ACID-BASE EQUILIBRIUM IN PATIENTS WITH CHRONIC RENAL FAILURE IN WHOM LIFE IS SUSTAINED BY PERIODIC HEMODIALYSES

Report of Five Representative Cases

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IN the absence of normal renal function, acid-base equilibrium depends on the buffering capacity of the blood, the intracellular shift of hydrogen ions, and respiratory compensation. Pulmonary complications, to which the uremic patient is prone, render the respiratory compensatory mechanism a precarious one. Thus impairment of gaseous diffusion through the walls of the pulmonary alveoli may occur as a result of congestion secondary to heart failure, infection, or repeated pulmonary emboli.

That hemodialysis can correct the acidosis of uremia was reported by one of us (W.J.K.) in 1944[1] and in 1947,[2] and reconfirmed by Weller, Swan, and Merrill[3] in 1953. However, the seriousness of the deviations that cause comparatively slight clinical symptoms in patients with chronic uremia has not been generally appreciated. Some of our patients with severe renal failure in whom life was sustained by periodic hemodialyses had pH values so low that they would have been considered incompatible with life only a few years ago. Surprisingly, these patients were living at home, had no obvious signs of discomfort, and returned to the hospital only for treatment with the artificial kidney. Periodic hemodialyses can maintain patients without excretory renal function in reasonably good clinical condition for months or years. Permanently indwelling arteriovenous shunt cannulas of the type described by Hegstrom and co-workers[4] facilitate access to the blood vessels.

Schwartz and Relman[5] have recently indicated that the traditional measurements of pH, pCO_2, and plasma bicarbonate concentration continue to be the most reliable biochemical guides in the analysis of acid-base disturbances. The ease with which these data can be obtained using the Astrup equipment and diagram was the main reason for following the Scandinavian method in our investigation.

It is the purpose of this paper to describe our methods for the analysis of acid-base equilibrium and to report and to evaluate our findings in five representative cases.

Methods

The Astrup pH meter† was used for all determinations. The pH readings were made directly; the pCO_2 values were obtained from the nomogram designed by

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†*Radiometer, The London Company.*

Astrup. This nomogram is formed by a coordinate system in which the pH value in decimal scale is plotted on the abscissa, and the pCO_2 in logarithmic scale is plotted on the ordinate. The curve of the relationship between pH and log pCO_2 for a particular blood sample is, for all practical purposes, a straight line. The line can be determined if two points on it are known.[6]

Two aliquots of the blood sample are equilibrated at two different known values for pCO_2, and the pH of each is checked. These values are represented by two points on the nomogram, and so determine the line. The actual pH value of the blood sample being checked is then determined. This value intersects the previously determined line, and the value on the ordinate at the point of intersection is the pCO_2. In a similar way, and with simple mathematical operations, blood values for the standard bicarbonate, the actual bicarbonate, total CO_2 content of plasma, buffer base, and base deficit or excess may be obtained from the nomogram.[7]

Arterial blood samples, drawn under anaerobic conditions, were obtained before and after dialysis. The blood was drawn from the arterial cannula used for repeated dialyses. Readings were made either immediately after the sample had been drawn, or, if this was not possible, within a few hours.[8] All blood samples that were not immediately read were refrigerated. Double readings were made on all samples; the mean value was accepted as definitive.

All dialyses were performed with the twin-coil artificial kidney, using either a 100-liter tank or a 368-liter cold tank for the rinsing solution. Composition of the bath was the same in all dialyses, made according to a standard solution previously reported.[9] The pH value of the bath was adjusted between 7.4 and 7.5 by adding sufficient amounts of an 85 percent lactic acid solution. The pH value of the bath was determined with the same pH meter; no change in the pH value of the bath was observed at the end of dialysis. During dialysis, the rinsing fluid was oxygenated by bubbling a gas mixture of 90 percent oxygen and 10 percent CO_2 through the bath. This helped to maintain a stable pH level. The pCO_2 concentration of the bath was between 58 and 68 mm. Hg.

Report of Representative Cases

The following are reports of five patients in the terminal stages of chronic renal failure in whom life was being maintained by periodic hemodialyses; the patients were studied from the point of view of acid-base equilibrium (*Tables 1 and 2, Fig. 1*).

