disturbances of base, chloride and protein.

7. Hyperchloremia was frequently observed; chloride deficiency never. This, together with a tendency to develop excessive chloride retention with little diuretic response after ammonium chloride force the conclusion that the patient with hydropigenous nephritis has especial difficulty in excreting Cl.

8. Base was extremely variable, but more often low than high, an indication that water is excreted with quite as much or more difficulty than sodium.

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