TOTAL ACID-BASE EQUILIBRIUM OF PLASMA IN HEALTH AND DISEASE

XI. Hypochloremia and Total Salt Deficiency in Nephritis

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In the preceding article (1) it was pointed out that one of the electrolyte disturbances most frequently encountered in the serum of patients with nephritis with uremia was deficiency of the total electrolyte (base) concentration of the serum and that this was apparently instrumental in the determination of acidosis (reduction of bicarbonate) in a certain and rather large proportion of cases. It was also pointed out that chloride as well as bicarbonate was diminished in most of the cases with deficient base. Statistically a definite correlation between Cl and base reductions was demonstrated. It was also shown that slightly better correlation was obtained between Cl + HCO_3 and base, indicating that base reductions were compensated by both Cl and HCO_3. The correlation between base and HCO_3 was not clear because HCO_3 also yielded base to other acids, including Cl, which at times, accumulated in excess in the serum. This is an illustration of what Gamble (2) has called the "mendicant position of bicarbonate."

It was stated that reductions of Cl and base were encountered usually when: (*a*) vomiting was a serious symptom or (*b*) patients had received limited amounts of salt and had excreted large amounts of fluid. It was suggested that these patients have a tendency to waste salt through the kidneys and also, possibly, by extrarenal channels. The present article is intended to present in more detail the evidence on which these hypotheses were based.

METHODS

The procedures for collection and analysis of blood have already been discussed at some length.

The methods for control of diet and collection and analysis of excreta were only gradually developed as the work proceeded.

In earlier studies salt poor diets or salt poor diets to which a known amount of salt had been added were given. The Cl in such salt poor diets, estimated by the aid of the usual tables of food composition never exceeded 35 mM. (2 grams of NaCl) daily. Although low or falling serum Cl was usually attended by negative Cl-balances when patients were on salt poor diets, the addition of Cl to such diets sometimes resulted in positive Cl balances although serum Cl continued to fall. More rigid dietary control was therefore instituted.

All diets were prepared salt poor in the diet kitchen and their Cl-content carefully calculated from the best available food tables. Extra salt, carefully weighed, was provided in small flasks from the laboratory, to be added to the food during the day by the patient. Food refused by the patient was carefully reweighed, the salt and nitrogen in the refusals estimated and subtracted from the salt offered. The flasks were also reweighed in the laboratory at the end of the day if the extra salt had not all been used.

The decision to put added salt on the food in the wards was taken because it was appreciated that if such additions were made in the diet kitchen it was practically impossible to insure the complete transfer of the salt from cooking utensils to dishes; because such a technique required the separate preparation of each article of diet for every individual; and because it required separate weighing of the salt to be used on each individual dish in the diet. On the other hand, with the system adopted, if a patient was unable to eat any of the food he had salted it was impossible to estimate the amount of salt refused. As both appetites and digestions of some of these patients were most capricious, such occurrences were not uncommon. If salt thus lost were neglected apparent positive balances would result. When salt was given subcutaneously or intravenously, as it was in some of the most severe cases, salt intake could be calculated with considerable accuracy.

At first urine alone, collected with all the usual precautions, was analyzed for nitrogen and Cl. Attempts were also made to collect all vomitus, with only partial success. In later experiments great efforts were made to collect all excreta, urine, vomitus and feces.

Special urinals and bed-pans were provided by the laboratories to the wards. All specimens of urine, vomitus or feces were brought to the laboratory and placed immediately in the refrigerator in the receptacles in which they were originally collected. In the laboratory these specimens were quantitatively transferred, measured and subjected to analysis. If the stools were contaminated by urine, a surprisingly common occurrence considering the precautions taken against it, the urine was decanted and treated with the other urine.

Urine, feces, and vomitus were analyzed for both nitrogen and chloride. Urinary nitrogen was determined by the usual Kjeldahl procedure, Cl by Volhard-Harvey titration. In some of the earlier studies of vomitus Cl was determined in the same manner, while total and free acid were titrated with phenolphthalein and

dimethyl amidoazobenzol respectively as indicators. Later both feces and vomitus were treated separately by a special technique. They were transferred from their original containers to weighed covered two quart Pyrex "bean pots." A small amount of concentrated sulfuric acid was added and the mixture placed in the icebox. Before analysis container and contents were weighed together; the whole partially digested mass was thoroughly mixed to a homogeneous consistency and duplicate aliquots were weighed out for analysis. Nitrogen was determined by the usual Kjeldahl procedure; chlorides by the method of Van Slyke (3) with digestion for 12 or 24 hours. Control experiments showed that it was possible to obtain homogeneous mixtures and excellent checks by this method and that neither nitrogen nor Cl was lost in the course of the procedure.

In two cases urine was also analyzed for total base and inorganic phosphate. Base was determined by the method employed for the analysis of serum, phosphorus by uranium titration.

The most serious difficulties resulted from the physical and mental condition of the patients under investigation. Base and Cl deficiencies are seldom encountered except in advanced nephritis when uremic symptoms have appeared. Even before stupor and coma with incontinence develop to make all metabolism studies futile, minor, sometimes temporary mental disturbances appear to interfere with the proper coöperation between the patient and the metabolism staff. Seldom were complete collections secured daily for long periods.

DISCUSSION

The cases discussed in this article are the same as those from which serum electrolyte data were presented in the preceding paper (1). In table 1 are listed all the cases in which hypochloremia was observed. Complete data from these cases are not given, but only sufficient values of base and Cl to include the periods of hypochloremia with its development, when the latter was observed. Vomiting is also noted and some remarks are made concerning the factors that might have been responsible for the chloride deficit.

