CHEMICAL CHANGES OCCURRING IN THE BODY AS THE RESULT OF CERTAIN DISEASES

III. The Composition of the Plasma in Severe Diabetic Acidosis and the Changes Taking Place during Recovery

By ALEXIS F. HARTMANN AND DAN C. DARROW

WITH THE TECHNICAL ASSISTANCE OF MARIE MORTON

(*From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital, St. Louis*)

In the first paper (1) of this series, the composition of the plasma was studied in cases of "acidosis" due chiefly to diarrhea and anhydremia. In contributing to the disturbances in the acid-base balance, the following factors were considered significant: (*a*) loss of $BHCO_3$ from the plasma by way of the pancreatic and intestinal secretions and diarrheal stools; (*b*) functional renal insufficiency (depending presumably chiefly on anhydremia and oliguria) leading to diminished excretion of acid neutralized by ammonia, and consequent failure to support diminished plasma $BHCO_3$, and (*c*) the excretion of $BHCO_3$ as such into the urine during periods of increased osmotic pressure in the plasma due either to loss of plasma water resulting from diarrhea or to salt administration or both. Effective treatment of severe cases of acidosis of this type seemed to require alkali as well as water administration. Salt administration was considered contraindicated in the presence of high plasma chloride and low bicarbonate.

In the second paper (2) the composition of the plasma in cases of nephritis was studied. It was concluded that when marked changes from the normal occurred in acute hemorrhagic nephritis, such symptoms as *vomiting* and *diarrhea*, *edema* and *oliguria*, and *convulsions* were responsible. In cases of chronic nephritis with renal damage, the characteristic plasma changes seemed due to a faulty secretion of urine, which led to a retention of phosphoric and sulfuric acid and a loss of plasma BCl and $BHCO_3$. The resultant low electrolyte con-

TABLE 1

Recovery from diabetic acidosis with the aid of insulin, water, and carbohydrate, but without salt, or alkali

Date	Time	BCl	BHCO₃	pH	Protein		B-HPO₄	Lactic acid	Diacetic acid	Total base	Undetermined (ketone) acid	Glucose	N.P.N.	Serum water	Osmotic pressure Observed	Osmotic pressure Calculated
					By refractometer	By Kjeldahl										
		$mM.$	$mM.$		$\frac{grams}{per\ cent}$	$\frac{grams}{per\ cent}$	$mM.$	$mM.$	$mM.$	$mM.$	$mM.$	$\frac{mgm.}{per\ cent}$	$\frac{mgm.}{per\ cent}$	$\frac{grams}{per\ cent}$	$mM.$	$mM.$
Case 1. Eddie S.																
September 16, 1926	11:30 a.m.	84.8	4.7	7.00	9.99		3.2	2.5				488	37.8		351	
September 16, 1926	4:30 p.m.	79.2	6.0	7.13	9.13							121	39.8		291	
September 16, 1926	9:30 p.m.	90.0	7.2	7.18	8.71							78	46.2		285	
September 17, 1926	7:30 a.m.	90.0	14.2	7.23	8.49							91	41.8			
September 17, 1926	5:00 p.m.	87.0	14.0	7.38	8.28							70	42.0			
September 18, 1926	8:00 a.m.	80.0	15.8	7.35	7.85							259	66.0			
September 21, 1926	8:00 a.m.	80.4	21.4	7.38	7.63							430	50.0			
Case 2. Billy R.																
June 3, 1926	11:30 a.m.	92.0	6.2	7.17	9.99							516	52.2			
June 3, 1926	4:00 p.m.	91.2	7.7	7.22	9.77							380				
June 3, 1926	9:00 p.m.			(7.35)			(3.0)	(2.0)				182				
June 4, 1926	8:45 a.m.	95.2	19.1		8.81					138	1.0	112	46.2			
June 5, 1926	8:45 a.m.	86.0	17.8		8.06							349	36.6			

Blood serum

Case 5. Francis H.

December 5, 1927	10:20 p.m.	90.0	8.6		10.4		3.6	2.2			475	35.0			
December 6, 1927	9:00 a.m.	92.3	16.0	7.30	8.28	2.3	3.1	1.2			53	28.3			

Case 6. James Y.

December 29, 1927	4:00 p.m.	99.2	10.0	7.25	8.49	2.1	3.6	4.4			305	26.0		294	
December 29, 1927	9:00 p.m.	99.2	13.0	7.31	8.28	2.0	2.4	3.3			176	23.0		264	
December 30, 1927	9:00 a.m.	99.2	14.6	7.32	8.06	2.0	1.8	2.0			82	27.0		270	

(Case 6—readmission)

May 26, 1928	10:00 a.m.	93.0	10.7	7.10	9.99	8.23 (3.0)	1.7		150	27	492	36.6	91.1	346	334
May 26, 1928	3:00 p.m.	94.8	10.3	7.25	8.60	7.79 (3.0)	2.9		144	18	222	26.6	92.3	303	298
May 27, 1928	8:30 a.m.	98.5	15.6	7.35	8.92	8.31 (3.0)	2.5		146	9	148	27.7	92.4	282	296

( ) Assumed values.

TABLE 2

Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate and Ringer's solution, but without alkali

Case 4. Loretta B.