Case 1. A 29-year-old woman was transferred to the Cleveland Clinic Hospital because of uremia. She had no history of antecedent renal disease or hypertension, but had been ill with fever and pharyngitis for a week before admission. Though she noticed a decrease in the output of urine, she was not aware of any change in its appearance. On admission she looked pale and chronically ill and exhibited Kussmaul's respiration. Multiple ecchymoses, edema, and a pericardial friction rub were present. The hemoglobin concentration was 5.5 gm. per 100 ml.; the blood urea content was 360 mg. per 100 ml.; and the total CO_2 content was 10.4 mEq. per liter. Proteinuria, hematuria, and pyuria were present as were coarse granular casts in the urinary sediment. A tentative diagnosis of chronic glomerulonephritis was made and conservative therapy begun. When the patient's condition failed to respond adequately to conservative

Table 1.—Summary of data in five patients having chronic renal failure

Case number	Creatinine clearance, ml./min.	Urine volume (24 hr.), ml.	Hypertension	Complications
1	3.2	300-400	Mild	Overhydration; upper gastrointestinal bleeding (2 occasions)
2	2.2	400-600	Extremely severe	Severe congestive cardiac failure
3	3.1	300-400	Mild	Hepatitis (chlorpromazine hydrochloride); residual scar from tuberculosis
4	4.0	300-500	Severe	Polyneuritis; insomnia; restlessness
5	0.4	Less than 200	Severe	Repeated bronchitis; bilateral pleural effusion; hemorrhagic pleuropericarditis; repeated pulmonary embolism; congestive cardiac failure

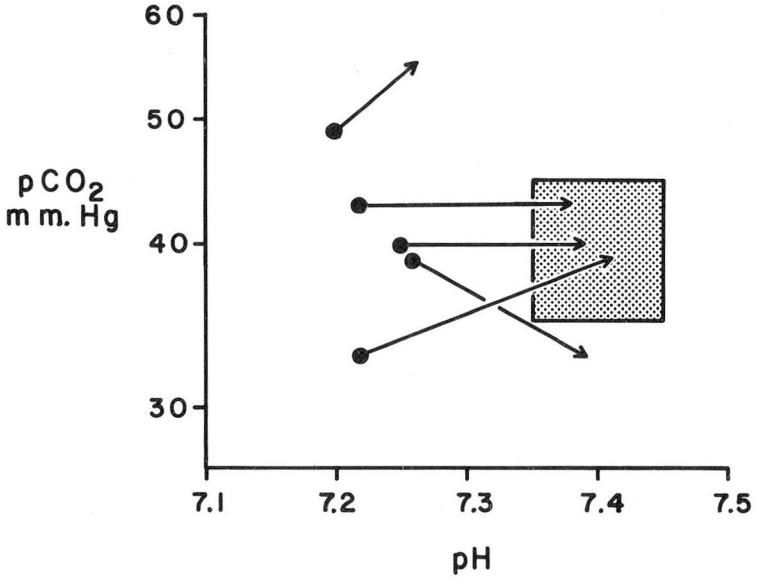

Fig. 1. Graphic representation of the pH and pCO_2 (mean values for each of the five patients as indicated in *Table 2*). Dots represent values before hemodialysis and arrowheads values after hemodialysis. The square indicates approximately normal values.

Table 2.—Mean values of factors indicating acid-base equilibrium before and after hemodialysis

Case number	Number of determinations	Time of determinations, before or after hemodialysis	pH (7.35 to 7.42)*	pCO_2 (34 to 45 mm. Hg)*
1	7	Before	7.22 (7.18 to 7.3)	43 (30 to 68)
		After	7.38 (7.3 to 7.4)	43 (38 to 51)
2	6	Before	7.25 (7.11 to 7.42)	40 (31 to 66)
		After	7.39 (7.31 to 7.45)	40 (34 to 54)
3	6	Before	7.22 (7.1 to 7.47)	33 (22.5 to 42.5)
		After	7.41 (7.31 to 7.49)	35 (33 to 41)
4	8	Before	7.26 (7.18 to 7.43)	39 (36 to 47.5)
		After	7.39 (7.34 to 7.48)	33 (16.5 to 49)
5	7	Before	7.2 (7.05 to 7.31)	49 (31 to 75)
		After	7.26 (7.19 to 7.34)	55 (47 to 65)

*Normal value.
†Value with normal hemoglobin.