It may be added, in passing, that fluctuations of Cl concentration were usually associated with variations of base corresponding in direction though not in magnitude. This suggests that the two elements are interdependent. Concerning the nature of this interdependence little can be said. Base balances were not determined for technical reasons. Calculations of dietary base were not attempted because it was believed that they would be subject to too great an error. Complete analysis of all diets and refusals was out of the question. Administration of some diet composed of simple standard

TABLE 1

Patients with hypochloremia

Number	Date	Serum		Vomit	
		Cl	Base		
		mM.	*mM.*		
26672		74.6		++	Urinary retention
14188	December 9	127.1		+	
	December 16	78.6		+	Water without salt
18826		80.7		+	
26555	December 10	95.1		+	
	December 12	90.1		++	
29522	March 6	91.8		++	Urine contained little salt, but patient received practically none
	March 17	89.6		++	
	April 1	92.6		++	
29039	January 25	109.5		+	On admission
	January 26	88.6			After fluids, including subcutaneous saline
	January 27	97.4			After bicarbonate, saline and glucose
	January 28	98.5			After further glucose and saline
33049	April 26	86.8		+	
	April 30	86.8			Fluids without salt
26409	November 20	82.9		++	
	November 28	82.9			After salt poor diet. Negative Cl balance from urine alone
	December 5	87.5		+	After 7 days with low fluids and 7 grams of extra salt
	December 17	81.9		+	After 2 days of salt poor diet with high fluids
	December 27	78.1		+	2 days before death. Stuporous, taking no fluids
15012	December 5	106.1		0	On admission
	December 22	90.4		0	After salt poor diet with forced fluids
	January 20	103.7		0	Records inadequate
28049	February 8	89.2		(+)	
	February 11	80.4		(+)	Salt poor diet, high fluids. Negative Cl balance
	February 16	86.9		+	Negative Cl balance
	February 25	87.4			Negative Cl balance
	March 1	87.2		+	Negative Cl balance
	March 4	93.0			Subcutaneous saline on March 2 and 3
	March 7	87.2			Deep stupor
	March 8	89.9			12 hours before death — Taking no food, fluids nor salt
35795		92.2	146.3	++	On admission
52843	October 11	99.8	146.3	+	
	October 20	93.9	142.2	+	Vomited until October 17 and took little food, fluids or salt

TABLE 1—*Continued*

Number	Date	Serum		Vomit	
		Cl	Base		
		mM.	*mM.*		
35805	January 30	75.6	137.7	+	Vomited constantly and received little or no food, fluids nor salt
	February 3	70.7	135.6	+	
	February 5	67.2	135.1	+	
29267	November 19	105.5	173.0	+	On admission
	November 27	96.4	132.9	+	Cl balance slightly + (Urine alone studied. Collections incomplete)
	December 1	95.3	148.0	+	Bicarbonate and saline on November 30. Cl balance +
	December 6	96.2	137.5	+	Cl balance +
	December 17	102.4	133.6	0	Cl balance + ?
	January 2	94.4	128.1	+	Cl balance −
	January 9	90.8	120.5	+	Cl balance ?
56247	December 27	106.8	154.3	+	On admission
	January 4	99.2	149.4	+	After salt poor diet with high fluids
	January 11	99.0	149.2	+	Total Cl balance negative
	January 18	94.7	144.7	+	Total Cl balance negative
	January 25	92.5	140.5	+	Total Cl balance negative
	February 1	87.0	130.9	+	Cl balance somewhat uncertain, apparently slightly +
15900	February 19	76.6	127.4	+	
	February 26	89.6	138.7	0	Total Cl balance +
		88.7	155.8	+	
29796	April 7	93.7		++	Vomited constantly and took little or no food, fluids nor salt. Also received bicarbonate
	April 14	93.4		++	
	April 23	87.2		++	
	April 25	83.4		++	
22684	December 13	93.7		++	Vomited constantly and took little food, fluids nor salt. On salt poor diet
	December 19	90.3		+	
	December 31	75.4		+	
29635	March 18	107.4		0	On admission
	March 26	96.4		0	After salt poor diet with high fluids
	April 18	88.8		0	3 grams of extra salt added after April 5
18496	June 2	95.0	145.1	+	On admission
	June 9	99.2	158.1	0	After high salt and fluids
55948	November 25	90.9	132.6	+	
	December 9	86.7	134.2		No salt studies
18925	June 15	94.9		+	On admission
	June 20	78.1		+	No food, fluid nor salt taken
34802		91.6	137.9	+	On admission
		79.7	142.3	+	Practically no fluid nor salt taken
		82.8	145.4	+	Practically no fluid nor salt taken
23706		88.6	135.2	+	On admission
20921		105.6	151.2		
		91.6	149.6	+	Receiving bicarbonate and saline. Edema appeared

foods was contemplated, but was not adopted. Such diets would have been highly desirable from the standpoint of securing superior data, but, from the standpoint of therapy and the happiness of the experimental subjects, would have been less satisfactory than the diets actually given, which were chosen with attention to the tastes and caprices of the patients and with careful consideration of existing psychological and physiological disturbances of appetite, digestion and other functions.

Examination of table 1 shows that in 25 out of 63 instances low serum Cl was observed in patients who had, during a preceding period, received little or no salt, either because they had been given salt poor diets or because, on account of coma, stupor or vomiting, they had been unwilling or unable to take diet or fluids. Besides this in every one of the 16 examinations in which hypochloremia was found at the time of admission to hospital persistent vomiting had been an outstanding symptom. In three other instances Cl balances had been distinctly negative. In still another three, Cl was still low, but had risen from a previous lower level in response to the administration of sufficient salt to produce a positive balance. Data are inadequate for the analysis of four determinations. On three occasions bicarbonate had been given. Twice edema appeared to explain the coexistence of hypochloremia and a positive Cl balance.

This leaves only 7 out of 63 instances in which, while patients were in the hospital, reduction of Cl, which could not be explained on the basis of relative dietary deficiency, persisted.

Vomiting, which was a prominent feature in 55 of the total 77 and in 48 of the 63 hypochloremic observations, offers the most obvious explanation for the deficits of Cl and base. It was, however, entirely lacking on 7 of the 15 occasions when low Cl followed or was associated with insufficient salt intake.

It has generally been held, with much experimental support, that it is impossible by limiting salt intake to reduce significantly the chloride concentration of the serum of normal individuals, even if high fluids are given unless, at the same time, Cl loss by extrarenal channels is augmented. The normal kidneys appear to offer an effectual bar to chloride depletion. Furthermore, if chloride loss by other channels is increased as, for instance, in pyloric obstruction,

TABLE 2

Excretion of Cl in urine by patients with serum Cl less than 96.0 mM.