Date	Time	BCl (mM.)	BHCO₃ (mM.)	pH	Protein By refractometer (grams per cent)	Protein By Kjeldahl (grams per cent)	B-HPO₄ (mM.)	Lactic acid* (mM.)	Diacetic acid* (mM.)	Total base (mM.)	Undetermined (ketone) acid (mM.)	Glucose (mgm. per cent)	N.P.N. (mgm. per cent)	Serum water (grams per cent)	Osmotic pressure Observed (mM.)	Osmotic pressure Calculated (mM.)
January 24, 1927	11:45 a.m.	95.0	12.9	(7.30)	8.92		3.5	(2.0)	5.1	146	15	248	31.7			303
January 25, 1927	9:00 a.m.	96.5	5.4	(7.20)	9.13			(2.0)	7.4			386	29.6			
January 25, 1927	2:00 p.m.							(2.0)	7.7			297				
January 26, 1927	9:00 a.m.	98.7	5.9	(7.20)	9.99		3.3	(2.0)	8.0	147	14	457	36.8			309
January 26, 1927	2:00 p.m.	102.0	7.0	7.25	9.77		3.2	(2.0)	8.4	143	11	300	40.0			302
January 27, 1927	9:00 a.m.	101.0	10.8	7.30	7.85		3.0	(2.0)	6.5	143	13	295	32.8			300
January 28, 1927	9:00 a.m.	96.0	13.2	7.34	7.63		(3.0)	(2.0)	5.8			297	34.4			
January 29, 1927	9:30 a.m.				7.63			(2.0)	5.0			500				
February 4, 1927	9:00 a.m.	95.0	24.9	7.49	6.55		(3.0)	1.8	(0)	146	6	282	25.0			301
February 7, 1927	9:00 a.m.	96.0	25.4	7.49	6.55		(3.0)	1.4	(0)	144	4	56	(25.0)			274

Case 1. Eddie S.

Date	Time	BCl (mM.)	BHCO₃ (mM.)	pH	Protein By refractometer (grams per cent)	Protein By Kjeldahl (grams per cent)	B-HPO₄ (mM.)	Lactic acid* (mM.)	Diacetic acid* (mM.)	Total base (mM.)	Undetermined (ketone) acid (mM.)	Glucose (mgm. per cent)	N.P.N. (mgm. per cent)	Serum water (grams per cent)	Osmotic pressure Observed (mM.)	Osmotic pressure Calculated (mM.)
April 15, 1927	11:00 a.m.	92.3	5.3	7.07	11.8		4.6	5.6	4.5	141	10	734	45.0		309	325
April 16, 1927	9:00 a.m.	95.3	16.2	7.35	8.06		2.5	2.1	2.2	135	3	29	38.0			273

( ) Assumed values.

* Determined together in Case 4.

TABLE 3

Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate, Ringer's solution and alkali

Date	Time	BCl	BHCO₃	pH	Protein By refractometer	Protein By Kjeldahl	B-HPO₄	Lactic acid*	Diacetic acid*	Total base	Undetermined (ketone) acid	Glucose	N.P.N.	Serum water	Osmotic pressure Observed	Osmotic pressure Calculated
		mM.	mM.		grams per cent	grams per cent	mM.	mM.	mM.	mM.	mM.	mgm. per cent	mgm. per cent	grams per cent	mM.	mM.
Case 3. Neville O.																
January 31, 1927	2:00 p.m.	96.0	6.4	7.10	9.56		2.7	(2.0)	6.8	133	9	413	33.0			291
January 31, 1927	5:00 p.m.	96.8	17.1	(7.30)	6.77		(3.0)	(2.0)	6.7	140	7	120	(33.0)			283
January 31, 1927	10:00 p.m.	96.8	26.1	(7.45)	6.98		(3.0)	(2.0)	3.3	144	2	73	(33.0)			291
February 1, 1927	8:30 a.m.		10.6		6.98			(2.0)	6.0			396				
February 1, 1927	4:30 p.m.	91.8	14.6	(7.30)	7.20			(2.0)	3.2			76				
February 2, 1927	8:45 a.m.	91.8	17.8	(7.30)	6.55			(2.0)	3.3			287				
February 2, 1927	4:30 p.m.	93.0	21.7	(7.40)	7.42			(2.0)	3.9			123	32.0			
February 7, 1927		94.0	10.2	(7.30)	8.49			(2.0)	4.5			145				
Case 1. Eddie S.																
April 3, 1928	11:45 a.m.	89.1	7.9	7.00	13.0	7.88	4.9	4.9	6.5	147	27	700	48.0	88.7	394	354
April 3, 1928	3:45 p.m.	97.2	9.7	7.15	9.77	6.83	1.7	16.1	11.5	165	28	633	46.7	90.7	406	381
April 4, 1928	8:30 a.m.	84.8	39.3	7.57	5.90		2.9	2.7	0.4	146	3	40	46.4	94.2	452(?)	320
April 5, 1928	8:30 a.m.	84.0	19.3	7.34	6.55		2.6	2.1	4.6	142	21	474	66.0	93.7	352	319
April 6, 1928	8:30 a.m.	98.8	25.5	7.47	6.34		2.2	7.4	2.0	155	7	142	65.0	93.9	315	322
June 6, 1928	11:00 p.m.	80.8	2.9	(6.97)	10.8	6.8	(3.0)	(4.4)		149	45	922	(60.0)	88.5		377
June 7, 1928	1:30 a.m.	84.8	3.1	6.97	10.4	6.7	(3.0)	4.4		141	35	682	60.0	90.0		341
June 7, 1928	9:30 a.m.	90.0	22.9	7.43	7.4	7.2	(3.0)	1.8		153	20	22	(60.0)	92.5		314

( ) Assumed values.