Table 2.—(concluded)

Base excess (+3 to −3 mEq./l.)*	Buffer base (44.8 mEq./l.)†	Standard bicarbonate (21.3 to 24.8 mEq./l.)*	Actual bicarbonate, mEq./l.	Total CO_2 (22 to 27 mEq./l.)*
−9.7 (−18.5 to 2.5)	38.3 (32 to 48)	16.5 (13.5 to 21)	17.7 (10.4 to 24.5)	19 (11.3 to 26.5)
+1.5 (−6.2 to 6.1)	49 (39 to 57.5)	24 (18.4 to 27.5)	24.5 (18 to 29.6)	25.8 (19.1 to 31.1)
−9.3 (−20 to 2)	41 (31.6 to 54)	16.9 (13.2 to 21.4)	16.9 (14 to 20.1)	18.1 (15 to 22.1)
+0.8 (0 to 3.7)	50.8 (48 to 53.5)	23.8 (21.7 to 25.6)	23.8 (21.6 to 26.5)	25 (22.6 to 28.1)
−13.5 (−20.5 to −5)	36.9 (30 to 49)	14.6 (11.2 to 19.7)	13 (9.9 to 19)	14 (10.8 to 20.2)
0 (−8 to +3.6)	52.5 (48 to 57.5)	22.8 (19 to 25.6)	21.5 (16 to 25.6)	22.5 (17 to 26.8)
−8.9 (−15 to +2.5)	41.5 (33 to 46)	17.2 (13.8 to 24.8)	17 (12.8 to 24.5)	18.2 (13.8 to 25.6)
−2 (−8 to +8.3)	54 (46.5 to 67)	21.5 (18.3 to 29.7)	19.2 (11.2 to 30.7)	20.2 (11.7 to 32.1)
−11.3 (−13 to −7.5)	42.4 (35 to 64)	16.2 (14.4 to 18.2)	18.3 (13.7 to 20)	19.8 (14.7 to 22.3)
−2.9 (−9.9 to +4)	45.5 (34.5 to 49)	21 (16.2 to 26)	24 (17 to 28)	25.6 (18.4 to 29.8)

therapy, hemodialysis was started with subsequent dramatic improvement. She has been maintained with periodic hemodialyses for over six months, first once, and more recently twice, weekly (*Fig. 2*). Clinically she is fairly well, but her blood pressure is rising.

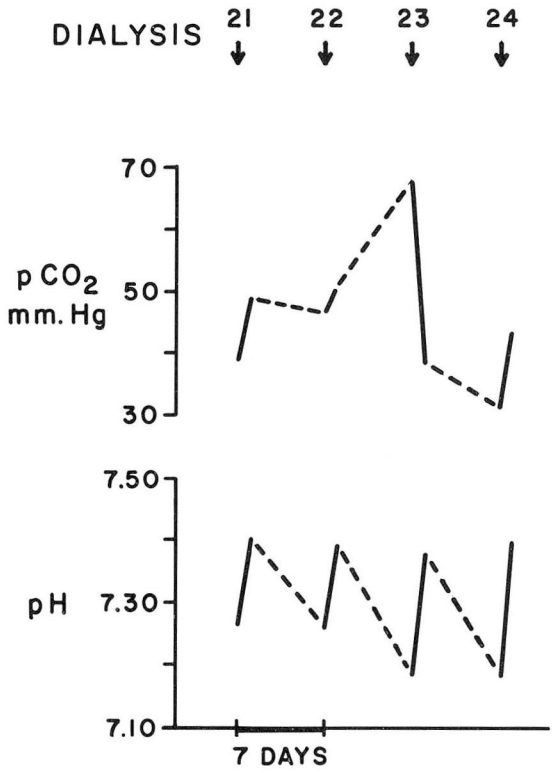

Fig. 2. Case 1. Correction of pH value with each dialysis; pCO_2 high at the onset of dialysis 23. There were rales in the lungs (only a few determinations are presented in this and in the following graphs).

Case 2. A 36-year-old man was admitted to the Cleveland Clinic Hospital in congestive heart failure. He had a six-month history of severe headache, decreasing vision, and weight loss. Cardiac decompensation occurred during the week before his admission, and was accompanied by a decreased urinary output. He was aware of having had hypertension and proteinuria for six months but he never had urinary tract symptoms. On admission he was pale and dyspneic, with rales in both lungs and a pleural friction rub in the left lung base. Pulse rate was 122, and the blood pressure was 210/130 mm. Hg without postural changes. A gallop rhythm was present and the liver was palpable 3 cm. below the right costal margin. Funduscopic examination revealed arteriolar constriction and exudates, without hemorrhages or papilledema. The hemoglobin concentration was 8.0 gm. per 100 ml.; the blood urea content was 120 mg. per 100 ml.; and the serum creatinine concentration was 14.9 mg. per 100 ml. Urinalysis disclosed a specific gravity of 1.011, 2-plus protein, red blood cells, white blood cells, and coarse granular casts. A urine culture was sterile. The patient's condition failed to improve with restriction of fluid and salt intake, and administration of digitalis and ganglionic blocking agents; a program of periodic hemodialyses was begun (*Fig. 3*). Oliguria has persisted. Uremia has been controlled with repeated hemodialyses for more than one year, but congestive heart failure and hypertension remain problems.