Case number	Date	Serum Cl	Urine volume	Urine Cl		
	1923	*mM.*	*cc.*	*mM. per liter*	*mM. per day*	
18826	June 7	80.7				Extreme oliguria with almost no Cl
	1925					
35795	January 30	92.2				
	February 1		765	44	34	By catheter
	February 2					
	1924					
26409	November 20	82.9				
	November 27		3,640	25	90	
	November 28	82.9	1,580	36	57	
	December 4		1,840	85	158	
	December 5	87.5	2,680	57	154	
	December 16		1,220	42	52	
	December 17	81.9	1,830	45	83	
29039	January 25	109.5	400	54	22	
	January 26	88.6	200	60	12	
	January 27	97.4	65	41	5	
	January 28	98.5	45	24	1	
	January 29	At autopsy				
35805	January 30	76.5				
	January 31		440	14	6	
	February 1		580	7	3	
	February 2		510	7	3	
	February 3	70.6				
	February 4		550	7	3	
	February 5	67.2				
28049	February 8	89.2	1,380	36	50	
	February 10		1,530	25	38	
	February 11	80.4	710+	14	10	
	February 15		2,540	18	47	
	February 16	86.9	2,400	21	49	
	February 24		3,130	32	100	
	February 25	87.4	2,880	28	81	
	February 29		1,760	38	67	
	March 1	87.2				
	1923					
26555	December 10	95.1				
	December 11		205+	59	12	
	December 12	90.1	1,390	54	76	

TABLE 2—*Continued*

Case number	Date	Serum Cl	Urine volume	Urine Cl		
	1924	*mM.*	*cc.*	*mM. per liter*	*mM. per day*	
29522	March 6	91.8	360	16	6	
	March 16		1,280	24	31	
	March 17	89.6	1,080	21	22	
	April 1	92.6	380	33	11	
	1925					
29267	November 26		2,520	41	10	
	November 27	96.4	2,800	40	11	
	November 30		1,270+	39	50+	
	December 1	95.3	1,770	42	74	
	December 5		950	164	156	
	December 6	96.2	520	263	137	
	1926					
	January 1		2,860	44	125	
	January 2	94.4				Involuntary
56247	January 17		1,560	18	27	
	January 18	94.7	1,500	30	44	
	January 24		1,500	24	36	
	January 25	92.5	1,560	19	29	
	January 31		1,390	21	29	
	February 1	87.0	1,390	21	29	
29635	April 17		1,970	18	26	
	April 18	88.8				
18496	June 2	95.0				
	1923					
22684	December 13	93.7	370	33	12	
	December 18		1,950	100	195	
	December 19	90.3	800	15	12	
	December 30		325	5	2	
	December 31	75.4	540	8	4	
	1924					
29796	April 7	93.7	580	30	17	
	1923					
18925	June 15	94.4				
	June 18			59		
	June 20	78.1		64		

urine Cl diminishes rapidly to vanish, finally, when serum Cl has fallen to a certain minimum level. Ambard (4) claims that Cl disappears from the urine when its concentration in the serum drops below 96 milliequivalents (5.62 grams per liter). In a series of

vomiting cases reported by Hartmann, Smyth and Moser (5) Cl seldom appeared except as qualitative traces in the urine when serum Cl was below 90 milliequivalents. Although it is doubtful whether the "threshold" concept of chloride excretion is tenable and although the level of the supposed threshold is probably not so exactly fixed as Ambard believed, there is an undoubted tendency to prevent the dissipation of chloride in urine when its concentration in the serum falls below a certain level. That this conservative property is lost in advanced nephritis is suggested in the general discussion above. It is more clearly demonstrated in table 2.

In this table are listed all patients with hypochloremia who had urine analysis at the time of the blood study. When data were available the concentration and the total amount of Cl are given for the day on which blood was taken and also the preceding day. As blood examinations were made before breakfast in the morning, they came approximately half-way between the two urine specimens. The amount of Cl excreted in the urine by some of these patients was surprisingly large. In two cases the 24-hour excretion amounted to as much as 70 mM. when the serum Cl lay between 80 and 85 mM. and in one instance 157 mM. was eliminated when serum Cl was only 87.5. That the ability to conserve chloride is not entirely lost is, however, evidenced by the fact that only minimal amounts were recovered from the urines in the three instances when serum Cl was below 80 mM.

Because the kidneys do not function in the normal manner for the prevention of chloride depletion one can not infer that the fault lies in the kidney itself. The authors (6) have shown that hypochloremia may develop in diabetes when there is no evidence of renal impairment. In this case Cl is displaced from combination with base to permit the latter to aid in the neutralization of ketone acids. Presumably the displaced Cl escapes through the kidneys. It is possible and not improbable that the leakage of chloride in nephritis is a response to disturbances of acid-base equilibrium in the body.

It has been claimed by Volhard and by others before him, that, as renal function diminishes, the ability of the organism to pass a concentrated urine is lost, resulting in a condition of hyposthenuria. When renal impairment becomes still more advanced the ability to

dilute the urine is also supposed to be lost so that the specific gravity of the urine becomes fixed at a constant level, which is that of a