* Determined together in Case 3.

centration was compensated for osmotically by urea increase. In severe cases of acidosis of this type alkali administration seemed indicated and, together with salt administration, was at least partially effective in restoring the normal plasma electrolyte content and in promoting urea excretion.

It is the object of this paper to present data obtained by studying, in a similar way, the composition of the plasma in cases of severe
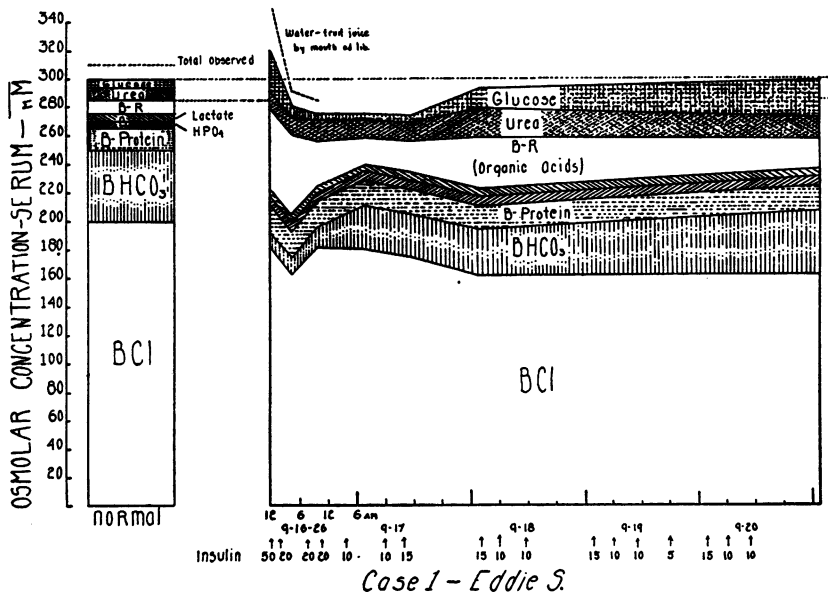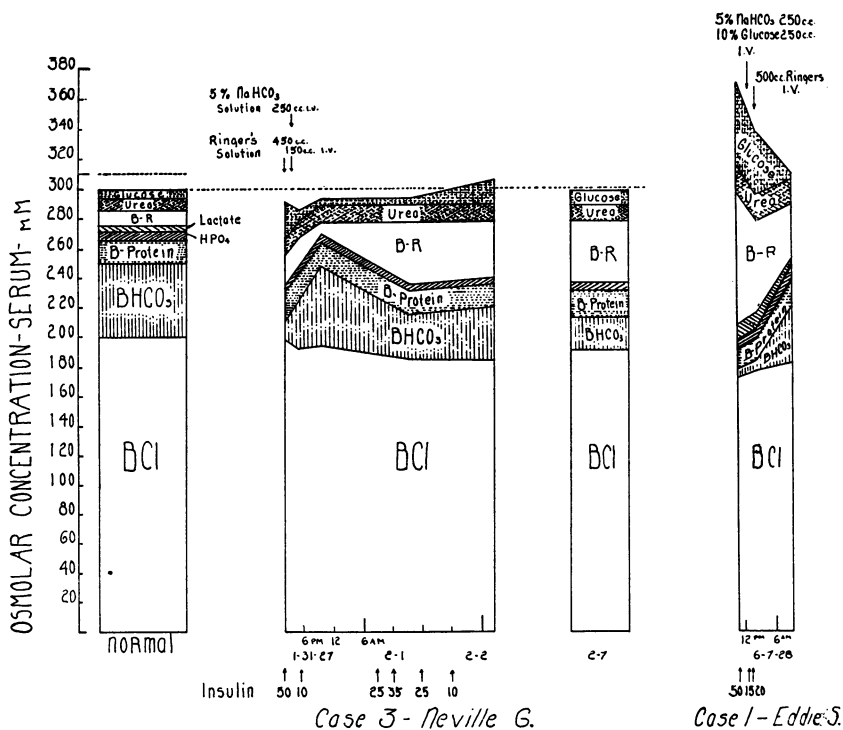

CHART 1. THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN AND CARBOHYDRATE

diabetic "acidosis," and the changes which occurred during recovery, when treatment consisted principally of administration of: (a) *insulin* and *water*, with and without *carbohydrate;* (b) insulin, water, carbohydrate and *salt solution;* and (c) insulin, water, carbohydrate, salt solution and *alkali.* From such a study it was hoped that a rough evaluation could be made, as far as their effect, at least, on the recovery of plasma $BHCO_3$ and pH is concerned, of *oxidation* of *organic acid, urinary excretion* of chloride bound to ammonia, and alkali

administration. Also by following the changes occurring during recovery, it was felt that a deeper insight could be obtained into the changes taking place during the production of diabetic acidosis, on the assumption that they are essentially reverse processes.