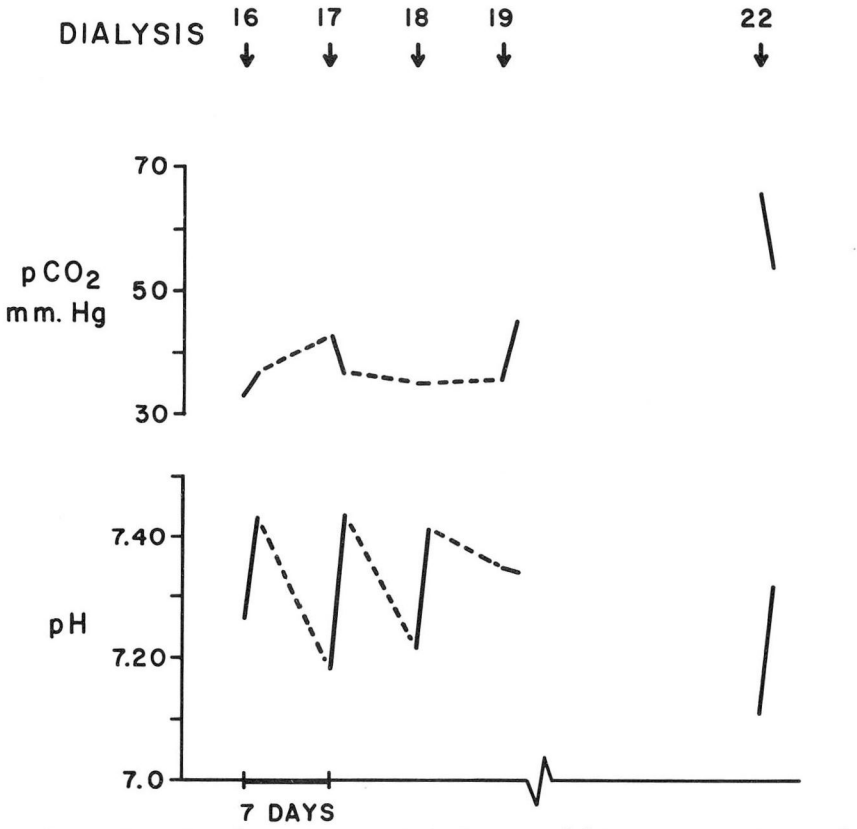

Fig. 3. Case 2. Correction of pH value as usual. At the onset of dialysis 22, the patient was in frank congestive heart failure relieved by ultrafiltration; pCO_2 was lowered.

Case 3. A 35-year-old man was found to have proteinuria 10 years before his admission to the Cleveland Clinic Hospital. He had, however, been well until two months before his admission when chest pain and hemoptysis developed. He was found to have acid-fast bacilli in one sputum culture, and antituberculous therapy was started. Although the respiratory symptoms improved, he became oliguric and uremic, and was pale and overhydrated without evidence of cardiac decompensation. The blood pressure was 130/70 mm. Hg; funduscopic examination revealed normal eye grounds. The right lower lung field was dull to percussion. The hemoglobin concentration was 5.7 gm. per 100 ml., and the blood urea content was 231 mg. per 100 ml. Urine specific gravity was 1.013; protein, white blood cells, and red blood cells were present in the urine. Sputum cultures were negative for acid-fast bacilli. His condition improved slowly with restriction of protein and sodium intake but he left the hospital against medical advice. Three months later he was readmitted to the hospital with uremia. His condition failed to stabilize with medical management, and hemodialysis was begun. The uremia was controlled with twice weekly hemodialyses, and, initially, he did well (*Fig. 4*). Three months after the first dialysis, jaundice developed. His condition deteriorated and further dialyses were withheld. The pathologic findings in the liver were compatible with drug-induced hepatitis. This was probably secondary to multiple small doses of chlorpromazine hydrochloride.