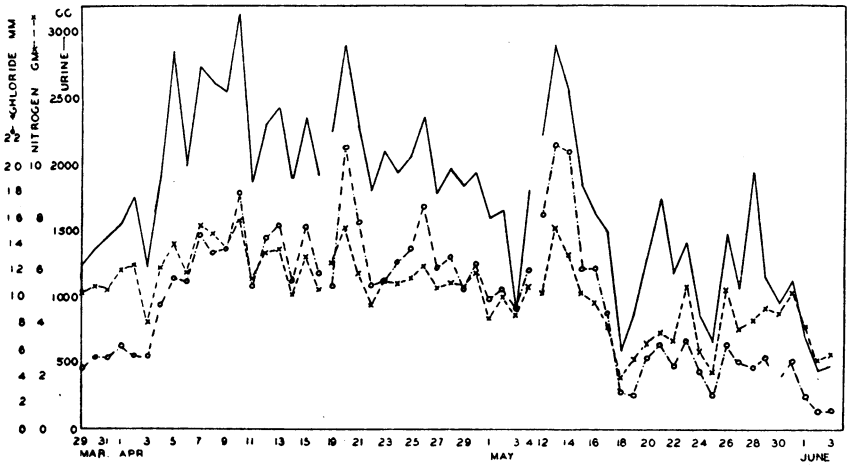

FIG. 1. CASE 20921

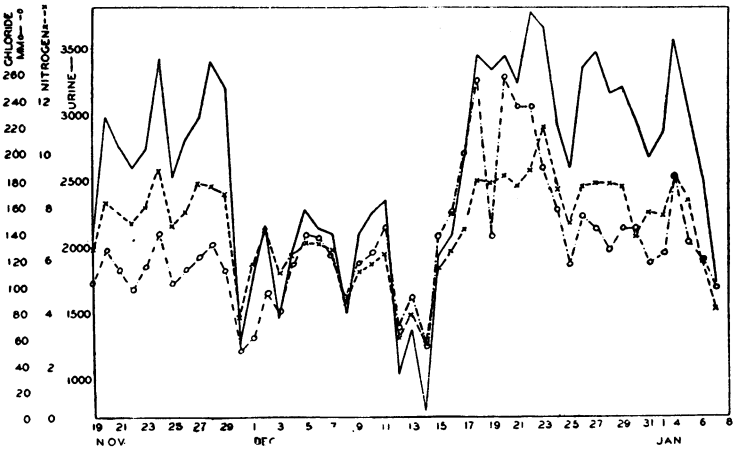

FIG. 2. CASE 29267

solution of the same molecular concentration as blood serum. This fixation of concentration is supposed to be exhibited in the excretion

of both salt and nitrogenous elements. It is quite conceivable that, under these circumstances; Cl might pass through the kidney at a fixed concentration related to the concentration of Cl in the serum. Some of the Cl metabolism data from 2 cases in late stages of nephritis are presented graphically in figures 1 and 2. Urine chloride

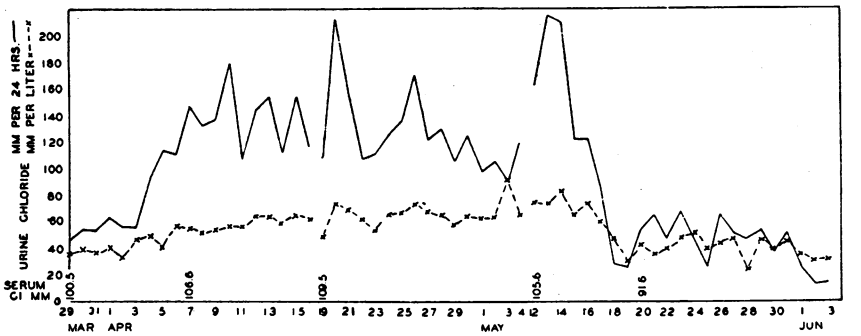

FIG. 3. CASE 20921

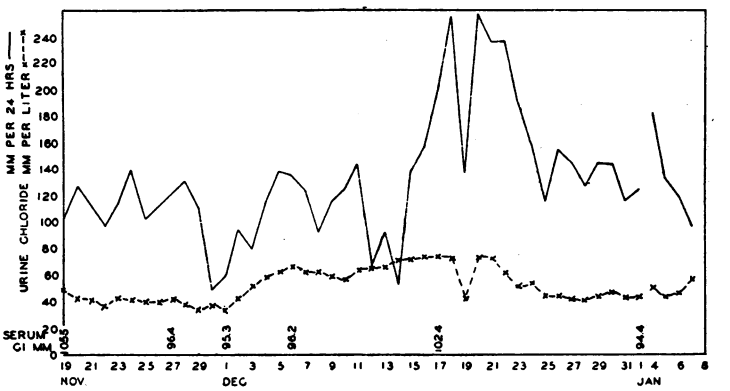

FIG. 4. CASE 29267

seems to follow rather closely urine volume, suggesting a close relation between them and lending some support to the theory of fixed concentration. On the other hand, when concentration and total Cl excretion are plotted together, as they are in figures 3 and 4, it becomes at once apparent that concentration is quite variable, over

long periods, although it is relatively fixed over shorter intervals. Comparison with the level of serum chloride also reveals no close relation with either concentration or total amount of chloride in urine. To be sure both rise considerably when the serum chloride is pushed up by the administration of large amounts of chloride as, for example, in the middle period of figure 3. On the other hand at the end of the course of study of this case both total excretion and concentration were at almost the same level as they were at the beginning, although serum Cl had fallen from 100.5 to 91.6 mM.

It is, apparently, possible to elevate the concentration of chloride in serum and in urine and to augment its excretion by the administration of sufficiently large amounts of salt. On the other hand, water and chloride excretion seem to be more dependent upon one another than normal under any given conditions, as is evidenced by the rough parallelism between them in the charts. Furthermore, chloride continues to be eliminated at a rather constant rate at levels of serum Cl that usually result in achloruria. Finally, in no case studied did even the most vigorous administration of salt lead to the elimination of a urine of high salt concentration even if serum Cl was driven far above the normal level. In fact only on two or three isolated occasions on single days in different patients did the urine chloride concentration equal that of the nearest serum observations. In these instances it is quite possible that serum chlorides were higher at the time of passage of the concentrated urine than they had been when the blood was withdrawn for analysis.

There is, then, an evident tendency to hyposthenuria and isosthenuria for Cl, although it is possible to cause considerable variation in the concentration of Cl below a certain level. The data suggest that the limit of concentrating power is the concentration of Cl in the serum.

If there is a definite hyposthenuric tendency, administration of either salt or water, within the capacity of the organism, should facilitate the excretion of the other. If there is any tendency at normal or high levels of Cl for salt excretion to be accelerated and for diuresis to occur, it would seem advisable to adopt measures to promote such a process. If, even at low levels of Cl ingestion and of serum chloride, excretion continues and is facilitated by water diuresis, administration

of large amounts of water without comparable quantities of salt can only lead to hypochloremia.