Chemical methods similar to those described previously (1) were used. All the total base determinations, however, were made by
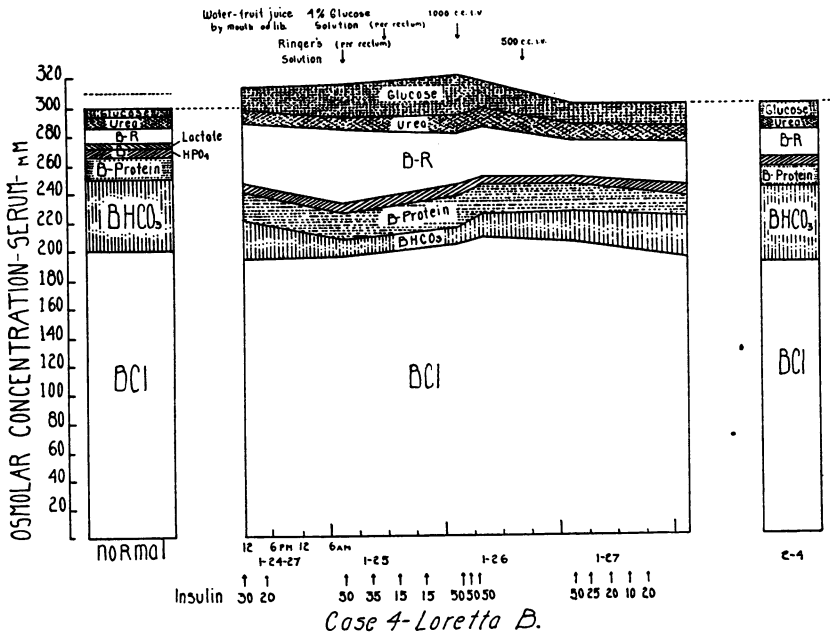
CHART 2. THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN, CARBOHYDRATE AND SALT SOLUTION

the method of Stadie and Ross (7). In a number of instances, the serum protein concentration, as indicated by the refractive index, was checked by Kjeldahl determination of total nitrogen. By weighing before and after drying at 110°C. the changes in the content of plasma water and total solids were sometimes followed. In addition, performed acetone and diacetic acid were frequently determined in at

least a roughly quantitative fashion in the same manner that lactic acid was determined.[1]

CHART 3. THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN, CARBOHYDRATE, SALT SOLUTION AND ALKALI

In estimating the concentration of the total ketone acids, the sum of the principal normal acids ($Cl' + HCO_3' + protein' + HPO_4''$

---

[1] By titrating as rapidly as possible the bisulfite freed from combination with acetaldehyde and acetone, lactic acid and diacetic acid together were determined. Lactic acid alone was then determined in the usual manner after preliminary distillation in acid solution of preformed acetone and diacetic acid, the distillate being caught in Scott-Wilson reagent and furnishing a rough check on the value obtained by titration difference.

+ lactate') was subtracted from the observed total base concentration. The value so obtained includes also the small amount of normally undertermined acid. Since the base-binding value of protein is sometimes exaggerated, due to erroneously high values obtained by the refractometer, it was thought best not to attempt to correct for such normal undetermined acids.

Clinical protocols of the individual cases, containing only essential points and data, are given in the preceding tables and charts.

PROTOCOLS

Case 1. Eddie S. Clinical symptoms of diabetes mellitus were first noted in March, 1924, when the patient was 6 years of age. During his first hospital admission in July, 1924, he was found to be a moderately severe diabetic, but otherwise normal, and did well while in the hospital. After discharge, dietary indiscretions were frequent, and occasionally, for one reason or another, insulin was withheld or given inadequately, and acidosis requiring hospital treatment resulted. During such periods abdominal pain, referred to the right upper quadrant as a rule, vomiting and leucocytosis were marked. Fever or other evidence of infections were never present, and almost immediate relief of all the symptoms followed the recovery from acidosis.

Therapy, bearing on the results shown in the tables, follows:

Admission of September 16, 1926 (table 1):

September 16, 1926:

    12:00 noon. Insulin 50 units, intravenously.

    1:30 p.m. Insulin 20 units, subcutaneously. Orange juice and water by mouth, ad. lib.

    8:00 p.m. Insulin 20 units, subcutaneously.

    11:00 p.m. Insulin, 20 units, subcutaneously.

    11:00 p.m. Orange juice 200 cc. plus 40 grams cane sugar.

    4:00 a.m. Insulin 10 units, subcutaneously.

September 17, 1926:

    5:00 a.m. Orange juice 200 cc. + 40 grams cane sugar.

    12:00 noon. Insulin 10 units subcutaneously.

    4:00 p.m. Insulin 15 units, subcutaneously.

September 18, 1926: Regular diet. Exact insulin requirement not yet ascertained.

Admission of April 15, 1927 (table 2):

April 15, 1917:

    11:00 a.m. Insulin 50 units intravenously.

    11:00 a.m. Ringer's solution 450 cc. intravenously.

    1:15 p.m. Insulin 30 units, subcutaneously.

    6:00 p.m. Insulin 15 units, subcutaneously.

    12:00 p.m. Insulin 12 units, subcutaneously.

April 16, 1927: 6:00 a.m.   Insulin 15 units subcutaneously.

Admission of April 3, 1928 (table 3):

April 3, 1928:

     11:45 a.m.   Insulin 40 units, intravenously.

     11:45 a.m.   Insulin, 40 units, subcutaneously.

     11:45 a.m.   7.5 per cent glucose solution, 400 cc., intravenously.

     11:45 a.m.   Ringer's solution, 400 cc., intravenously.

     11:45 a.m.   5 per cent sodium bicarbonate solution 500 cc., intravenously.

     3:00 p.m.   Insulin, 50 units, subcutaneously.

     4:00 p.m.   Ringer's solution by Murphy drip per rectum.

     9:00 p.m.   Insulin 15 units subcutaneously.

April 4, 1928:

     3:00 a.m.   Insulin, 15 units, subcutaneously.

     9:00 a.m.   Meal: P 20, F 50, CH 20.

