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Research Article

SERUM ELECTROLYTE STUDIES IN NORMAL AND PATHOLOGICAL CONDITIONS: PNEUMONIA, RENAL EDEMA, CARDIAC EDEMA, UREMIC AND DIABETIC ACIDOSIS

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In the past ten years there has been an increasing interest in the electrolyte structure of the blood. This interest grew from a realization of the impossibility of interpreting isolated changes in single constituents. Methods for partitioning the anions developed with much greater rapidity than did a similar approach to the cations. In 1923 the authors published with Loeb and Palmer a series of studies on the serum acids including a few base partitions. Although the acid determinations were quite consistent, base results were unsatisfactory due to the unreliability of the sodium and potassium methods. With the development of an accurate method for estimating total cations, a more satisfactory understanding of the total electrolyte structure is possible. This method has evolved slowly and in our hands has not been considered reliable prior to the past three years, when our data became sufficiently consistent to report. We have discarded most of our work before that time.

Even before an acceptable method for total base appeared, Van Slyke and co-workers filled the only essential remaining gap in anion analysis by determining a formula for base bound to protein. It is now possible, therefore, to arrive at a fairly accurate picture of the total electrolyte distribution in serum. It is proposed in this paper to discuss the results obtained by studies carried out on normals and patients with pneumonia, nephritic acidosis, nephritic edema, and diabetic acidosis. A few observations during diuresis are included.

METHODS

The methods employed are those described in a previous paper (1). We are using the formula for base bound to protein published by Van Slyke and associates in 1928 (2). There remain, however, two points to be discussed; first, the technique of blood removal, and, second, the limit of error in the methods.

A tourniquet was used in most instances. The duration of stasis, however, was so short that the order of magnitude of the changes caused by it does not approach that of the alterations caused by disease. Moreover, 60 cc. of blood were removed rapidly through a large needle decreasing thereby still further the possibility of changes due to stasis. Table 1 shows, in normals, the negligible effect of a tourniquet properly used. Since the conditions in which we were most interested are often associated with an extremely low blood pressure, it is practically impossible to draw blood without increasing venous pressure. Also, those particular conditions are characterized by a concentrated blood, requiring more blood to provide the usual amount of serum. Unless the supply of material for analysis is adequate for duplicates and provides a slight surplus for accidents, the whole study may be wasted; for it must be emphasized that our particular interest is in the balance of acid and base as well as in individual ionic variations. Each experiment, therefore, should include a measurement of every component.

A critical examination of the various methods employed brings greater satisfaction with the bicarbonate analysis than with any other method. This is accurate and reliable to a high degree, both in the mechanical procedures and the calculation of resulting milliequivalents. Chloride also causes few misgivings. Phosphate analysis is relatively easy and whatever uncertainty there may be regarding calculations is minimized by the small total phosphate content of serum. The high percentage of error in sulphate analysis on normal blood becomes insignificant when it is recalled that total sulphate is usually less than 1.0 m.Eq.; as sulphate increases, accuracy improves so that high figures can be accepted to within 1.0 m.Eq. We find the sulphates important only in renal insufficiency (where they are elevated). There are two possible defects in dealing with base bound to protein. The formulae are based on data so difficult to obtain that they undoubtedy will be altered by further study, and the albumin-globulin ratios are, in our hands, unreliable determinations. We have assumed Van Slyke's "normal" ratio $\left(\frac{1.6}{1}\right)$ for all bloods. A maximal and unusual error, such as would occur in a case of renal edema with a very abnormal ratio, is 1.0 m.Eq. The influence of clinical changes in hydrogen ion concentration is too slight to be significant. A constant pH of 7.35 is, therefore, assumed. At this reaction the simplified formula is protein m.Eq. = P $\times$ 2.36 (P = protein per cent of serum). It is safe to say that base bound to protein is at the present time the most unreliable estimation on the acid side. Base bound to ketones leaves much to be desired in the translation of grams per liter to milliequivalents and we offer our figures as approximations only.

Total base is a far more important determination than any single acid, because as the term implies, it, alone, gives an idea of the amount of base present in the serum, and serves the further important function of delimiting the level of total electrolytes. It is a treacherous method, requiring constant use of the reagents with frequent blanks to prevent occasional errors. No method in clinical chemistry requires more vigilance to make it acceptable. It is still the weak link in any such study as the present one; a fact much under emphasized in the literature of this field. The limit of error of the total base method under the best conditions is ±2.0 m.Eq., whereas the total error in the various anions is approximately ±1.7 m.Eq.

NORMALS

Table 1 requires no explanation. Attention is called to the relatively insignificant effect of the tourniquet and to the unimportance of brief exercise. Duplicate observations on single individuals within a few hours agree in all details. A much larger group would be required before one could give reliable averages. The anions need no comment. Total base, however, is surprising in its narrow range between maximum and minimum (148.4 to 155.1 m.Eq.) and its low mean 151.9 m.Eq. For example, Peters, 1926, (3), finds an average of 155.7 m.Eq. and in 1929, (4), 153.8, and Sunderman, Austin and Camac, (1926), (5), give 154.7 m.Eq. Darrow and Hartmann, 1929, (6), however, on children and adults find 150.7 m.Eq. The more recent results reveal lower rather than higher concentrations.

Undetermined acid or total base minus total acid (B−A) is low. We do not find large quantities of acid that must be called "organic acid." Our usual figures would be covered by the amounts of lactate and sulphate normally present in serum (1 to 2 m. Eq.). This differs strikingly from the earlier results reported by Peters. Recently he gives values for "organic acid" which more nearly resemble ours. This difference would seem to be due largely to lower total base concentrations.

PNEUMONIA

The literature on chemical studies in pneumonia, prior to the past few years, was well covered by Sunderman, Austin and Camac in 1926 (5). The present authors with Loeb and Palmer in 1923 (7) found during this disease: (1) decreased chloride; (2) normal bicarbonate; (3) low serum protein (by Kjeldahl); (4) decreased freezing point