It has been claimed that in hyposthenuria not the concentration of any one substance, but the total molecular concentration of the urine becomes fixed and limited. In our studies it has been impossible to detect any inverse relationship between Cl and nitrogen concentrations. In figure 4, for instance, nitrogen concentration remains extremely constant throughout, seldom exceeding the limits, 2.5 to 3.0 grams per liter, while Cl at the same time varies from 24 to 78 mM. per liter. It is also worthy of note that the highest total excretion of nitrogen coincided with the period in which both salt concentration and salt excretion were maximal. Furthermore, it is at the close of this period that the blood non-protein nitrogen reached its lowest point, 137 mgm. per 100 cc. and the patient showed the greatest clinical improvement. Even if there were an inverse relationship between concentrating ability for Cl and nitrogen, it might be advantageous to give salt and water in large amounts to produce diuresis and thus to augment the total excretion of nitrogen.

It has already been stated that, if salt poor diets are given, at least when the ability to excrete water is not lost by reason of cardiac decompensation or some other complicating condition, hypochloremia develops. In this case the loss of Cl in urine alone is sufficient to cause a negative balance and may be held responsible, therefore, for the hypochloremia. When larger amounts of acid were given it often proved impossible to recover all the Cl ingested in the urine even when serum chloride was low or falling.

Because vomiting is such a frequent symptom in uremia it was expected that a large part of the Cl not found in the urine would be recovered in the vomitus. This did not, however, prove to be the case. The vomitus of uremic patients, although not a negligible source of Cl loss, is usually not an important one. This is clearly demonstrated in table 5. In this table urine and vomitus for the same days have been compared with respect to volume, Cl concentration and total excretion and, in some instances, free and total hydrochloric acid titrations. Although chloride concentration in vomitus often exceeds that in urine, the total volume of vomitus is so small in comparison with that of urine that the Cl actually lost in the latter is

usually far in excess of that in vomitus. In another sense vomiting is by no means a negligible factor in the production of hypochloremia. When vomiting seriously interferes with the ingestion of adequate amounts of food and fluids, the salt intake becomes of necessity limited and chloride wastage through the kidneys ensues as it does when a salt-poor diet is given.

It is of some interest to note that hypochloremia does not have the same limiting influence on gastric Cl elimination as it does on urine chloride excretion. Cl may be excreted in relatively high concentration in vomitus when the urine has become almost chloride free. This is best illustrated by case 35805, tables 1 and 5. Studies of pyloric stenosis would lead us to expect these results. In most of the observations deductions concerning the concentrating powers of the stomach can not be drawn because it is uncertain how much of the Cl recovered was derived directly from recently ingested food. A few cases, especially 35805 and 56247 received nothing by mouth except occasionally salt-free carbohydrate fluids; all salt was given subcutaneously.

Analysis of both vomitus and urine still failed to account for all the salt lost from the serum in some cases, so examination of feces was undertaken. In most instances the amount of Cl in the stools was appreciable but not great and appeared to be due to the loss of urine during defecation, a frequently neglected factor that in these experiments has proved to be a source of large error. It is surprising how few patients, especially among women, can control the vesical and anal sphincters independently with any consistent measure of success. Case no. 56247, table 4, however, does show a loss of Cl in the stools so large that it can not be explained as due to urine. Whether similar leakage of chloride via the bowel is a common cause of salt loss in nephritics or only a peculiar anomaly of this individual remains to be determined when other subjects presenting similar conditions are observed. It at least offers a possible explanation of some hitherto inexplicable chloride deficiencies.

Low serum base

In general fluctuations of serum Cl are reflected in parallel variations of base, although there are exceptions to this rule, as has been indi-

cated in the preceding article. This dissociation is especially common when, by the administration of sodium chloride, Cl is raised to or maintained at a normal level in the face of factors that would otherwise produce hypochloremia. Under these conditions base usually rises somewhat, but may fail to rise to the same extent as chloride. As a consequence at least a relative hyperchloremia develops. In the statistical analysis in the preceding article low base was found to be more frequent than low Cl.

To understand these changes certain new factors must be considered. Mention has already been made of the fact that determinations of base balances were not attempted. However, the urinary excretion of base was determined in two cases for short periods. The results in one of these are shown in table 3. Case no. 29267 (table 3) excreted large amounts of base in his urine throughout the period of observation, even when the concentration of base in the serum was far below the normal level. The concentration of base was at all times far more than sufficient to neutralize all the Cl (and, in addition, all the phosphorus) in the urine. Gamble (2, 7) has shown that when it becomes necessary to excrete an excessive amount of acid and, at the same time, to conserve base for the organism, the latter can be effected by the substitution of ammonia for fixed base in the urine. This mechanism is activated not only when organic acids accumulate in the body, as in carbohydrate starvation (2), but also when chloride is the acid which has accumulated (7). Apparently in nephritis this mechanism for the conservation of base is lost, or, at least, not exercised. Van Slyke et al (11), Linder (12), Rabinowitch (13) and others have shown that in advanced nephritis the formation of ammonia is impaired. This impairment may be the reason that the nephritic subject, even in the presence of a base deficiency, continues to excrete base to neutralize acids. Cl is such a strong acid that it can be excreted in the urine only as the neutral salt, carrying with it an equivalent amount of base or ammonia. Some weaker acids may appear in an acid urine in part in the free state. If, then, there is chloride wastage in nephritis and, at the same time, an incapacity to form ammonia, that chloride must be excreted chiefly as neutral salts of the form BCl. In other states the body when offered sodium chloride for the satisfaction of base deficiency is able to retain the base for