     9:00 a.m.   Insulin 20 units, subcutaneously.

     12:30 p.m.   Meal as above.

     12:30 p.m.   Insulin 15 units subcutaneously.

     6:00 p.m.   Meal as above.

     6:00 p.m.   Insulin 15 units, subcutaneously.

April 5, 1928: Meals and insulin as on April 4, 1928.

Admission of June 6, 1928 (table 3):

June 6, 1928:

     11:45 p.m.   Insulin 50 units intravenously.

     1:00 a.m.   500 cc. 5 per cent Glucose solution containing 12.5 grams. $NaHCO_3$ and 15 units insulin, intravenously.

June 7, 1928:

     1:30 a.m.   Ringer's solution 400 cc. intravenously.

     1:30 a.m.   Insulin 20 units subcutaneously.

     9:00 a.m.   Previous diet and insulin dosage resumed.

Case 2. Billie R. This patient developed symptoms of diabetes mellitus in January, 1924, when 8 years of age. During hospital admission in February, 1924, he was found to be a mild diabetic, showing no hyperglycemia on the usual diabetic diet without insulin. After discharge from the hospital, dietary indiscretions were frequent, and gradually carbohydrate tolerance was lost, and daily insulin administration became necessary. As punishment for one such lapse on June 1, 1926, he was put to bed without supper or insulin. The next morning he complained of abdominal pain, felt nauseated and vomited. Because he would not eat breakfast, insulin was again withheld. Abdominal pain and nausea persisted, hyperpnea and drowsiness were noted and he was then brought to the hospital. As in Case 1, leucocytosis of 40,000 without fever, was noted, and all symptoms disappeared when recovery from acidosis occurred (table 2).

Therapy was as follows:

June 3, 1926:

    11:45 a.m.   Insulin 30 units intravenously.

    1:00 p.m.   Insulin 15 units, subcutaneously. Fruit juice with added cane
           sugar ad lib.

    6:00 p.m.   Insulin 30 units, subcutaneously.

    12:00 p.m.   Insulin 15 units, subcutaneously.

June 4, 1926: Regular diet and insulin.

Case 3. Neville G. Her first diabetic symptoms were noted in April, 1923, when she was 8 years of age. At this time she was admitted to the hospital, where it was found that she could tolerate an adequate diet without the aid of insulin. Home supervision was excellent, but gradually carbohydrate tolerance was lost and insulin two or three times daily was required. On January 30, 1927, she became ill, complaining of abdominal pain and nausea, and vomited. The next day she complained of abdominal and thoracic pain, the latter aggravated by respiratory movements of the chest. She was then brought to the hospital at 2:00 p.m. on January 31, 1927. Her appearance was alarming. She appeared shocked; her eyes were sunken and dull, her skin was dry, cold and mottled, cyanosis of the lips and nail beds was present and hyperpnea was extreme. She complained of pain, aggravated by inspiration in the lower part of her chest. A few sharp crackling râles were heard at the left base posteriorly and in the axilla, but no friction rub. The pulse was very rapid and of poor quality. After $\frac{1}{16}$ grain of morphine was administered hypodermically, the following treatment was given: with almost immediate and unexpected improvement (table 3).

    January 31, 1927:

        2:00 p.m.   Insulin 50 units intravenously.

        2:00 p.m.   Ringer's solution 450 cc. intravenously.

        3:00 p.m.   5 per cent sodium bicarbonate solution 250 cc. intravenously.

        3:00 p.m.   Ringer's solution 150 cc. intravenously.

        5:00 p.m.   Insulin 10 units subcutaneously followed by supper.

Case 4. Loretta B. Diabetic symptoms were first noted early in 1924 when the child was 10 years of age. In April, 1924, she was admitted to the hospital, where she was given an adequate diet with 30 units of insulin daily. She later contracted upper respiratory infections on several occasions, leading to acidosis which, as in the previous cases, was usually accompanied by abdominal pain, vomiting, and marked leucocytosis. Particularly severe acidosis following such infections was present at the time of the hospital admission on January 24, 1927. Therapy leading to recovery at this time was as follows:

    January 24, 1927:

        11:45 a.m.   Insulin 30 units subcutaneously.

        5:00 p.m.   Insulin 20 units subcutaneously.

January 25, 1927:

    9:00 a.m.   Insulin 50 units intravenously. Ringer's solution per rectum by Murphy drip.

    3:25 p.m.   Insulin 35 units subcutaneously. Orange juice 200 cc. 4 per cent glucose per rectum as Murphy drip. Orange juice 200 cc.

    8:00 p.m.   Insulin 15 units subcutaneously.

January 26, 1927:

    2:00 a.m.   Insulin 15 units subcutaneously.

    9:00 a.m.   5 per cent glucose 1000 cc. intravenously.

    9:30 a.m.   Insulin 50 units intravenously.

    10:45 a.m.   Insulin 50 units subcutaneously.

    12:45 p.m.   Insulin 50 units subcutaneously.

    11:00 p.m.   Ringer's solution 500 cc. subcutaneously.

January 27, 1927:

    Insulin 125 units subcutaneously.

    Ringer's solution 500 cc. subcutaneously.

    Regular diet.

January 28, 1927: Insulin 110 units, subcutaneously, with full diet.