Case 4. A 23-year-old man, a school teacher, had been found to have asymptomatic proteinuria, with a normal-appearing intravenous pyelogram, at the age of 15 years. Since that

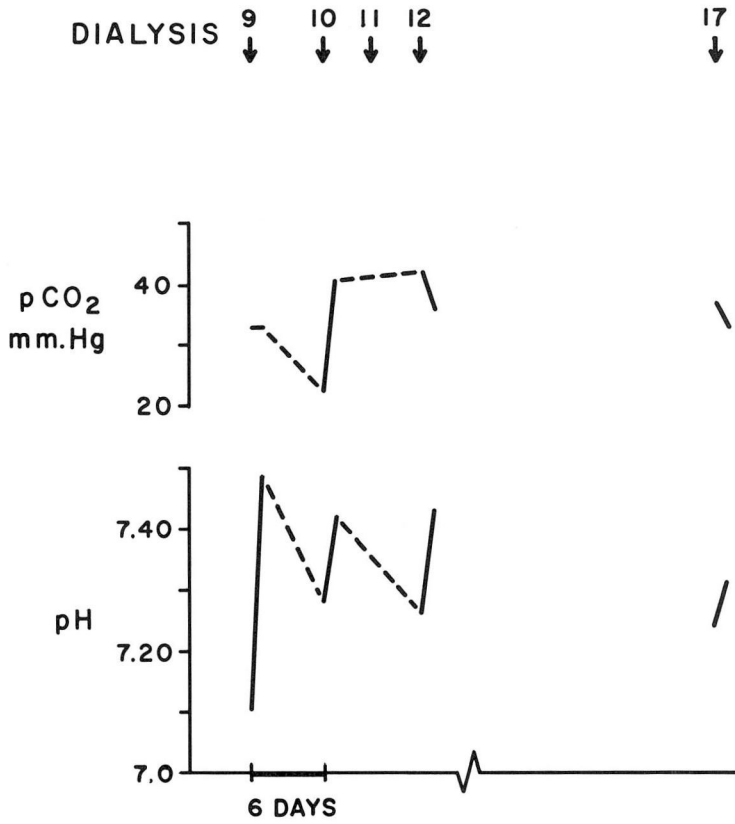

Fig. 4. Case 3. Low pH value at onset was corrected. This man had pulmonary complication, hence pCO_2 at beginning of dialysis 9 was not so low as it might have been otherwise.

time he had had nocturia, frequency, and occasional dysuria, without chills, fever, or edema. When he was first examined at the Cleveland Clinic he was uremic and his blood pressure was 160/110 mm. Hg; this pressure had increased slowly. Conservative treatment was successful for two months, but then the uremia could no longer be controlled by these measures, and repeated hemodialyses were begun (*Fig. 5*). Though the uremia was well controlled, the patient at times was nervous and was unable to sleep. Arterial pressure varied with the state of hydration; he was observed to have grade 2 retinopathy. Two years after the onset of the dialysis program the patient is doing well.

Case 5. A 30-year-old man was well until three months before his admission to the Cleveland Clinic Hospital when a severe cold with back pain, fever, and extreme weakness developed. Following this he had repeated respiratory infections, and gradually uremia developed. He was hospitalized for one month elsewhere without improvement in his condition. On admission here, he was pale and dyspneic, with distention of neck veins, hepatomegaly, and a left pleural effusion. A pericardial friction rub was audible. The blood pressure was 160/100 mm. Hg, and grade 2 retinopathy was present. The blood urea concentration was 195, and the serum creatinine content was 8.0 mg. per 100 ml. Urine specific gravity was 1.010; 2-plus protein, red blood cells, white blood cells, and granular casts were present in the urinary sediment. Hemodialysis was begun and resulted in great symptomatic improvement. Following the third hemodialysis, cardiac tamponade developed and a surgical window was required because of persistent reac-