TABLE 3

Case no. 29267

Date	Weight	Fluid		Nitrogen			Cl			Urine		Blood N. P. N.	Serum	
		Intake	Urine	Intake	Urine		Intake	Urine		Base	B − Cl		Cl	Base
1925	*kgm.*	*cc.*	*cc.*	*grams*	*grams per liter*	*grams*	*mM.*	*mM. per liter*	*mM.*	*mM.*	*mM.*	*mgm. per 100 cc.*	*mM.*	*mM.*
November 19	59.0	2,900	2,060	9.7	3.1	6.4	127	50	103			167	105.5	173.0
November 20		3,500	2,980	9.8	2.8	8.2	128	43	128	178	50			
November 21		3,100	2,740	9.4	2.8	7.8	118	41	112	178	66			
November 22		3,400	2,600	9.6	2.8	7.4	142	38	98	164	66			
November 23		2,800	2,720	9.3	2.9	8.0	169	42	114	177	63			
November 24	58.8	4,750	3,420	8.2	2.7	9.4	147	41	140	196	56	160		
November 25		3,700	2,520	8.1	2.9	7.3	118	40	102	136	34			
November 26		4,900	2,800	7.1	2.8	7.8	118	40	112	154	42			
November 27	59.0	3,850	2,960	7.1	3.0	8.9	118	41	121	181	60	168	96.4	132.9
November 28		3,900	3,400	7.4	2.6	8.8	113	39	131	175	44			
November 29	58.1	4,530	3,200	6.9	2.7	8.5	149	35	111	188	74			
November 30		3,950	1,270+	5.5	3.0	3.8+	309	39+	50+					
December 1		5,000	1,770	6.0	3.3	5.8	39	34	60	104	44	167	95.3	148.0
December 2		2,230	2,170	0	3.3	7.1	53	44	96	155	59			
December 3		4,180	1,470	0	3.7	5.5	212	54	80	118	38			
December 4		2,880	1,950	5.1	3.2	6.2	75	59	116	164	48			
December 5		3,720	2,290	3.3	2.9	6.6	272	61	139	190	51			
December 6		4,550	2,040	0	3.2	6.6	282	67	137	192	55	163	96.2	137.5
December 7		3,670	2,000	1.8	3.2	6.4	60	62	123	172	49			

December 8		4 260	1,500+	2.9	2.9	4.4+	152	61	95+					
December 9		3,170	2,000	7.4?	2.8	5.5	73	59	117	154	37			
December 10		4,400	2,160+	4.1	2.7	5.8+	357	58	125+	163+	38			
December 11		4,470	2,250+	3.3	2.8	6.2+	222	64	144+	188+	44	158		
December 12		4,550	1,040+	4.5	2.9	3.0+	234	66	69+	86+	17			
December 13		1,720	1,380+	1.9	2.9	4.0+	86	67	92+	123+	31			
December 14		4,400	750+	4.6	3.7	2.8+	161	71	53+					
December 15		3,420	1,920+	2.0	3.0	5.7+	173	72	138+					
December 16		2,900	2,090+	2.1	3.0	6.3+	219	75	157+					
December 17		4,150	2,660+	4.6	2.7	7.2+	233	75	200+			145	102.4	133.6
December 18		4,500	3,440+	7.7	2.6	9.0+	239	74	255+					
December 19		4,320	3,340	8.1	2.7	8.9	251	41	138	297	159			
December 20		4,760	3,440	7.9	2.7	9.2	239	75	258	300	42			
December 21	56.2	4,450	3,230+	7.0	2.7	8.8+	402	73	236+					
December 22		4,600	3,780	8.1	2.5	9.4	92	62	236			137		
December 23		4,450	3,660	8.1	3.0	11.0	91	52	190					
December 24		4,550	2,920	5.5	3.0	8.7	68	54	159	267	108			
December 25	51.8	4,500	2,600	7.5	2.8	7.4	79	45	116	179	63			
December 26	52.3	4,520	3,360	6.1	2.6	8.8	137	45	152	217	65			
December 27	51.8	5,420	3,460	7.1	2.6	8.9	121	42	144	210	66			
December 28	51.0	4,550	3,160	9.2	2.8	8.9	118	41	128	198	70			
December 29	51.4	4,580	3,200	9.5	2.8	8.8	132	45	144	183	39			
December 30	50.6	4,510	2,960	9.7	2.3	6.9	185	49	144					
December 31	51.1	4,250	2,680	9.6	2.9	7.8	183	44	118					
1926														
January 1	51.8	3,960	2,860	9.6	2.7	7.7	178	44	125			165	94.4	128.1
January 4		4,600	3,570	8.0	2.6	9.2	178	51	183	229	46			
January 5		4,050	3,000	8.1	2.8	8.3	183	44	133	188	55			
January 6		4,000	2,520	3.7−	2.3	5.9	260	48	120	137	17			
January 7		6,060	1,720+	8.0−	2.4	4.1+	578−	58	97+					

TABLE 4

Case no. 56247

Period	Days		Fluid		Nitrogen					Cl					Initial		
			Intake	Urine	Food	Urine	Stools	Vomit	Balance	Intake	Urine	Stools	Vomit	Balance	Weight	Blood N. P. N.	Serum Cl
			cc.	*cc.*	*grams*	*grams*	*grams*	*grams*	*grams*	*mM.*	*mM.*	*mM.*	*mM.*	*mM.*	*kgm.*	*mgm. per 100 cc.*	*mM.*
II	7	Total	16,130	11,530	56.6	53.0	21.6	0	−12.0	265	540	910	0	−1,185	61.6	77	99.2
		Daily	2,300	1,650	8.1	7.6	3.1	0	−2.6	38	77	130	0	−169			
III	7	Total	19,330	9,100	65.6	42.8	12.9	0	−9.9	327	253	503	3	−433	59.3	98	99.0
		Daily	2,760	1,300	9.4	6.1	1.8	0	−1.4	46	36	72	0	−62			
IV	7	Total	21,240	8,530	60.9	39.8	12.9	0	−8.2	301	320	503	0	−422	60.4	88	94.9
		Daily	3,030	1,220	8.7	5.7	1.8	0	−1.2	26	31	72	0	−60			
V	8	Total	28,280	14,630	12.4	42.2	3.7		−33.5	758	243	253	116	145	60.9	121	92.5
		Daily	3,540	1,830	1.6	5.3	0.5		−4.2	94	31	32	15	19			