Case 5. Frances H. Diabetic symptoms were first noted in December, 1923, when he was 9 years of age. Shortly afterwards he was admitted to the hospital, where he was found normal except for moderately severe diabetes. After a temporary improvement, his carbohydrate tolerance again diminished. On March 1, 1927, he was admitted with alkalosis, following too vigorous treatment with alkali and insulin administered by his family physician. Proper diet and insulin routine were frequently interrupted and he was admitted to the hospital again on December 5, 1927, with moderately severe acidosis (table 1). Therapy was as follows:

December 5, 1927:

    10:20 p.m.   10 per cent glucose 500 cc. intravenously. Insulin 40 units intravenously.

    11:00 p.m.   Insulin 40 units, subcutaneously.

December 6, 1927: Usual diet and insulin.

Case 6. James Y. Diabetic symptoms were first noticed in June, 1926, when he was 13 years of age. After hospital admission, he was found normal except for moderately severe diabetes and was given an adequate diet and insulin dosage. He did well in the hospital and after discharge until he developed a respiratory infection, which resulted in severe acidosis on December 29, 1927. Therapy at that time was as follows:

December 29, 1927:

    5:30 p.m.   Insulin 35 units subcutaneously.

    9:00 p.m.   10 per cent glucose 250 cc. intravenously.

    9:00 p.m.   Insulin 13 units, intravenously.

Later, on May 26, 1928, hospital admission was again necessary because of severe acidosis resulting from a cellulitis of the face and neck. Therapy at that time consisted of:

May 26, 1928:

    10:00 a.m.   Insulin 50 units intravenously. Water by mouth ad. lib.

    6:00 p.m.   Insulin 15 units subcutaneously.

    12:00 p.m.   Insulin 15 units subcutaneously.

May 27, 1928: 6:00 a.m.   Insulin 15 units, subcutaneously.

DISCUSSION

The composition of the plasma in severe diabetic acidosis

As emphasized recently by Peters, Bulger and their co-workers (3), the plasma in severe diabetic acidosis may become very *concentrated*. In Case 1 on April 3, 1928 (table 3) the water content of the first sample of serum was 88.6 and the true protein concentration 7.88 grams per cent by volume, while after complete recovery on April 6, 1928 the water content increased to 93.9 and the protein fell to 6.34 per cent. Very similar values were seen in the other cases. It should be noted, however, that absolutely no true indication of plasma concentration can be obtained from the refractometric values for protein, since, especially when marked lipemia exists, such values tend to be much too high. In Case 1 on April 3, 1928 for instance, the refractometer indicated a protein concentration of 13.0 when actually a concentration of 7.88 per cent existed.

Despite such anhydremia, the concentration of total base tends to be slightly below normal, as pointed out also by Peters, Bulger and their co-workers (3). The lowest value found by us was that in Case 3 on January 31, 1927 (table 3), amounting to but 133 mM.

The sum of the most important normal acids (Cl' + HCO'_3 + protein' + HPO_4'' + lactate') is always below normal and in some instances extremely low. The difference between the observed total base value and this sum, representing undetermined acid, is always high, but varies greatly. The lowest indicated value in severe acidosis was 9.0 mM. (Case 3 on January 31, 1927 (table 3)) and the highest 45 mM. (Case 1, June 6, 1928, Table 3), the average being 20 mM. Such undetermined acid presumably is chiefly diacetic and beta-oxybutyric.

In the more severe cases, $BHCO_3$ may be but 5 mM. (corresponding to about 12 vols. per cent CO_2 content) and the pH may be 7.00 or less. In most instances, increase in ketone acids more than accounts for such diminution of the bicarbonate ion. In one case, however (Case 3, table 3) there was noted a 17.0 mM. decrease in $BHCO_3$ with but an indicated 9.0 mM. increase in ketone acid.

Of the remaining acids, chloride is most regularly affected. Its concentration is always below normal, sometimes by as much as 20 mM. Occasionally lactic acid is significantly increased, as in Case 1 on April 3, 1928 (table 3). Phosphoric acid concentration tends to be elevated slightly, but such elevation is not significant from the standpoint of its base-binding capacity. Increase in protein concentration, although sometimes very marked, usually increases but little the base bound to protein because of the fall in pH which accompanies the plasma concentration.

From the osmolar viewpoint, we note a reduction in total electrolyte concentration, with an increase in glucose concentration sufficient to maintain a normal or a high osmotic pressure. The initially highest observed total osmolar concentration as indicated by the freezing point depression was 394 mM. and occurred in Case 1 on April 3, 1928 (table 3). In this instance the theoretical osmolar concentration was 354 mM., 84 per cent of which was contributed by electrolyte. The least depression of the freezing point (309 mM.) was noted in case 1 on April 15, 1927 (table 2). In this instance the theoretical osmolar concentration was 325 mM., electrolyte accounting for 82.2 per cent of it.

Recovery resulting from the administration of water, insulin and carbohydrate

The results of therapy as indicated above can be seen in table 1 and chart 1.[2] The outstanding feature is the rapid disappearance of blood sugar, frequently sufficient, even despite carbohydrate administration, to produce marked hypoglycemia, without the simultaneous return of $BHCO_3$ to anywhere near its normal concentration. Thus in Case 1 on September 16, 1927 ten hours after the beginning of

[2] In constructing this chart, total base values, equivalent to the average found on other occasions, were assumed.

treatment, the blood sugar dropped from 488 to 78 mgm. per cent while $BHCO_3$ increased from 4.7 to 7.0 mM.   In Case 5 during about the same interval, the blood sugar dropped from 475 to 53 mgm. per cent, while $BHCO_3$ rose from 8.6 to 16 mM.   In the other three cases very similar findings were noted.