TABLE 1

Normals

Date	Initials and sex	Serum									Remarks
		Non-protein nitrogen	Serum protein	Total base	Total acid	B − A	Chloride	Carbonate	Phosphate	Protein	
		mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	
May 14, 1926	R. F. L.	24	7.4	149.0	148.8	0.2	100.8	29.1	1.4	17.5	Tourniquet
February 15, 1927	Male	30	7.9	151.9	149.4	2.5	102.6	26.6	1.7	18.6	Without tourniquet, subject fasting
March 1, 1929		34	7.6	155.2	155.1	0.1	102.6	32.6	1.5	18.4	
January 25, 1927	D. W. A.	27	7.2	152.3	154.4	−2.1	104.4	30.7	2.3	17.0	Without tourniquet
January 25, 1927	Male		7.4	152.9	153.0	−0.1	104.4	28.8	2.3	17.5	After exercise—without tourniquet
March 4, 1927		24	7.5	151.2	152.5	−1.3	103.0	30.0	1.8	17.7	Without tourniquet
March 4, 1927			7.5	151.4	151.6	−0.2	103.0	29.1	1.8	17.7	Without tourniquet—usual minimum time
February 14, 1929		24	7.0	153.2	150.9	2.3	104.2	28.4	1.8	16.5	
February 25, 1927	R. H. Male	17	7.6	149.8	152.6	−2.8	105.6	26.8	2.1	17.9	Without tourniquet
January 27, 1927	W. W. P. Male	42	7.5	151.8	151.8	0.0	104.2	28.6	1.3	17.7	Without tourniquet
March 1, 1927	W. S. L. Male	28	7.3	149.5	152.5	−3.0	105.6	28.2	1.5	17.2	Without tourniquet
February 11, 1927	G. M. M.	30	7.6	148.5	148.4	0.1	101.2	27.4	1.9	17.9	Without tourniquet
February 11, 1927	Male		7.9	151.5	150.3	1.2	101.2	28.6	1.9	18.6	Tourniquet 1½ minutes

February 15, 1929	G. G. Female	25	7.1	152.3	152.9	−0.6	106.6	27.7	1.9	16.7	
January 21, 1929	Y. K. Male	(30)	7.5	156.7	152.9	3.8	105.0	28.6	1.6	17.7	
March 1, 1929	K. T. Male	30	7.5	152.0	150.8	1.2	100.8	30.8	1.3	17.9	
March 9, 1929	J. M.	26	7.2	153.0	152.1	0.9	104.0	29.3	2.0	16.8	
March 10, 1929	Male	26	7.2	152.5	152.9	−0.4	104.0	29.8	2.0	17.1	
Mean				151.9	151.8	+0.1	103.5	29.0	1.8	17.6	

TABLE 2

Pneumonia

Date	Initials, hospital number and sex	Case number	Serum									Whole blood		Relation to crisis	Remarks
			Nonprotein nitrogen	Serum protein	Total base	Total acid	B − A	Chloride	Carbonate	Phosphate	Protein	Hemoglobin	Hematocrit		
			mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*per cent*	*volumes per cent*	*days*	
February 17, 1927	W. W.	1	41	7.0	139.0	136.0	3.0	88.0	29.6	1.9	16.5	70	28.2	0	A male negro of 33 with a right lower lobe—Group III. Crisis on sixth day—uneventful recovery
February 19, 1927	61454		39	7.7	142.6	140.3	2.3	89.6	30.1	2.0	18.2	77	32.0	+2	
February 24, 1927	Male		18	7.7	147.0	147.3	−0.3	97.2	29.6	2.3	18.2	71	30.0	+7	
February 21, 1927	W. G. 68042 Male	2	51	7.4	139.8	133.7	6.1	88.8	24.4	3.0	17.5	69	27.7		Fatal Group II, left lower lobe. Blood taken fourth day
April 19, 1927	C. W.	3	24	6.3	134.7	133.1	1.6	90.6	26.3	1.3	14.9	70	29.8		Chart lost
April 26, 1927	68547		22	6.6	139.5	138.8	0.7	91.8	29.1	2.3	15.6	80	31.6		
May 3, 1927	Female		20	7.3	146.9	147.4	−0.5	100.8	26.7	2.7	17.2				
February 23, 1927	S. F.	4	26	6.9	144.5	140.9	3.6	92.8	30.1	1.7	16.3	85	31.9	+1	White male of 22 with a left lower lobe—with crisis on fifth day—recovery uneventful
February 28, 1927	68064		23	7.7	145.4	147.2	−1.8	98.6	28.5	1.9	18.2	90	31.3	+5	
March 11, 1927	Male		20	8.3	153.1	151.2	1.9	100.0	29.3	2.3	19.6	96	36.7	+17	
March 9, 1927	T. L.	5	27	6.7	136.1	133.5	2.6	89.4	26.6	1.7	15.8	85	935.0	0	A male negro of 27 with a left lower lobe—Group IV. Crisis on ninth day. Recovery uneventful
March 14, 1927	68177 Male		28	8.0	143.0	143.6	−0.6	94.6	27.4	2.7	18.9	89	37.2	+5	

depression; (5) low specific conductivity; and (6) in one instance, low sodium. Sunderman, Austin and Camac, in their paper mentioned above, made a much more comprehensive study, confirmed these findings and by base determinations proved a low total electrolyte content in the febrile period and some days after it. Peters and co-workers (8), on the other hand, reported in 1926 normal to high total base concentrations (except in one case), although their total determined acids were very low. They suggested that the large amount of undetermined acid was organic acid recalling the high organic acid excretion in pneumonia noted by Palmer (9).

The data appearing in table 2 and figure 2 confirm our observations of 1923, and demonstrate clearly that the decrease in total acid occurring in pneumonia is accompanied by a corresponding decrease in

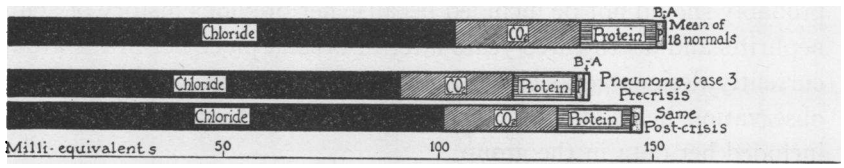

FIG. 2—Case 68547

total base and is, therefore, a decrease in total electrolytes. Quantitatively, this change consists mainly in the disappearance of BCl, although the changes in protein and phosphate are proportionately as great. Indeed, one is tempted to suggest serum dilution when the relative changes in protein, base, phosphate, and chloride are studied; only bicarbonate remains constant. Without blood volume data, however, such a suggestion cannot be proved, as Sunderman, Austin and Camac point out.

It is clear that the undetermined acid in pneumonia is quite normal, with no change coincident with recovery that is larger than the errors of the methods. We are inclined to view the high "organic acid" concentrations reported by Peters as due to erroneously high values apparently characteristic of earlier total base measurements and to the inaccurate formula for base bound to protein in use at that time. Neither the data here presented nor a study of the literature provide any reasonable hypothesis (other than the possible hydremia men-

tioned above) to account for the striking changes in the blood serum occurring in this disease.

In summary, electrolyte partitions in pneumonia and during convalescence show:

(1) Decrease in total base, protein, chloride and phosphate with slow and roughly parallel return to normal following the crisis.

(2) No increase in undetermined acid (B – A) at any stage of the disease.

RENAL EDEMA

Classification of these cases is difficult, but 70979, 81971, 236030 and 84788 are fairly typical uncomplicated cases of renal edema or nephrosis; in other words, simple edema without real hypertension, vascular changes or decreased general renal function. Case 61957 probably should not be included because her previous history of acute nephritis and death three years later in uremia place her in the group currently designated as chronic glomerular nephritis. At the time of observation her clinical picture was so similar to nephrosis that we included her data in the group.