TABLE 5

Vomit and urine Cl and serum Cl

Case number	Date	Urine			Vomit							Serum Cl
		Volume	Cl		Volume	Cl		Free acid		Total acid		
		cc.	mM. per liter	mM.	cc.	mM. per liter	mM.	mM. per liter	mM.	mM. per liter	mM.	mM.
52843	October 15	1,400	55	77	220	44	10	0	0	14	3	
	October 16	1,800		27	515	55	29	0	0	32	16	
	October 17	2,000	19	38	145	55	9	5	1	25	4	
	October 20	2,200	36	80	525	58	31	16	8	27	14	
					255	24	5	0	0	2	1	
	Total	7,400		222	1,660		84				38	
35795	January 30				425	55	22	20	9	85	36	92.2
					45	84	0	0	0	0	0	
	February 1	730	44	32	63	149	10	Trace	Trace	76	5	
	Total			32			32				41	
45891	October 4	1,200	72	87	450	89	39	21	9	40	18	
	October 5	1,800	46	84	145	111	15	31	4	54	8	
	October 6	1,000	63	65	270	75	21	0	0	24	6	
	October 8	1,000	68	72	170	63	10	0	0	12	2	
	October 9	1,300	43	56	730	68	50	0	0	48	3	
	Total	6,300		364	1,765		135				69	
35805	January 30											75.6
	February 1	500	7	3	770	34	26					
	February 2	500	7	3			22					
	February 3	500	7	3	470	36	17	22	10	28	13	70.6
	February 4				600	43	26	20	12	33	19	
	February 5											67.2
	Total	1,500		9	1,840		91					
35407	January 12				100	82	9					
					200	55	12					
	Total						21					
60345	May 17–26						51					
48570	January 15	1,500	26	39	106	66	7	32	3	50	5	
	January 18	800	93	70	100	170	17	0	0	5	1	
	January 19	1,500	70	108	90	67	6	0	0	30	3	
	Total	3,800		217	296		29				9	

TABLE 5—*Continued*

Case number	Date	Urine			Vomit							Serum Cl
		Volume	Cl		Volume	Cl		Free acid		Total acid		
		cc.	*mM. per liter*	*mM.*	*cc.*	*mM. per liter*	*mM.*	*mM. per liter*	*mM.*	*mM. per liter*	*mM.*	*mM.*
34802	October 9											91.6
	October 10				200	82	16	4	1	21	4	
					230	31	7	0	0	2	0	
	October 11				57	29	2	0	0	18	1	
					153	94	15	19	3	73	11	
					418	34	14	0	0	23	10	
	October 14				78	50	4	6	0	28	2	79.7
	October 15				255	72	18	0	0	22	6	
					125	46	6	0	0	22	3	
	October 19				200	79	16	9	2	38	8	
	October 21				73	98	7	0	0	45	3	
	October 22				136	89	12	0	0	24	3	
					160	123	20	0	0	50	8	82.8
	October 23				70	140	10	0	0	39	3	
					122	87	11	0	0	13	2	
	Total				2,277		158				64	
29267	December 1	1,700	42	73	260	50	13	0	0	41	11	95.3
	December 2	2,200	51	111	230	62	14	12	3	73	17	
	December 4	2,000	60	118	31	70	2	16	0	73	2	
	December 5	2,300	68	156	186	96	18	8	1	46	9	
	Total	8,200		458			47		4		39	
	December 6											96.2
56247	January 13	1,170	38	32			3					
	January 25	1,560	45	29	1,100+	45	41+					92.5
	January 26	980	34	34	1,400+	79	56+					
	January 27	1,470	45	31	290+	55	19+					
	Total	4,010		94	2,790+		116+					

combination with endogenous carbonic acid while excreting the Cl neutralized by ammonia. In nephritis such adjustment is difficult, if not impossible. Therefore, to restore complete normal equilibrium, it may be necessary to administer bicarbonate as well as chloride at times.

de Wesselow (8) has suggested that vomiting is itself an adaptive

reaction tending to compensate for accumulation of other acids in the serum in the presence of base deficit. In theory vomiting, by causing specific excretion of Cl by extrarenal channels, should provide base in the body to combine with other acids and to maintain bicarbonate more nearly at the normal level. Whether vomiting is an adaptive reaction or not, a little study and reflection must show that its actual effect can only be to aggravate the deficiency it is aimed to correct. Even if it did cause the elimination of large amounts of chloride without corresponding quantities of base, by interfering with the intake of base, it could only further the essential deficiency it was intended to combat. It has already been shown, however, in table 5, that the actual total Cl excretion in vomitus in nephritis is usually relatively small. Further analysis of the vomitus figures shows that the greater part of the Cl lost is combined with base. Achlorhydria or hypochlorhydria is the rule in nephritic vomitus and not only the "free" but also the "combined" acid is low. Although the difference between acid thus titrated and total Cl can not be interpreted quantitatively as chloride combined with fixed base, it must afford a rough measure of the latter.

One must conclude, then, that vomiting in nephritis does not eliminate Cl alone, but also a considerable amount of base. This offers a partial explanation of the fact, already noticed (1), that even the most persistent emesis was not attended, in these studies, by bicarbonate excess. Further reason for the absence of such alkalosis is doubtless found in the tendency, discussed above, to lose base in the urine in combination with other acids which could, ordinarily, be neutralized by ammonia.

The total Cl content and state of hydration of the body

Thus far attention has been confined to the concentration of Cl in the serum—and, by inference, in the body—and consideration of the true Cl content of serum and tissues has been neglected. Unfortunately this is almost impossible to estimate because the distribution of chloride in the body and the factors which influence this distribution are little known.

The subject will be discussed at greater length subsequently. It is sufficient to state here that even across membranes that appear to

be permeable to anions, peculiarities of distribution appear that suggest that such permeability is relative. It is, apparently, conditioned by (*a*) certain acid patterns that are characteristic of individual tissues and (*b*) the need for readjustments in response to local endogenous acid production.

Such considerations alone would make the estimation of the chloride content of the body, or even its changes, from corresponding serum concentrations exceedingly hazardous. The data that have been presented dealing with salt balances indicate that, in general, increases in blood salt concentration, other things being equal, are associated with retention of salt. Attempts to relate the two quantitatively have not been eminently successful. Besides the incalculable distribution of Cl in body fluids and tissues, the proportions of these fluids and tissues themselves are constantly changing to increase the difficulty. In certain studies that will be presented later attempts have been made to estimate gains or losses in tissue by means of the nitrogen balance and, employing these for the correction of weight changes, to determine by difference alterations of the water content of the body. Similar methods applied to some of the cases of this series tend to show that the body water content in advanced nephritis is quite variable and that fluctuations in water content are attended by similar changes in salt balance.