In all instances large amounts of insulin were given, and presumably glucose oxidation was maximal.   We cannot be certain in the first four instances, because of failure to determine total base, whether or not acetone body acid accumulation equalled or exceeded $BHCO_3$ reduction.   In Case 5, on December 6, 1927, and Case 6 on December 30, 1927 however, diacetic acid (and therefore presumably beta-oxybutyric acid) was still present in the plasma in considerable amount ten hours after the beginning of treatment.   In Case 6 on May 26, 1928, a total organic acid concentration of 27 mM. was indicated, while $BHCO_3$ was 10.7, approximately 13 mM. below normal.   In this instance, therefore, there was known to have been present enough base bound to organic acid to restore $BHCO_3$ completely.   Yet 22 hours after the beginning of treatment, although organic acid was reduced by 18 mM. $BHCO_3$ increased only 4.9 mM.

It seems apparent, therefore, that much of the base released by organic acid on oxidation is claimed by acid other than carbonic, or is excreted from the body.   In Case 6, on April 27, 1928, chloride increased in concentration during recovery, and must have claimed 5.5 mM. of base, slightly more than claimed by carbonic acid.   Lactic acid increased 0.8 mM.   Protein, in this instance actually changing but little in concentration if we accept the Kjeldahl figures as correct, must have claimed 2.1 mM. because of the rise in pH from 7.10 to 7.35.   Thus, together, Cl', HCO'_3, protein and lactic acid claimed 13.3 of the 18.0 mM. of base released by organic acid oxidation.   The difference, 4.7 mM., was well accounted for by the decrease in total base of 4.0 mM., resulting either from plasma dilution or from excretion of base into the urine.

In three of the four remaining cases in this group, BCl increased significantly in concentration, despite apparent plasma dilution, and must have been chiefly responsible for preventing more rapid restoration of $BHCO_3$.   Evidently, during developing acidosis, plasma and lymph chloride had shifted not only into the red blood cells in accord-

ance with the Donnan principle of ionic and osmotic equilibrium, as shown by Van Slyke and his co-workers (4) to occur, but also into the fixed tissue cells, as suggested recently by Peters, returning to the plasma later as the hydrogen ion concentration of the cells diminished.

It is of interest to note, however, that ultimately chloride *aids* in the recovery of plasma $BHCO_3$. In Case 1, for instance, it may be noted that as $BHCO_3$ increased from 14.2 mM. on September 17, 1926 to 21.4 mM. on September 21, 1926, BCl diminished from 90.0 to 80.4 mM. This diminution of plasma chloride occurred after re-establishment of urinary secretion and during a time in which the hydrogen ion concentration of the plasma was diminishing. It seems reasonable to assume, therefore, that when urinary secretion is re-established, $BHCO_3$ is supported by excretion of ammonium chloride into the urine.

From such data as shown in table 1, therefore, we may conclude that administration only of water and insulin, with or without carbohydrate, restores but very slowly the $BHCO_3$ of the plasma, and therefore of the body fluids in general, the probable explanation being that as the hydrogen ion concentration of the fixed tissue cell decreases, the cell proteins claim base liberated from organic acid and chloride, the latter shifting into the plasma and claiming base originally held by organic acid, which otherwise might have combined with carbonic acid. Later chloride may be further shifted into the urine, bound to ammonia and thus release base for combination with carbonic acid.

With these points in mind, it should be of interest to note whether or not *salt solution* administration along with insulin, water, and carbohydrate, by causing an earlier and more intensive secretion of ammonium chloride into the urine causes a speedier restoration of plasma $BHCO_3$.

The effect of salt administration

In Case 4 (table 2, chart 2) on January 24, 1927, during the first 48 hours of treatment consisting of administration of water, insulin, carbohydrate and Ringer's solution, "acidosis" actually became more marked, the plasma $BHCO_3$ falling from 12.9 to 5.9 mM. During this interval, despite considerable insulin, little change in the blood sugar level was noted, and total organic acid concentration remained

about 15.0 mM. Later, with similar treatment, but with very large amounts of insulin, recovery occurred. Most unfortunately, however, no data was secured between January 28, 1927, and February 4, 1927. What data there is, however, would indicate that salt administration had little effect other than that of keeping the plasma BCl at a higher level.

In Case 1 on April 15, 1927, salt was also administered. Twenty-two hours after the beginning of treatment, base released by organic acid, phosphate and lactate amounted to 12.6 mM. $BHCO_3$ increased 10.9 mM. The base binding value of protein, allowing for the probable erroneously high value of the first sample as indicated by the refractometer, in all probability changed very little, dilution of the plasma being balanced by the rise in pH. Chloride increase claimed only 3.0 mM. base. In this instance, therefore, administration of salt, besides supporting plasma BCl may have hastened to some, but certainly to no great extent, $BHCO_3$ restoration.

From data as shown in table 2, therefore, we may conclude that administration of salt solution, in moderate amount, while possibly aiding to some extent $BHCO_3$ restoration, caused by glucose and organic acid oxidation, does not provide any marked or immediate relief from severe acidosis. This, however, alkali does, as can be seen from table 3 and chart 3.