The low percentage of protein in renal edema has been recognized for years and Epstein's original conception of its causal relationship is more and more widely accepted as new data appear. The low protein concentrations to be found in table 3 are consistent with previous work.

Two frequent but not constant alterations in the electrolyte structure appear: first, a decrease in the total base, and second, an elevation of chloride. Only one base in ten was above our normal average and there were no very high concentrations, such as observed by Peters, et al (10). As their high total base values all occurred before 1927 it is possible that the difficulties in the method before that time may account for the discrepancy. The concentrations of phosphate in our cases were within normal limits. This is the only disease in which such high chloride concentrations have been observed either individually or in average (105.6 m.Eq.). However, some cases have values within normal limits without differing clinically from the individuals with high chlorides, nor can one correlate the ordinary course of the disease with the electrolyte levels.

The amount of undetermined acid (B – A) was not abnormal; the

very high negative results (i.e., excess of acid over base) found by Peters did not occur in our briefer series. Our cases were in the stage of relatively normal general renal function, so that retention of phosphates and sulphates did not appear. The changes, then, that occur with simple renal edema are: (1) decreased serum protein, an essential and consistent alteration; (2) decreased total base which is usually present; and (3) fairly frequent great increases in chlorides, in most instances with relative decrease in bicarbonate. The importance of salt (NaCl) restriction as a causative factor in decreasing total base in these conditions was not studied. The alterations enumerated above occur without any abnormalities in the acid base balance of the serum and without the slightest relationship to the amount of edema (excepting, of course, the constant parallelism between edema and serum protein content).

An attempt to interpret from available serum analyses the nonprotein factors influencing renal edema, leads at once to the opinion that chloride retention is the most striking and important variation. Not only is the chloride ion increased, but the response to introduction of chloride in any form is a striking elevation of the chloride concentration of the serum (except when vigorous diuresis occurs). The authors with Palmer and Loeb (11) in 1923, administered NaCl to a patient suffering from renal edema; Linder, in 1926, (12) gave HCl; and Peters and co-workers, in 1929 (loc. cit.), gave NH_4Cl, all results agreeing in that extraordinary increases of serum chloride were observed. Albright and Bauer (13) have recently published a careful study of the effect of NaCl, NH_4Cl, and $NaHCO_3$ ingestion in a case of nephrosis. NaCl dosage increased both serum base and chloride, whereas NH_4Cl, causing a diuresis, decreased them. On the other hand, urine studies and clinical observation point to base difficulties. Linder, for example, made the significant observation (in one case) that, whereas normal individuals respond to administration of HCl by increased excretion of BCl and NH_4Cl, the hydremic nephritic responds by increased elimination of NH_4Cl, holding back base while excreting chloride. This result, together with the well-known clinical difference between the effects of NaCl and NH_4Cl administration, indicates that it is impossible from serum studies alone, no matter how complete they may be, to affirm or deny the truth of the current hypothesis

TABLE 3

Renal edema (nephrosis)

Date	Initials, hospital number and sex	Case number	Serum									Edema	Remarks
			Nonprotein nitrogen	Serum protein	Total base	Total acid	B − A	Chloride	Carbonate	Phosphate	Protein		
			mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*		
February 25, 1926	J. L. 61957 Female	1	33	4.5	153.0	149.9	3.1	112.0	24.8	(2.5)	10.6	+	A girl of 29; acute nephritis following scarlet fever as a child with steadily progressive chronic nephritis, dying in uremia in 1929. In edematous stage when blood was taken
November 22, 1927	70979	2	58	3.9	144.6	144.3	0.3	101.4	31.8	1.9	9.2	++	Steadily progressive renal edema in man of 61. No general impairment of renal function. Typical nephrosis
December 6, 1927	Male		40	3.9	144.9	144.6	0.3	103.0	30.1	2.3	9.2	++	
January 21, 1929			33	3.2	146.3	144.4	1.9	103.2	31.8	1.8	7.6	+++	
May 9, 1929	81971	3	41	3.6	149.1	142.8	6.3	103.8	26.1	2.8	8.6	++	A typical nephrosis of 35 with good general renal function. Spontaneous diuresis occurred between samples
June 28, 1929	Female		22	4.5	145.8	143.2	2.6	106.0	24.6	2.0	10.6	0	
December 19, 1929	84878	4	76	4.5	150.8	148.8	2.0	112.0	24.1	2.1	10.6	+	A woman of 34 with 1 year's history of edema, good general renal function. Blood Pressure 135/80, Heavy albuminuria. She had two transfusions between second and third samples. Her serum protein in July 1929 was 3.9 per cent and she had general edema; in October it was 3.7 per cent with even more edema
January 16, 1930	Female		25	4.3	147.7	146.8	0.9	111.4	23.4	1.9	10.1	+	
February 3, 1930			40	4.9	151.3	148.6	2.7	107.4	27.1	2.5	11.6	0	

December 20, 1929	236030	5	33	3.6	147.3	143.5	3.8	102.0	30.9	2.0	8.6	+++	A girl of 23 with 7 weeks' history of edema; without hypertension; excessive albuminuria; good general renal function. She had 20 grams urea daily from January 6 to February 4 with no effect on weight; she had NH_4Cl from March 3 to 12 (12 grams a day) without diuresis; transfusion 600 cc. on February 13
January 6, 1930	Female		35	4.2	147.4	141.9	5.5	100.8	28.5	2.8	9.8	+++	
February 7, 1930			46	4.2	139.9	138.8	1.1	96.6	29.8	2.4	10.0	+++	
March 12, 1930			40	3.8	145.5	145.0	0.5	110.4	22.5	3.1	9.0	+++	

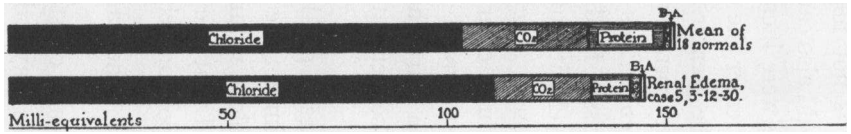

FIG. 3—Case 236030

attributing importance to sodium in the production of edema (Blum). Base and acid balance studies are very difficult in any patient, but particularly so with the albuminous urine of nephrosis; such an approach, however, seems of prime importance.