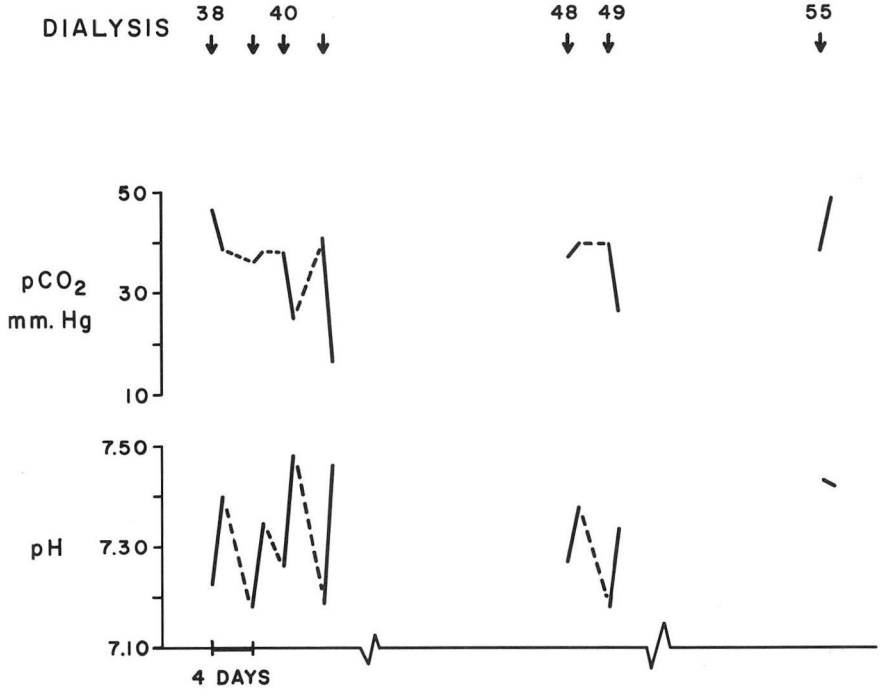

Fig. 5. Case 4. Correction of pH value with each dialysis, as usual. The pCO_2 dropped during most dialyses because of hyperventilation.

cumulation of pericardial fluid. Severe oliguria has persisted and it has been necessary to maintain the patient with periodic prolonged hemodialysis twice weekly (*Fig. 6*). Hypertension and hydration are difficult to control; cardiac failure develops easily. He has had repeated pulmonary complications, with hemorrhagic effusion, pneumonia, and recurrent pulmonary infarctions. His clinical condition is only fair; the uremia is well controlled, but the pulmonary function is obviously diminished. The patient was sustained for more than one year but died after transplantation of a kidney from a dead donor.

Results and Comments

The results described here are representative of those observed in a much larger number of patients.

Changes in pH values. In all five patients, the arterial pH value before dialysis was unusually low; the average predialysis pH was 7.20, and occasionally it was as low as 7.02. In those cases in which the interval between dialyses was extremely short the predialysis pH value was normal, or almost normal.

The tolerance of the patients for acidosis was surprisingly good. Most of our patients live at home and return to the hospital just for dialysis. Except in rare cases of extreme acidosis, the patients did not have Kussmaul's respirations, nor did they have any other clinical symptoms of acidosis. The serum potassium concentration

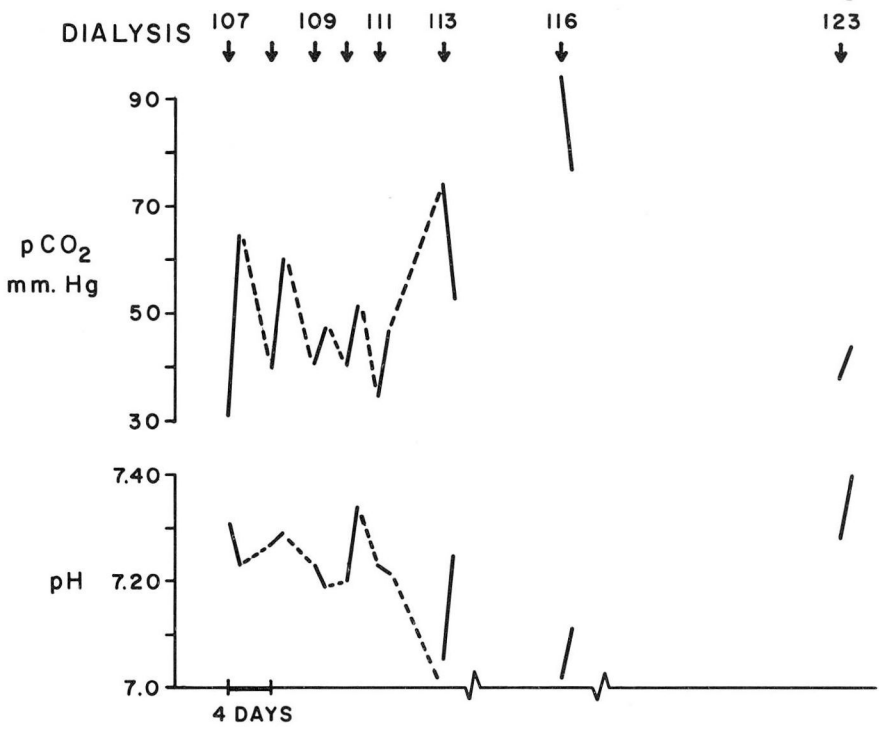

Fig. 6. Case 5. Man with diminished pulmonary function. Extremely low pH value at onset of dialyses 113 and 116. Exceedingly high pCO_2 at the onset of dialysis 116 because of overhydration and pulmonary edema. The pCO_2 improved after dialysis and ultrafiltration but not to normal value.

was almost always high, as were the blood urea content and the concentrations of other retention products. One or two days before dialysis the patients were sometimes anorectic, and occasionally had nausea and vomiting.