The effects of alkali administration

When Case 3 was admitted to the hospital at 2 p.m. on January 31, 1927, marked acidosis and dehydration were associated with severe thoracic pain, which made hyperpnea distressing. Signs of severe circulatory failure were also in evidence, and, in the opinion of all who saw her, the chance of recovery was slight. Yet, within but a few hours after the beginning of therapy which included alkali administration, as well as insulin, glucose and salt solution, recovery from acidosis had occurred. As can be seen from table 3 and chart 3, $BHCO_3$ was but 6.4 mM. (a reduction of approximately 17.0 mM.) and pH 7.10, and an unusually low total organic acid content was present, 9.0 mM. In three hours, during which ketone acid had decreased but 2.0 mM., $BHCO_3$ rose from 6.4 to 17.1 mM. and hyperpnea ceased. Five hours later, when apparently complete oxidation

of ketone acid had occurred, $BHCO_3$ reached a high normal value, 26.1 mM. In addition to this rapid and complete relief from acidosis, alkali administration had also the effect of diluting the plasma very rapidly, if we can judge from the refractometric values of protein.

In Case 1, on June 6, 1928, extreme acidosis was present, $BHCO_3$ was but 3.0 mM. and pH was less than 7.00. Despite immediate administration of insulin intravenously, no improvement was noted in two and one-half hours. Alkali was then given, and there followed immediate clinical improvement and in seven and one-half hours plasma $BHCO_3$ was 22.9 mM. and pH 7.43.

· Similar almost perfect chemical restitution of the plasma in 12 to 24 hours by means of combined insulin and alkali therapy was noted earlier in our experience (5). At that time, however, we were not as convinced as we are at present of the necessity of alkali in extreme cases of diabetic acidosis, and feared the development later of alkalosis. It is very doubtful whether moderate alkalosis does any more harm than moderate acidosis, and certainly extreme alkalosis has been observed in cases of pyloric stenosis (6) with little in the way of alarming symptoms. Similarly marked increase in plasma $BHCO_3$ developed in Case 1 on April 4, 1928, after combined insulin and alkali treatment without symptoms or apparent harm. If tetany had occurred, we feel that it could easily have been controlled by inhalation of carbon dioxide and administration intravenously of calcium chloride. We quite agree, however, that marked alkalosis should be avoided if possible and critical study of those cases who received alkali and developed alkalosis is indicated.

Such a study, including observation of both blood and urine will be reserved for a later paper.

In the meantime, however, we feel that cases of diabetic acidosis as severe as the cases described in this paper will be greatly benefited if, in addition to the usual water, insulin, carbohydrate and salt administration, alkali equivalent to one-fourth of that normally present in the body fluids is also administered. For calculating such a dosage it is assumed that the body fluid comprises two-thirds of the body weight, and at its normal pH contains 3.0 grams of sodium bicarboate per liter.

SUMMARY AND CONCLUSIONS

The composition of the blood serum in severe diabetic acidosis and during recovery was studied as follows:

1. The concentrations of the principal normal anions, Cl', HCO_3', protein', HPO_4'', and lactate', and the actual pH were determined.

2. Total base was determined directly, and from its value and the sum of the five principal acids determined, the concentration of undetermined acid (presumably chiefly ketone acid) was obtained.

3. The principal non-electrolyte substances, non-protein nitrogen (urea) and dextrose were determined.

4. The freezing point of the serum was determined, and compared with theoretical total osmolar concentration (calculated from the individual acids, total base, glucose and urea).

The principal conclusions drawn are that:

1. In severe acidosis, marked concentration of the plasma occurs, with, however, slight diminution of total base. Bicarbonate and chloride are diminished relatively more than ketone acid and protein are increased, although increase in ketone acid usually exceeds diminution of $BHCO_3$.

2. When therapy consists only of administration of water and insulin, with or without carbohydrate, $BHCO_3$ and pH are at first restored relatively very slowly because, as base is released by oxidation of the salts of the ketone acids, it is claimed in large part by acids other than carbonic, chief among which is chloride. Later secretion of chloride into the urine bound to ammonia aids in the restoration of plasma $BHCO_3$.

3. Salt solution administration adds little if any towards the early recovery of plasma bicarbonate.

4. Alkali (sodium bicarbonate) when properly administered along with water, insulin, carbohydrate and salt solution, may provide a very rapid, safe, and complete relief from acidosis.

BIBLIOGRAPHY

1. Hartmann, A. F., Am. J. Dis. Child., 1928, xxv, 557. Chemical Changes Occurring in the Body as a Result of Certain Diseases: I. The Effects of Diarrhea, Vomiting, Dehydration and Oliguria on the Acid-Base Balance of the Plasma of Infants with Mastoiditis.

2. Hartmann, A. F., and Darrow, D. C., J. Clin. Invest., 1928, vi, 127.   Chemical Changes Occurring in the Body as a Result of Certain Diseases: II. Acute Hemorrhagic Nephritis; Subacute Nephritis; Chronic Nephritis.
3. Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C., Clin. Invest., 1925, ii, 167.   Total Acid-Base Equilibrium of Plasma in Health and Disease. VI. Studies of Diabetes.
4. Van Slyke, D. D., Wu, H., and McLean, F. C., J. Biol. Chem. 1923, lvi, 804. Studies of Gas and Electrolyte Equilibria in the Blood.   V. Factors Controlling the Electrolyte and Water Distribution in the Blood.
5. Hartmann, A. F., Med. Clin. N. Am., 1925, ix, 1.   Diabetes Mellitus in Infants and Children.
6. Hartmann, A. F., and Smyth, F. S., Am. J. Dis. Child., 1926, xxxii, 1.   Chemical Changes in the Body Occurring as the Result of Vomiting.
7. Stadie Wm. C., and Ross, E. C., J. Biol. Chem., 1925, lxv, 735.   A Micro Method for the Determination of Base in Blood and Serum and other Biological Materials.