The effect of a low value for serum protein on the distribution of chlorides between blood stream and tissue spaces according to the Donnan equilibrium, is not negligible and would tend to increase serum chlorides; it would also cause a greater elevation of serum chloride if chloride intake were increased. This, of course, is dependent on the fact that the greater the difference between serum protein and tissue fluid protein, the greater is the excess of chloride in the latter fluid over that in the corresponding serum. Therefore, the closer the two protein concentrations approach each other (i.e., as serum protein decreases or tissue fluid protein increases) the higher will be the serum chloride level without any increase in total body chloride. Moreover, the addition of a definite amount of BCl to the body in such cases would produce, ceteris paribus, relatively higher increases in serum figures than would similar amounts in normals. This factor may explain in part the unusual serum chloride results in nephrosis where the concentration of serum protein is consistently low.

Blood volume studies in renal edema would supply a needed factor for proper understanding of the fluid and electrolyte changes. Bock, in 1921 (14) followed blood volume during diuresis in cardiac and renal edema, and discovered that the nephritic patient lost plasma volume and body weight proportionately so that there was no change in the ratio $\frac{\text{plasma volume}}{\text{body weight}}$. The cardiac case, however, maintained his plasma volume practically constant with a striking increase in plasma volume per kilo. This may indicate that all body fluids are equally involved in the disturbance of water balance in the true edematous nephritic, whereas the edema of vascular stasis involves mainly the tissues.

DIURESIS

In the papers with Loeb and Palmer, cited above, we called attention to a change in the relationship between the chloride and bicar-

TABLE 4

Diuresis

Date	Hospital number and sex	Case number	Serum									Remarks
			Nonprotein nitrogen	Serum protein	Total base	Total acid	B − A	Chloride	Carbonate	Phosphate	Protein	
			mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	
April 17, 1926	60406	1	41	5.4	144.3	144.3	0	100.0	30.3	1.7	12.3	A cardiac of 53 due to chronic vascular changes in myocardium. Before diuresis and during diuresis with diuretin
April 20, 1926	Male		26	6.0	146.0	146.4	−0.4	99.2	31.8	1.6	13.8	
April 27, 1926	65651	2	48	6.8	148.8	147.1	1.7	102.8	26.4	2.0	15.9	A cardiac edema of 34 due to mitral disease. Blood taken before diuresis, and after diuresis. Lost 13 kgm. of weight
May 5, 1926	Female		25	7.2	148.3	144.8	3.5	92.2	33.9	1.7	17.0	
January 10, 1927 10:45 a.m.	41962	3	21	6.6	147.0	143.7	3.3	94.4	32.5	1.8	15.0	2 mgm. novasurol at 10:50 a.m. with marked diuresis. A cardiac of 69 with mitral and aortic disease
3:45 p.m.	Female		(21)	6.0	147.0	141.1	5.9	91.8	33.8	1.8	13.7	

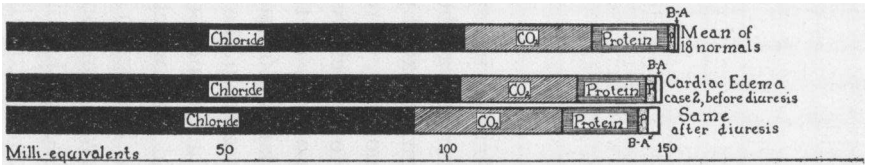

FIG. 4—Case 65651

bonate concentrations following cardiac diuresis. This consisted of a striking decrease in the former with a coincident increase in bicarbonate. Because of the constancy of conductivity it was assumed that no appreciable change in total electrolytes took place, and the lack of variation in the serum protein made great changes in dilution unlikely. We have repeated this observation with a complete electrolyte partition in case 65651 (table 4). A drop of 10.6 m.Eq. in chloride was accompanied by an increase of 7.5 m.Eq. in bicarbonate and 1.1 m.Eq. in protein, but base remained constant, i.e., total electrolytes did not change. The decrease in chlorides paralleled loss of edema more obviously than did fixed base. In the previous section it was seen that chloride was often elevated in renal edema; here, as cardiac edema disappears, the concentration of this ion falls.

Two other cases are reported in table 4 showing less striking changes with diuresis.

NEPHRITIC ACIDOSIS

Acidosis in nephritis was first observed by von Jaksch (15) in 1888. By titrating whole blood he discovered an "Alkalescenz" of 24 to 40 mgm. of NaOH per 100 cc. in uremia as compared to 250 to 300 mgm. in normals. Frequent confirmation since that date has left no doubt as to the relative accuracy of this early work. The first satisfactory hypothesis of the mechanism of nephritic acidosis was offered by Sellards (16) in 1914. He suggested that there is a "very gradual decrease in the excretion of acid in the urine and a corresponding reduction of carbonates in the blood corresponding to the amount of acid salts which are suppressed." At about the same time Palmer and Henderson (17) observed that a discrepancy in the usual relation between ammonia excretion and urinary acidity occurred in nephritic acidosis; this discrepancy lay in the relatively small amount of ammonia excreted as the urine became more acid. Since it has been shown that ammonia formation probably occurs in the kidney, their findings are easily explained, and impaired ammonia formation takes its place as one of the important factors in renal acidosis.

Sellard's hypothesis received further support when it was discovered that phosphate (Marriott (18)) and sulphate (Loeb and Benedict, 1927 (19)) retention occurred in uremia; the total electrolyte dis-

tribution, however, had not been investigated. Peters and his co-workers in 1923 did partial partitions of serum electrolytes in uremia and attributed acidosis to: (1) a reduction in total base, and (2) an increase in undetermined acids which he believed included a "marked increase in organic acids." The authors (1) in 1927 studied the effect of complete urinary retention in dogs by ligation of the ureters, demonstrating that in this simple experiment, phosphate and sulphate represent the entire increase in "undetermined acids" and easily account for the acidosis of this condition.

Hartmann and Darrow (20) in an excellent study in 1928 also observed low base levels in chronic nephritis. They explained this loss on the basis of (1) the work of Linder (loc. cit.) (12) and others who have shown that the damaged kidney cannot normally conserve base by ammonia formation; and (2) the loss of BCl due to the polyuria of advanced nephritis. The first suggestion seems to require no further support but the second, while attractive, remains to be proved experimentally. As a matter of fact it is the inability of the kidney to save base that makes the polyuria significant for it can be seen in the data presented under "diuresis" that large loss of body fluids through normal kidneys can occur with considerable decrease in serum chloride and yet no change in total base. Hartmann and Darrow believe that phosphate and sulphate account for the increase in undetermined acids. They found lactic acid to be unimportant except during convulsions, and ketones to be negligible.

More recently Peters, 1929, (4) reaffirmed his conclusions of 1923, offering the additional suggestion that ketosis due to starvation may be an important factor and further states (p. 529) that "sulphate accumulations must play a comparatively minor rôle in the production of the acidosis of nephritis." The dependence of phosphate and sulphate retention upon renal insufficiency could be proved only by successful studies of renal physiology, but the fact remains that many observers have found a fairly consistent relationship between severe kidney damage and phosphate and sulphate retention. At least one investigation (Boyd, et al. (21)) demonstrated increased blood phosphates in those cases where urine phosphate excretion was strikingly decreased.