A good correction of the pH value was obtained with dialysis (*Table 2, Fig. 1*) in all but one patient (Case 5). In his case the pH value remained low. This patient had a history of respiratory infection, and, later, hemorrhagic pleuropericarditis and recurrent pulmonary emboli developed. He also had several episodes of congestive heart failure. The multiplicity and severity of his pulmonary problems explain the respiratory component in the genesis of his acidosis.

Occasionally other patients had an incomplete correction of acidosis following dialysis, generally related to some type of pulmonary complications, usually congestive heart failure. Correction was incomplete when the dialysis was of too short duration. Overcorrection of the pH with resultant alkalosis was not seen, but on two or three occasions the postdialysis pH value was as high as 7.48.

Changes in pCO_2. In all five patients, the pCO_2 before dialysis was generally lower than normal, indicating a partial respiratory compensation for the metabolic acidosis.

It is of interest that in 11 of 29 dialyses, pCO_2 fell rather than rose during dialysis. In 4 of these 11 instances initial pCO_2 was abnormally high; and the explanation for the fall, at least in some of these, was that an element of pulmonary edema was relieved by ultrafiltration: rales in both lungs in case 1 (*Fig. 2*, dialysis 23); frank pulmonary edema in case 2 (*Fig. 3*); pulmonary infection, emboli and pleural effusion in case 5 (*Fig. 6*, dialyses 112 and 116). When the elevated pCO_2 values were associated with congestive heart failure, the ultrafiltration during dialysis tended to alleviate the failure; thereby improving the pCO_2. In the remaining seven instances, pCO_2 initially was either normal or low and fell further during dialysis at a time when pH and bicarbonate concentration were rising. In these circumstances then, dialysis was associated with an element of respiratory alkalosis. Similar findings have been presented by Cowie, Lambie, and Robson.[10]

An explanation is available for the changes in pCO_2 in case 4 (*Fig. 5*). In this patient the pCO_2 was lower than normal before dialysis, and decreased rather than increased during dialysis, despite an adequate correction of the pH value. This happened several times, and the postdialysis pH value on two occasions was 7.48. The patient at that time was restless and agitated, and often became anxious during dialysis, requiring hypnotics. The decrease in the pCO_2 was attributed to hyperventilation. In case 5 (*Fig. 6*) the explanation for the increase in the pCO_2 during some dialyses remains in doubt.

Changes in contents of buffer base (B.B.) and base excess (B.E.). The term "buffer base" was introduced by Singer and Hastings[11] in 1948. It refers to the base that is associated with bicarbonate and nonbicarbonate buffer anions including hemoglobinate, proteinate, and phosphate. The buffer base value is useful in the evaluation of the origin and extent of acid-base disturbances, because it is not affected by respiratory function. Disturbances in buffer base content, therefore, reflect metabolic acidosis or alkalosis.

The term "base excess" was coined in Copenhagen.[6] It compares the amount of true base in the blood with respect to the amount found under normal conditions. The normal range is between $+3$ and -3 mEq. per liter.

All five patients studied had low concentrations of buffer base and of base excess before dialysis (*Table 2*). Both deficits were corrected after dialysis. No overcorrection was observed. In two patients, case 5 (*Fig. 6*) with respiratory acidosis, and case 4 (*Fig. 5*) with respiratory alkalosis, both the buffer base and the base excess concentrations were normal after dialysis, indicating good correction of the metabolic components of their acidosis.

Changes in concentrations of standard bicarbonate, of actual bicarbonate, and of total CO_2 of plasma. "Standard bicarbonate of plasma" is another new term introduced

by Astrup's group.[7] It is defined as the concentration of bicarbonate in plasma when the whole blood has been equilibrated with carbon dioxide at a pCO_2 of 40 mm. Hg, at 38 degrees C., with the hemoglobin fully oxygenated. Respiratory changes do not influence the value of this parameter; it reflects metabolic changes alone. The normal values range from 21.3 to 24.8 mEq. per liter. Total CO_2 content of plasma is determined on samples sealed off from the air.