Although it is quite evident that blood water and tissue water are not always closely related, in the majority of instances anhydremia is attended by hemo-concentration. Striking exceptions may be pointed out, usually in the presence of edema, when the blood may be inspissated while the tissues contain an excess of fluid. Examples of this may be found in a diabetic case previously reported by the authors (9), and in one case of this series. With the exception of such cases, however, in which hydrostatic factors may have played the chief part, the water content of the blood seems to reflect changes in the hydration of the body as a whole.

Attention has already been called to the variability of serum proteins in this series of cases and to the probability that these variations are partly due to changes in blood water. Simultaneous determinations of serum volume by the dye method of Keith, Rowntree and Geraghty (10), in case no. 56247 have shown that this is the case. The results

of this study have been presented in table 6. In other conditions reduction of the salt content of serum has been found only in states of dehydration or after dehydration. The normal organism certainly responds to changes of body salt by excreting or retaining excessive quantities of water. Only after the salt stores become definitely depleted does the body retain water without an equivalent amount of

TABLE 6

Case no. 56247

Date	O_2 capacity	Cell volume	Serum protein	Serum Cl	Serum base	Serum volume		
						Dye method	From proteins	From O_2 capacity and cell volume
	volumes per cent	*per cent*	*mM.*	*mM.*	*mM.*	*cc.*	*cc.*	*cc.*
December 27	10.7	25.6	12.5	106.8	144.1		4,170*	4,170†
December 28						4,170		
January 4	11.2	27.2	16.7	99.2	149.4	3,588	3,120	3,900
January 11			16.5	99.0	138.3	3,387	3,150	
January 18	10.6	27.5	16.0	94.7	144.7		3,250	4,110
January 25	12.4	28.6	15.0	92.5	140.5	3,170	3,480	3,450
February 1	9.3	23.8	13.7	87.0	130.9		3,800	4,910

* Assumed to be identical with that determined by dye method on the following day. Subsequent values in this column are calculated on the assumption that serum volume and serum proteins vary inversely.

† Assumed to be identical with that determined by dye method on the following day. Subsequent values in this column are calculated by the following formula

$$\text{Initial serum volume} \left(\frac{100 - \text{initial cell volume}}{\frac{\text{Initial oxygen capacity}}{\text{Subsequent oxygen capacity}}} (100 - \text{subsequent cell volume}) \right)$$

$$= \text{subsequent serum volume}$$

salt. In spite of the fact that the regulation of salt and water metabolism in nephritis is deranged some tendency for the two to be associated is apparently retained. Salt depletion in case no. 56247 is attended by steady reduction of serum volume and, until the terminal period, when heart failure determined the appearance of edema, by loss of body water.

This offers still another indication for the administration of both salt and water to such patients. Water alone, while it may overcome dehydration, further aggravates the hypochloremia by dilution.

CONCLUSIONS

Hypochloremia and deficiency of base in the serum in advanced nephritis seem to be the results of:

1. A tendency for both base and chloride to be excreted in the urine when serum Cl has fallen below the level which, in the normal individual determines achloruria.

2. Vomiting, which attains its effect less by producing direct chloride loss than by interfering with salt intake.

a. The vomitus in uremia contains little free hydrochloric acid. A considerable amount of the Cl in such vomitus exists in the form of BCl.

b. Although the concentration of Cl in vomitus remains high even in the face of advanced hypochloremia the total Cl loss by emesis is usually small compared with that in the urine.

3. Considerable quantities of Cl may be lost in the feces in certain cases even if there is no diarrhea.

There is no necessity of postulating any peculiar redistribution of chlorides in the body to explain the hypochloremia.

The distribution of Cl is discussed as are the relations of changes in body water and salt content. It is pointed out that hypochloremia and low serum base are usually attended by anhydremia and general dehydration.

The therapeutic implications of these findings are discussed.

BIBLIOGRAPHY

1. Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, Carter, J. Clin. Invest., 1929, vi, 517. Total Acid-Base Equilibrium of Plasma in Health and Disease. X. The Acidosis of Nephritis.
2. Gamble, J. L., Ross, G. E., and Tisdall, F. F., J. Biol. Chem., 1923, lvii, 633. The Metabolism of Fixed Base during Fasting.
3. Van Slyke, D. D., J. Biol. Chem., 1923, lviii, 523. The Determination of Chlorides in Blood and Tissues.
4. Ambard, L., Physiologie des Reins, 1919.
5. Hartmann, A. F., Smyth, F. S., and Moser, A. E., Am. J. Dis. Child., 1926, xxxii, 1. Chemical Changes in the Body Occurring as the Result of Vomiting.
6. Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, Carter, J. Clin. Invest., 1925, ii, 167. Total Acid-Base Equilibrium of Plasma in Health and Disease. VI. Studies of Diabetes.

7. Gamble, J. L., Blackfan, K. D., and Hamilton, Bengt, J. Clin. Invest., 1925, i, 359. A Study of the Diuretic Action of Acid Producing Salts.
8. de Wesselow, O. L. V., Quart. J. Med., 1925, xix, 53. The Excretion of Chlorides by the Healthy and Diseased Kidney.
9. Bulger, H. A., Peters, J. P., Lee, Carter, and Murphy, C. F., Arch. Int. Med., 1925, xxxvi, 857. The Concentration of the Blood and of the Urine in Diabetic Toxemia.
10. Keith, M. M., Rowntree, L. G., and Geraghty, J. T., Arch. Int. Med., 1915, xvi, 547. A Method for the Determination of Plasma and Blood Volume.
11. Van Slyke, D. D., Linder, G. C., Hiller, A., Leiter, L., and McIntosh, J. F., J. Clin. Invest., 1926, ii, 255. The Excretion of Ammonia and Titratable Acid in Nephritis.
12. Linder, G. C., Quart. J. Med., 1927, xx, 285. The Effect of Mineral Acid on Acid-Base Regulation in Health and in Nephritis.
13. Rabinowitch, I. M., Arch. Int. Med., 1924, xxxiii, 394. The Origin of Urinary Ammonia.