As Peters and co-workers were unable to include sulphate and ke-

TABLE 5

Nephritic acidosis

Date	Initials, hospital number and sex	Case number	Serum											Vomiting	Remarks
			Nonprotein nitrogen	Serum protein	Total base	Total acid	B – A	Chloride	Carbonate	Phosphate	Protein	Sulphate	Ketones		
			mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*		
June 11, 1926	P. S. 56851 Male	1	160	7.1	142.5	139.0	3.5	88.5	20.6	5.4	16.8	7.7		±	A rapidly fatal uremia in a man of 39, vomited 12 hours before blood taken. Autopsy: Chronic glomerular nephritis
March 20, 1929	B. 80150 Male	2	195	6.5	142.8	137.9	4.9	81.6	21.5	6.8	15.3	12.7	0	++	A man of 22 with repeated attacks of acute nephritis with 1 month vomiting and uremia
March 28, 1929	Mo. 80644 Male	3	231	5.7	146.7	144.7	2.0	105.2	12.4	8.7	13.5	4.8	0	0	A typical nitrogen retention nephritis of 29, dying April 11, 1929. Autopsy: Chronic glomerular nephritis. Fluids forced between March 28 and April 3 with polyuria after that date persistent vomiting
April 3, 1929			229	6.1	141.6	135.8	5.8	89.8	11.2	12.2	14.4	8.2	0	0	
April 11, 1929			390	6.6	137.6	132.1	5.5	60.4	11.9	23.2	15.6	19.5	1.5	++	
March 29, 1929	D. G. 80898 Female	4	208	7.0	153.9	148.9	5.0	96.4	16.6	10.7	16.5	7.0	1.7	0	A rapidly fatal uremia in a girl of 20

March 13, 1929	M. A. 80139 Female	5	91	5.1	147.5	145.2	2.3	104.4	20.6	4.8	12.0	3.4	0	0	Undernourished woman of 33 with 4 years of edema—very severe secondary anemia—very little uremia
April 17, 1929	Bur. 80036 Female	6	107	7.0	144.2	141.3	2.9	97.8	19.9	4.6	16.5	2.5	0	++	Pregnant woman of 29 with 5 years of cardiac insufficiency, obesity, hypertension, becoming uremic and dying thus
July 21, 1928	Map. 69185 Male	7	173	5.6	145.2	136.1	9.1	76.4	30.2	10.4	13.2	5.9		++	See appendix. July 27, 1928, Creatinin, = 29.2 mgm.
July 27, 1928			160	5.7	146.3	131.8	14.5	63.8	36.9	12.0	13.5	5.6		++	

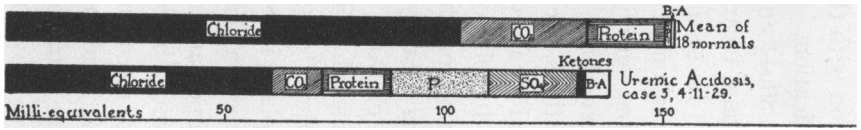

FIG. 5—Case 80644

tone analyses, we wish to present a group of cases studied during the past three years in whom sulphates and ketones were determined. Table 5 presents ten observations on seven cases of terminal uremia.

As a group these electrolyte studies show general characteristics similar to those that have been discussed above. Total base is below normal in all but one instance, and it is not possible with our cases to correlate this reduction with the vomiting, for it occurred even in the absence of this complication. Nor is it coincident with loss of chloride, as is shown by cases 80644 and 80139 who had normal chlorides and low total bases. Again, bicarbonate loss is obviously not the determining factor as can be seen in case 69185. Comparing total base with chloride plus bicarbonate shows equally inconsistent relationships. Case 80644 illustrates very clearly the inability of certain uremic individuals to conserve base in the presence of polyuria. Between the first two observations, the fluid intake was high and the resulting polyuria was followed by a decrease in base of 5.1 m.Eq. and in chloride of 15.4 m.Eq. In spite of these changes and in the presence of excessive water elimination through the kidneys, phosphate and sulphate concentrations steadily increased. This observation is contrary to the results of Denis and Reed (22) who noted in nephritic dogs a rapid drop of sulphate levels during diuresis.

On the acid side the effects of uremia are more varied and complicated. In the first place, it is obvious that ketones are quantitatively of no significance, even in the presence of excessive vomiting; in the second place, the importance of phosphate and sulphate retention is equally clear. It would be futile to insist, from our data, that sulphate and phosphate retention is the primary mechanism. The picture is too complicated and the physiological background too obscure. However, in a similar situation, i.e., in dogs with ligated ureters, the authors (loc. cit.) have shown that sulphate and phosphate accumulate with no apparent channel for chloride loss. There was no urine, of course, and a negligible chloride content in the vomitus. It would seem that there, at least, was a simple displacement of bicarbonate and chloride by retained acids, a relationship that might be carried over by analogy to the present data. To be sure, in uremia other factors complicate the picture, as has already been noted.

The effect of vomiting on chloride loss is most apparent in cases

80644 and 61985, who, when vomiting excessively, showed the lowest chloride concentration of the series. In case 80644 this complication became so pronounced that true tetany with alkalosis occurred at a time when the creatinine was 29 mgm. per 100 cc. We have never, hitherto, observed tetany in uremic patients except after administration of bicarbonate, to which they react with unusual promptness. It is unfortunate that we did not investigate lactic acid and ketones in case 69185, for they might together have made up the uncommonly high "undetermined acids."

It can readily be seen that there is, in most instances, little discrepancy between total base and total acid when sulphate studies are included. B − A is slightly higher in this group than in normals, but the assumed pH tends to be more incorrect and, therefore, the calculation of phosphate and protein is less certain, altogether making a limit of error close to the differences found. Even these differences might be cut down by the inclusion of lactate analyses. Hence the presence of other organic acid is not established by the data in table 5.

In summary, the essential disturbances of the electrolytes in uremia are: (1) decrease in total electrolytes; (2) decrease in total base due in part, at least, to defective base conservation by the kidney and, occasionally, to vomiting; (3) accumulation of phosphate and sulphate, due presumably to renal insufficiency; (4) decrease in chloride, related at times to vomiting, but still incompletely explained; (5) decrease in bicarbonate due to retention of inorganic acids (sulphate and phosphate).

DIABETIC ACIDOSIS

Peters and his associates in 1925, (23) published the first analysis of the factors producing serum electrolyte changes in diabetic acidosis. The validity of their hypotheses has received support by later and more complete analytical data. Peters called attention to: (1) loss of water, because of glycosuric polyuria, base excretion and vomiting; (2) loss of base bound to ketones and thus excreted in the urine; and (3) availability of base released from chloride for ketone neutralization. There results, therefrom, a state of dehydration and salt depletion, as well as acidosis.