The total CO_2 content and the actual bicarbonate content (another concept from Astrup) vary directly with the pCO_2 and, therefore, represent both the metabolic and the respiratory components. Their practical value in the evaluation of clinical acid-base problems is similar.

In our patients all three of these determinations were low before dialysis, and all returned toward normal after dialysis. In the patient with hyperventilation, case 4 (*Fig. 5*), the total CO_2 content understandably did not return entirely to the normal value.

Summary

A study of the acid-base equilibrium in five patients with negligible renal function is reported. These patients were maintained for as long as 19 months by periodic hemodialyses. The use of the equilibration technic and nomogram designed by Astrup and his co-workers facilitated the determinations, and conveniently provided a wide range of information.

The average predialysis pH values ranged from 7.20 to 7.26. The lowest recorded pH value was 7.02. Some degree of respiratory compensation was nearly always present, as indicated by the low levels of the pCO_2. The levels of buffer base, base excess, and standard bicarbonate, all indicated metabolic acidosis. Although the actual bicarbonate and total CO_2 contents were low, they did not reflect the metabolic changes as clearly as did the other parameters. Despite the acidosis, which, as our studies indicate, was sometimes severe, the patients had surprisingly few symptoms.

In most cases the acidosis was well corrected by hemodialysis. The following exceptions however must be mentioned. First, when the acidosis had a respiratory as well as a metabolic component, the pH value was lower than usual, and the pCO_2 was normal or high depending on the severity of the respiratory problem. Buffer base and base excess contents were low. The bicarbonate concentration was also low, but not so low as the buffer base content. Improvement of the respiratory components of the acidosis by ultrafiltration during dialysis occurred when they were related to overhydration. Often, however, their correction was incomplete.

A second exception includes instances in which respiratory alkalosis appeared during the correction of metabolic acidosis by dialysis. This alkalosis probably resulted from hyperventilation. The main findings after dialysis were a low pCO_2, and a pH value at or slightly higher than the upper limit of normal. Differentiation

of this condition from metabolic alkalosis is easily made, for in respiratory alkalosis the buffer base and base excess contents are within normal limits.

References

1. Kolff, W. J., and Berk, H. Th. J.: Artificial kidney; dialyzer with great area. Acta med. scandinav. **117:** 121-134, 1944.
2. Kolff, W. J.: Artificial Kidney, New Ways of Treating Uremia. London: J. and A. Churchill, 1947.
3. Weller, J. M.; Swan, R. C., and Merrill, J. P.: Changes in acid-base balance of uremic patients during hemodialysis. J. Clin. Invest. **32:** 729-735, 1953.
4. Hegstrom, R. M.; Murray, J. S.; Pendras, J. P.; Burnell, J. M., and Scribner, B. H.: Two years experience with periodic hemodialysis in treatment of chronic uremia. Tr. Am. Soc. Artif. Int. Organs **8:** 266-280, 1962.
5. Schwartz, W. B., and Relman, A. S.: Critique of parameters used in evaluation of acid-base disorders: "whole-blood buffer base" and "standard bicarbonate" compared with blood pH and plasma bicarbonate concentration. New England J. Med. **268:** 1382-1388, 1963.
6. Astrup, P.; Siggaard Andersen, O.; Jorgensen, K., and Engel, K.: Acid-base metabolism: new approach. Lancet **1:** 1035-1039, 1960.
7. Siggaard Andersen, O.; Engel, J.; Jørgensen, K., and Astrup, P.: Micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. Scandinav. J. Clin. & Lab. Invest. **12:** 172-176, 1960.
8. Siggaard Andersen, O.: Sampling and storing of blood for determination of acid-base status. Scandinav. J. Clin. & Lab. Invest. **13:** 196-204, 1961.
9. Brandon, J. M.; Nakamoto, S.; Rosenbaum, J. L.; Franklin, M., and Kolff, W. J.: Prolongation of survival by periodic prolonged hemodialysis in patients with chronic renal failure. Am. J. Med. **33:** 538-544, 1962.
10. Cowie, J.; Lambie, A. T., and Robson, J. S.: Influence of extracorporeal dialysis on acid-base composition of blood and cerebrospinal fluid. Clin. Sc. **23:** 397-404, 1962.
11. Singer, R. B., and Hastings, A. B.: Improved clinical method for estimation of disturbances of acid-base balance of human blood. Medicine **27:** 223-242, 1948.