Hartmann and Darrow, in 1928 (24), studied diabetic acidosis in

TABLE 6

Diabetic acidosis

Date	Hospital number and sex	Case number	Serum										
			Non-protein nitrogen	Serum protein	Total base	Total acid	B − A	Chloride	Carbonate	Phosphate	Protein	Ketones	Blood sugar
			mgm. per 100 cc.	*per cent*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq per liter*	*mgm per 100 cc.*
April 22, 1926	54592	1	39	9.4	143.8	147.6	−3.8	97.4	9.6	3.2	22.2	15.2±	
April 23, 1926	Male		27	7.8	135.0	134.5	0.5	96.4	18.4	1.3	18.4	0	
March 30, 1926	62918 Female	2	71	6.6	124.0	110.8	13.2	82.3	5.5	7.4	15.6		
June 1, 1926	Female 65967	3	50	6.0	141.9	129.7	12.2	100.4	13.6	1.5	14.2		
January 3, 1927	58570	4	51	7.3	139.3	127.7	11.6	105.2	3.6	1.7	17.2		5.40
January 4, 1927	Female		24	5.7	148.8	142.3	6.5	102.8	26.0	0.0	13.5		0.46
January 7, 1927			26	5.8	153.3(?)	143.4	9.9	102.8	26.0	0.9	13.7		1.52
March 22, 1926	65330	5	87	8.7	114.0(?)	119.8	−5.8	93.0	5.2?	?	20.1	1.5	
March 24, 1926	Male		34	5.5	139.0	139.4	−0.4	105.4	18.3	0.6	13.0	2.1	
April 26, 1926			39	7.4	143.5	145.6	−2.1	97.6	28.1	2.4	17.5		
March 30, 1927	66489	6	46	7.8	136.1	132.8	3.3	97.4	17.0	0	18.4		
March 30, 1927	Female		(46)	7.3	137.8	134.7	3.1	94.0	23.5	0	17.2		
April 2, 1927			24	6.6	142.4	138.5	3.9	93.2	28.4	1.3	15.6		
April 7, 1927			24	7.5	145.0	140.3	4.7	96.2	24.2	2.2	17.7		
June 3, 1927	61945	7	39	5.1	128.8	123.2	5.6	92.0	17.1	2.1	12.0		
June 6, 1927	Male		27	5.9	148.1	145.7	2.4	99.2	30.9	1.7	13.9		
June 27, 1928	63959	8	49+	8.5	141.5	140.1	1.4	90.8	4.9	4.1	20.0	20.3±	
June 28, 1928	Female		28	6.9	148.6	149.1	−0.5	102.6	28.7	1.5	16.3		
September 27, 1928	74710	9	64	7.5	138.9	132.8	6.1	87.8	5.9	4.1	17.7	17.3±	
September 28, 1928	Female		52	6.6	159.8	153.6	6.2	110.8	26.4	0.8	15.6		

children, and observed dehydration, loss of base and chloride. Most of their observations do not include complete electrolyte partitions.

In a group of 9 cases, we have been able to make more comprehensive analyses than hitherto reported. The determinations are found in table 6 and the case summaries are reported in the Appendix. In four cases ketones were directly measured but in the others they are found as part of B − A. Certain aspects peculiar to individual cases should be mentioned before engaging in general discussion.

The episode in case 54592 was extremely simple; no acute infection, very little vomiting and prompt recovery. At the end of the period there was no dehydration and the blood contained no ketones. The fact that the blood ketone figure was high enough to cause a negative B − A indicates clearly that it should be corrected downward at least 4.0 m.Eq., for we have already pointed out the inaccuracy of the

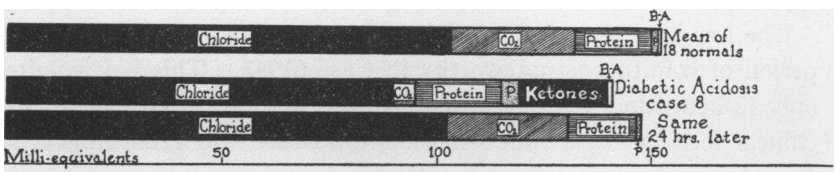

FIG. 6—Case 63959

calculation of m.Eq. from grams per liter of ketones. However, assuming 11.0 m.Eq. of ketones, there is a total anion drop in the 24 hours of 17.7 m.Eq. with only 8.8 m.Eq. of the liberated base forming bicarbonate; there was, therefore, a large loss of fixed base (8.8 m.Eq. as determined). There was no vomiting to explain this loss. Hence, it seems probable that the decrease in serum base represents base bound to ketones and excreted in the urine. Diuresis with extensive urinary elimination of ketones did occur. From the serum studies alone one can suggest that the disappearance of ketones was due, in part, to oxidation and, in part, to excretion. This patient obviously had too little NaCl in the course of treatment.

Case 62918 shows the extraordinary degree to which decrease of base, chloride and bicarbonate can occur with dehydration, the latter being indicated by a high protein per cent. Persistent vomiting played a major rôle here in the loss of BCl.

Case 65967 requires no special comment other than to note the effect of treatment in maintaining satisfactory levels of base and chloride. She died of shock. In both this case and in case 62918 the striking increase in B − A probably indicates the extent of the ketonemia.

No case except 58570 had a normal chloride at the onset; in this patient it was slightly above normal. As far as we know there had been no therapy that would explain this. After vigorous treatment the blood returned to a fairly normal level with a drop in Cl. The value for total base 3 days later was so out of line with the constant results for the other electrolytes that there appeared to have been an error in the measurement.

Case 66489 requires little comment except to observe that the administration of bicarbonate between the first and second samples increased the bicarbonate to some extent at the expense of chloride.

The low base concentration after treatment and after a very brief period of vomiting is noteworthy in Case 61945. This boy vomited only 12 hours and was then given vigorous and proper treatment with clinical recovery at a time when his total base was 128.8 m.Eq., although his blood contained practically no ketones.

Case 63959 was severely dehydrated with very low bicarbonate and chloride and high blood ketones. Base, however, in spite of these extensive alterations was less reduced than usual. Twenty-four hours of energetic treatment removed ketones and readjusted the electrolytes to a normal pattern.

Case 65330 illustrates the importance of shock in diabetic acidosis and its independence of ketones. This boy was near death from vasomotor collapse at a time when there was a relatively low concentration of ketones in the blood. About 24 hours later he grew worse again with a blood CO_2 that was not in the dangerous zone. Tremendous dehydration and salt depletion are apparent in the first analyses, inaccurate though they may be. (See appendix.)

Strenuous treatment in case 74710 resulted in overreaching the electrolyte needs, as shown by an abnormally high base and chloride in the last study. This treatment was necessary in order to combat shock, which was a very serious complication here. It shows, however, that it is possible correctly to readjust the electrolyte pattern by means of active therapy.

The mechanism of diabetic acidosis probably proceeds somewhat as follows. First, there is a production of ketone acids in a patient with already low electrolyte levels (due to decreased base and chloride). These acids take base from bicarbonate with loss of CO_2 through the lungs. At the same time, ammonia formation in the kidneys furnishes base for the elimination of ketones in the urine, although evidence increasingly emphasizes the ready availability of fixed base, even before ammonia. Increased water flow through the kidneys due to glycosuria may be of some assistance in the elimination of ketones at this stage.

Large quantities of ketones with fixed base as the cation appear in the urine, and salt depletion is further enhanced by the almost simultaneous appearance of vomiting which means loss of base, chloride and water. The final effect is a dehydrated blood, low in total base, chloride and bicarbonate, and high in ketones.

The dehydration causes a drop in blood volume with consequent decrease in blood pressure. Whether ketones themselves are vascular poisons and contribute thus to shock is not certain. At any rate vasomotor collapse appears regularly. The fall in blood pressure plus the increased osmotic pressure of the dehydrated serum (due to the rise in protein per cent) interferes greatly with renal function as the consistently increased nonprotein nitrogen seems to confirm. When anuria occurs one of the most important protective mechanisms fails so that the disturbances are even more pronounced and a vicious circle is initiated.

Retracing these steps therapeutically, the indications are: (1) restoration of blood volume and normal dilution by salt solution, if possible, and transfusion, if necessary (but by the intravenous route exclusively until blood pressure is normal); (2) replacement of base, chloride and, to a lesser degree, bicarbonate by intravenous introduction; and (3) interruption of ketone formation by glucose and insulin administration.

GENERAL DISCUSSION

The accumulation of data concerning serum electrolytes has reached a stage where certain simple generalizations are justified.

In the first place, the total concentration of ions is far less constant

than some earlier writers believed. Under a variety of conditions the levels are greatly lowered, (15 to 30 m.Eq.) but very rarely indeed in disease is there an elevation. Work by Bock (25) on fatigue and work from this laboratory (in press) on histamine shock demonstrate increase in serum fixed base as part of the response to lactic acid acidosis. Apparently the electrolyte concentration does not determine the water content of the serum, for within the relatively wide limits compatible with cell survival, water and electrolytes vary independently as various influences bear upon them. It is interesting that clinical recovery does not necessarily parallel the return of the electrolytes to normal.

Total base is very constant in casual studies of normals, but there are no satisfactory data as to the response to variations in diet or fluid intake. Most disease conditions studied to date cause a decrease in base if they influence it at all. This decrease is ordinarily dependent on cation loss in vomitus or urine. One is increasingly impressed by the ease with which fixed base is mobilized for urinary secretion under acid stress. In fact, some work suggests that it is a more mobile agent than ammonia formation (Odin, (26) and unpublished work of the authors). Base loss in diarrhea has not been included in this series but is well established as part of the pathological physiology of the cations. Although hypotheses as to the usefulness of fixed base in acidosis have become certainties, the complete mystery of the base changes in pneumonia indicates one of the many opportunities for further work in this field.

It seems clear that normal serum has no quantitatively significant acids other than chlorides, bicarbonate, phosphate and protein. Organic acids and sulphates are rarely more than 1 or 2 milliequivalents. It seems equally certain that in the disease conditions hitherto subjected to this type of scrutiny no discrepancy between total base and total acid has been found when sulphate, ketone and lactate analyses were included. The importance of complete electrolyte partitions consistently performed is apparent. Conclusions independent of such completeness are subject to errors even greater than those indigenous to all biological research.

When base is needed to neutralize acids pathologically present, bicarbonate offers it most readily but chloride takes an important part

when the load becomes heavy. It may even give up more base than does bicarbonate. There is an inconstant reciprocal relationship between chloride and bicarbonate; occasionally when chloride decreases, as in diuresis, bicarbonate fills the gap, but the reverse has not been observed, due probably to the lack of an analogous drop in bicarbonate.

The mechanisms which produce the changes in serum electrolytes found in diabetic and nephritic acidosis are relatively well understood and bear a consistent relationship to one another. Much has been accomplished there. But an understanding of the relation of edema and water balance to the electrolyte metabolism or an interpretation of the changes found in nephrosis, for example, are impossible with the evidence at hand.

SUMMARY

Serum electrolyte partitions have been made in normals, in pneumonia, during cardiac diuresis, in nephritic edema (nephrosis) and in nephritic and diabetic acidosis. The accuracy and reliability of the various methods have been discussed. The so-called "undetermined acids" sink to negligible figures if bicarbonate, chloride, protein, phosphate, sulphate and ketones are estimated in these conditions.

The mean total base of 18 determinations on *normals* is 151.9 m.Eq. and the total acid 151.7 m.Eq. Organic acids and sulphates are present in such small quantities as to be entirely unimportant.

In *pneumonia* there is a decrease in total base, chloride, phosphate and protein with a very slow and roughly parallel return to normal after the crisis. These changes received no elucidation from our data. There is no increase in undetermined acid.

Patients with *renal edema* showed invariably a low protein per cent and usually a low fixed base. Serum chlorides were often very high and increased as the result of chloride administration more strikingly than normals. A partial explanation of the behavior of the chlorides is offered by citing the effect of a decreased serum protein upon the Donnan equilibrium between serum and the fluids in tissue spaces.

Studies of *diuresis* in cardiac patients demonstrated the ability of the body to eliminate large amounts of chloride and water without parallel decrease in total base.

The *acidosis* of *advanced nephritis* was followed in several cases and the factors chiefly responsible seem to be: (1) decrease in total base dependent on loss of the base-conserving power of the kidney due to failure of ammonia formation; and (2) retention of phosphate and sulphate because of renal insufficiency. No significant ketosis was observed. BCl is a valuable source of base for neutralizing retained acids.

Observations on a group of patients suffering from severe *diabetic acidosis* showed: (1) dehydration with high serum protein; (2) loss of base, due probably to urinary excretion in combination with ketones; (3) great drop in bicarbonate dependent on neutralization of ketones; and (4) decrease in serum chlorides dependent in part on vomiting, but nevertheless a real aid in furnishing base for ketones. Shock plays an extraordinarily important rôle in treatment and prognosis. A return of total base to normal is not necessarily parallel to the clinical recovery.

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APPENDIX

Case 54592 was a man of 32, with diabetes of four years' duration. He was on a self-regulated dose of 60 units of insulin, but because of 2 severe shocks suddenly stopped all insulin. After one day of eating, without insulin, he began to vomit and was admitted at once to the hospital on the morning of April 22. He was dyspneic but not in coma. Blood was removed before any treatment. Between the initial sample and the second one, 20 hours later, he did not vomit and received 3000 cc. of fluids and 4 grams NaCl. During the same period he had a striking diuresis. Urine was free from ketones at the end of the period.

Case 62918 was a woman who had had diabetes for about 2 years. She was followed in the Out-Patient Department on a diet of C. 250; P. 70; F. 80 with 77 units of insulin. She had disappeared from the Clinic for 5 months before admission. On March 20 she had "grippe" mildly; on the evening of March 27 she began to vomit, which continued to admission; on March 30 she became hyperpneic and drowsy and was admitted to the hospital. Her "acidosis chart" was lost from the history so accurate data are unavailable. Her blood pressure dropped and she died in 10 hours

Case 65967 was a woman of 68 who had had diabetes for 12 years treated with casual dietary restriction. For 4 months there had been weakness and dyspnea on exertion, treated with digitalis by her local physician. For 2 weeks before admission she had been eating unusual quantities of rye bread and cream. About 12 hours before admission, on May 31st, she developed abdominal pain and vomiting, the latter continuing to her hospital entry. Her condition was poor on admission and her blood pressure continued dropping until death, at 9:20 p.m. June 1, 3 hours after the sample of blood was obtained. She received 3500 cc. of salt solution and 2500 cc. of 5 per cent glucose solution by vein or clysis in the approximately 36 hours between admission and removal of the blood sample. Cardiac failure may have played a rôle in her death, although it was due largely to shock.

Case 58570 was a woman of 40 who had had diabetes for 4 years, with varying tolerance but good general health. Four days before admission she caught cold,

lost her appetite and ate nothing for three days, taking no insulin. The day before admission she vomited and became gradually worse, arriving at the hospital January 1st in coma. Blood was taken before any therapy. She responded quickly to treatment with insulin, bicarbonate, salt solution and glucose, by clysis, vein and mouth. Her blood pressure was normal. When the second specimen was removed 23 hours later she was conscious, and voiding well and her urine was practically free from ketones. She was edematous at that time; on January 7 she was quite normal.

Case 65330 was a diabetic boy of 16 who had been progressing satisfactorily for three years on diet and insulin. On March 18 he had an upper respiratory infection; on March 20th he stopped insulin and began to vomit. He had diplopia, was thirsty and drowsy. On the 21st he was worse and entered the hospital at 4 p.m., pale, dehydrated, and hyperpneic. He was given insulin, and glucose and water by mouth and rectum. He improved at once but soon vomited again and became worse. His stomach was lavaged and 10 per cent glucose was given by clysis twice during the night. He became steadily worse, continued to vomit and early in the morning of March 22nd his blood pressure was 70/40; he was anuric and in shock. 500 cc. of normal saline and coffee by rectum helped but little. At noon a transfusion of 300 cc. of blood was given (the first sample in table 6 was taken just before it). In an hour the blood pressure was 90/60 and 120 cc. of urine was obtained which, on analysis, showed much albumin but very little of ketones. Salt solution by vein and rectum was continued and the boy improved until the afternoon of the following day, March 23, when he vomited, his blood pressure fell to 86 (blood CO_2 was 30.9 volumes per cent) and he grew drowsy. Intravenous saline brought his blood pressure up again and his improvement was steady thereafter. The second blood was taken after he was much improved. The third specimen was during a period of entire normality (except his diabetes) a month later. The data obtained on March 22nd are probably rather inaccurate due to poor technique in removing blood. The patient was so critically ill that it was impossible to prevent exposure to the air and a very small amount was obtained, quite insufficient for the usual duplicates.

Case 66489 was a diabetic girl of 22 who had been under treatment for 8 months. For six weeks she had been substituting a patent medicine for part or all of her insulin. Three days before admission she felt ill and took a purge; the following day she began to vomit. The next day she went into coma (no other details are available), and in the evening arrived at the hospital completely unconscious, hyperpneic, but not vomiting. Between admission and her first blood sample she received about 3700 cc. of fluids by mouth, 1000 cc. of 5 per cent glucose and 500 cc. of saline by vein. Between the first and second samples 2 hours elapsed during which 15 grams of bicarbonate were given intravenously. No ketones were excreted during that time. The third and fourth determinations were done at a

time when the patient had developed bronchopneumonia and pyelitis. Later, abscess of the lung and suppurative pleurisy caused her death on April 30.

Case 61945 was a 14 year old boy satisfactorily treated for diabetes over a period of three years. His diet was C. 200 P. 80 F. 130 and insulin 80 units. The day of admission (June 2) he awoke vomiting and continued all day without insulin or food. At 8 p.m. his CO_2 was 23 volumes per cent. He was given intravenous bicarbonate and saline, with the usual insulin and glucose. When blood was taken the next morning he was decidedly better and on June 6 he was quite well except for some glycosuria.

Case 63959 was a girl of 16 who had been successfully treated (with insulin) over a period of 3 years on a diet of C. 160 P. 65 F. 100. The day before admission she began to vomit, insulin was decreased and by afternoon of the day of admission (June 27) she was in coma. Blood was taken before therapy was started. Between the initial and final observations she had 1500 cc. of saline and 1500 cc. of 5 per cent glucose intravenously, 1000 cc. of saline subcutaneously and 1100 cc. of fluid by mouth; she was symptom-free and the urine was negative for ketones at the second study. Her blood pressure was always normal.

Case 74710 was a woman of 48 who came into the hospital late on September 26 for vomiting and was found to have diabetes; she went rapidly into coma and shock (blood pressure 88/58). There was no apparent precipitating factor. Blood was taken before treatment. Between the first and second samples she received approximately 800 cc. of whole blood and 3000 cc. of fluid intravenously, including 20 grams of bicarbonate and 36.4 grams of NaCl. She was much improved but the urine still showed large amounts of ketones.

Case 69185 was a woman of 38 with a history of toxemia of pregnancy. Fourteen years previously she had had headaches, ankle edema and dyspnea on exertion for 8 months with, more recently, blurring of vision, drowsiness and vomiting. Blood pressure 175/95, heavy albuminuria, normal fundi, oliguria persistently (250–500 cc.). She vomited large amounts constantly. She received infusions as follows:

July 2, 1928, 1000 cc. of 10 per cent glucose.
July 3, 1928, 1000 cc. of 5 per cent glucose and normal saline.
July 4, 1928, 1000 cc. of 5 per cent glucose and normal saline.
July 11, 1928, 1000 cc. of 10 per cent glucose.
July 12, 1928, 500 cc. of 10 per cent glucose.
July 23, 1928, 400 cc. of 10 per cent glucose and 200 cc. normal saline.
July 24, 1928, 500 cc. of 10 per cent glucose.
July 27, 1928, 1000 cc. of normal salt and 30 cc. of 50 per cent glucose.

She developed tetany on July 29 and died in coma on July 31.